IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
Southern Division

JENNIFER ELLER, *Plaintiff*, v. PRINCE GEORGE'S COUNTY PUBLIC SCHOOLS, et al., *Defendants*.	Case Number: 18-cv-03649-TDC

DECLARATION OF OMAR GONZALEZ-PAGAN

I, Omar Gonzalez-Pagan, do hereby declare and state as follows:

1. I am over 18 years of age.

2. I am Counsel at Lambda Legal Defense and Education Fund, Inc. and serve as counsel of record for Plaintiff Jennifer Eller in the above-captioned matter.

3. I have personal knowledge of the stated herein, except those stated on information and belief, and if called upon, could and would testify competently to them.

4. I submit this declaration in support of Plaintiff's Motion *In Limine* to Exclude Expert Testimony of Dr. Marcellus R Cephas.

5. Attached as **Exhibit A** is a true and correct copy of the expert witness report of Dr. Marcellus R. Cephas, M.D., M.B.A. (including a copy of his curriculum vitae) in the above-captioned matter, which was served upon plaintiff on December 30, 2019, and was entered as Plaintiff's Exhibit 78 during Dr. Cephas's deposition in this matter on February 5, 2020.

6. Attached as **Exhibit B** is a true and correct copy of the expert rebuttal report of Dr. Randi C. Ettner, Ph.D. in the above-captioned matter, which is dated January 9, 2020 and was served upon defendants on January 13, 2020.

7. Attached as **Exhibit C** is a true and correct copy of the American Psychiatric Association's *Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder*, which was entered as Plaintiff's Exhibit 79 during Dr. Cephas's deposition in this matter on February 5, 2020.

8. Attached as **Exhibit D** is a true and correct copy of the Endocrine Society's *Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline*, which was published in the peer-reviewed medical *Journal of Clinical Endocrinology and Metabolism* on September 13, 2017.

9. Attached as **Exhibit E** is a true and correct copy of the Endocrine Society's *Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline*, which was published in the peer-reviewed medical *Journal of Clinical Endocrinology and Metabolism* on November 1, 2015.

10. Attached as **Exhibit F** is a true and correct copy of the article "The Physicians' Desk Reference: Problems and Possible Improvements," published in the peer-reviewed medical journal *Archives of Internal Medicine* on July 8, 1996.

11. Attached as **Exhibit G** is a true and correct copy of the article "Discriminatory experiences associated with posttraumatic stress disorder symptoms among transgender adults," published in the peer-reviewed academic *Journal of Counseling Psychology* in October 2016, and which was entered as Plaintiff's Exhibit 83 during Dr. Cephas's deposition in this matter on February 5, 2020.

Pursuant to 28 U.S.C.§ 1746, I declare under the penalty of perjury that the foregoing is true and correct.

Dated this 7th day of September 2022.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
Southern Division

JENNIFER ELLER,

Plaintiff,

v.

PRINCE GEORGE'S COUNTY PUBLIC SCHOOLS, et al.,

Defendants.

Case No. 18-cv-03649

PLAINTIFF'S RULE 26(a)(2) REBUTTAL EXPERT DISCLOSURE

Pursuant to Rule 26(a)(2) of the Federal Rules of Civil Procedure and the Court's scheduling order (Dkt. 44), Plaintiff Jennifer Eller, by and through her attorneys, make the following disclosures of expert rebuttal testimony. These disclosures do not waive any privilege or work-product protection, and are made without prejudice to any other issue or argument. These disclosures do not waive any privilege or work-product protection, and are made without prejudice to any other issue or argument.

Dr. Randi C. Ettner, Ph.D.
1214 Lake Street
Evanston, Illinois 60201

A copy of Dr. Ettner's Rebuttal Expert Report is enclosed. Copies of Dr. Ettner's curriculum vitae and a bibliography were previously provided as attachments to her expert report, which were served on Defendants on August 5, 2019.

Dated this 13th of January, 2020.

Respectfully submitted,

/s/ Omar Gonzalez-Pagan

Omar Gonzalez-Pagan
(admitted *pro hac vice*)
Carl Charles (admitted *pro hac vice*)
LAMBDA LEGAL DEFENSE AND
EDUCATION FUND, INC.
120 Wall Street, 19th Floor
New York, NY 10005
Telephone: (212) 809-8585
Fax: (212) 809-0055
ogonzalez-pagan@lambdalegal.org
ccharles@lambdalegal.org

Puneet Cheema (admitted *pro hac vice*)
LAMBDA LEGAL DEFENSE AND
EDUCATION FUND, INC.
1776 K Street NW, Suite 722
Washington, DC 20006
Telephone: (202) 804-6245, ext. 596
pcheema@lambdalegal.org

Paul Pompeo (admitted *pro hac vice*)
Elliott Mogul (admitted *pro hac vice*)
Michael Rodríguez (admitted *pro hac vice*)
Thomas McSorley (No. 18609)
Jocelyn Wiesner (admitted *pro hac vice*)
ARNOLD & PORTER
KAYE SCHOLER LLP
601 Massachusetts Ave., NW
Washington, DC 20001-3743
Telephone: +1 202.942.5000
Fax: +1 202.942.5999
paul.pompeo@arnoldporter.com
elliott.mogul@arnoldporter.com
michael.rodriguez@arnoldporter.com
tom.mcsorley@arnoldporter.com
Jocelyn.Wiesner@arnoldporter.com

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was served by electronic mail (email) on the following counsel of record for Prince George's County Public Schools:

James E. McCollum, Jr.
Amit K. Sharma
McCollum & Associates, LLC
7309 Baltimore Avenue, Suite 117
College Park, Maryland 20740
Tel: (301) 864-6070
Fax: (301) 864-4351
jmccollum@jmlaw.net
asharma@jmlaw.net

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
Southern Division

JENNIFER ELLER

Plaintiff,

v.

PRINCE GEORGE'S COUNTY PUBLIC SCHOOLS, et al.,

Defendants.

Case Number: 18-cv-03649

EXPERT REBUTTAL REPORT OF DR. RANDI C. ETTNER, Ph.D.

1. I have been retained by counsel for Plaintiff, Jennifer Eller, as an expert in the above-captioned matter. I submitted my expert report on August 5, 2019. My qualifications as an expert were provided in that document.

2. Since then, I have testified as an expert at trial or by deposition in the following cases: *Ray v. Acton*, No. 2:18-cv-00272 (S.D. Ohio 2019), and *Monroe v. Jeffreys*, No. 3:18-cv-00156 (S.D. Ill. 2019).

3. I have been asked by counsel for Plaintiff to respond to certain opinions of Dr. Marcus R. Cephas, M.D. In preparing to write this rebuttal report, I relied upon or reviewed the expert report of Dr. Cephas and its accompanying attachments; my review of Ms. Eller's medical records, as outlined in my report; the materials referenced in the Bibliography attached as Exhibit B of my report; and my extensive experience as a licensed clinical and forensic psychologist with expertise concerning the diagnosis and treatment of gender dysphoria, as well as of trauma and Post Traumatic Stress Disorder (PTSD), all of which is outlined on my curriculum vitae attached as Exhibit A to my report.

4. I have actual knowledge of the matters stated herein. If called to testify in this matter, I would testify truthfully and based on my expert opinion.

5. The opinions expressed in this rebuttal report are based on the information that I have reviewed to date. I reserve the right to revise and supplement the report if any new information becomes available in the future.

6. I am being compensated for my work on this matter at a rate of $375.00 per hour for preparation of declarations and expert reports. I will be compensated $500.00 per hour for any pre-deposition and/or pre-trial preparation and any deposition testimony or trial testimony. I will receive a flat fee of $2,500.00 for any travel time to attend deposition or trial, and will be reimbursed for reasonable out-of-pocket travel expenses incurred for the purpose of providing expert testimony in this matter. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I may provide.

I. EXPERT OPINIONS

7. I have reviewed Dr. Cephas's report and curriculum vitae, and find no indication that Dr. Cephas has training, continuing education, or clinical experience in the highly specialized area of gender dysphoria, or with the assessment and/or treatment of transgender patients. What is more, Dr. Cephas appears to use in his report inaccurate or outdated terms for cross-sex hormonal treatment and gender confirmation surgery, two modalities that are the standard of care for gender dysphoria. Indeed, his report is peppered with language that reflects a deficit of knowledge regarding conditions of gender incongruity. For example, Dr. Cephas appears to conflate nuanced terms like sex and gender in referencing Ms. Eller's "sexual identity."

8. I believe Dr. Cephas committed an egregious error by stating that Estrace (a brand name for estradiol) is "life-threatening," causes "anxiety, depression, nervousness, … [and

insomnia," is a "dangerous" medication, and that therefore "the use of Estrace may cause or contribute significantly to the previous mentioned symptoms of depression, anxiety, and PTSD." These statements are not backed up by science. A search for the treatment guidelines for gender dysphoria would direct one to the Endocrine Society's Guidelines, as well as to the statements and guidelines of the Mayo Clinic, the American Medical Association, the American Psychiatric Association, the World Professional Association for Transgender Health (WPATH), and dozens of other medical organizations, all of which illuminate how inaccurate and misleading Dr. Cephas's statements regarding Estrace are.

9. The suggestion that Ms. Eller's very significant post-traumatic stress disorder (PTSD) symptoms are the side effect of estrogen has no scientific basis whatsoever. In fact, the opposite is true: A preponderance of medical literature documents that cross-sex hormone therapy (estradiol) is associated with improved mental health, improved quality of life and a significant decrease in psychological symptoms in gender dysphoric patients. Estradiol is within the standards of care for the treatment of gender dysphoria for transgender patients, and Ms. Eller's dosage is appropriate and consistent with the prescribing guidelines. In our clinic in Chicago, we have treated over 3,000 patients with cross sex hormonal protocols (estrogen therapy) and have never seen any of the "symptoms" Dr. Cephas has described, with the exception of weight gain.

10. Dr. Cephas's statements regarding the provision of cross-sex hormonal treatment are particularly disconcerting. Gender dysphoria is a serious medical condition. One has to wonder if Dr. Cephas is unaware that estradiol is one of the only efficacious forms of medical treatment? By asserting that estrogen is "dangerous," is he arguing that this medically necessary medical treatment for transgender patients should be withheld? By analogy, should medically indicated

anti-cholergenic medications be withheld from patients because these medications may have side effects, including an elevated risk of dementia?

11. Dr. Cephas goes to great lengths to dismiss Ms. Eller's PTSD symptoms, despite the fact that she has received this diagnosis from the mental health professionals who provided her treatment. He suggests, for example, that because Ms. Eller has engaged in DBT therapy (dialectical behavior therapy) she may have borderline personality disorder. Although DBT, a talk therapy, was originally developed in 1980 to treat borderline personality disorder, its main aim is to teach people to live in the moment and to cope with stress. Research shows that DBT has been successfully used to treat depression, bulimia, PTSD, and other disorders and to enhance mindfulness and effective communication and interaction with others.

12. In addition to proposing "alternative" diagnoses, among which are depression and medication side effects, Dr. Cephas opines that Ms. Eller's history of depression (attendant to her lifelong gender dysphoria) makes accurate assessment too complicated to confirm a PTSD diagnosis as a result of the hostile work environment, harassment, threats, and discrimination she endured at Prince George's County Public Schools following her decision to socially transition. But people with a history of depression, anxiety or those who have personality disorders are not immune from developing PTSD, given exposure to highly averse circumstances. The WPATH promulgated Standards of Care, Section VII "Competency of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria," includes the criteria that such clinicians have the "Ability to recognize and diagnose coexisting mental health concerns and to distinguish these from gender dysphoria."

13. Many, if not most, people have experienced upsetting or traumatic incidents during their lifetime. These historic events in no way preclude the subsequent development of PTSD, if

one is subjected to ongoing humiliation, discrimination, verbal and physical abuse, as was Ms. Eller. By analogy, the presence of type-one diabetes in childhood does not prevent the development of cancer or other chronic or acute diseases across the lifespan.

14. Regarding Ms. Eller's prior treatment for depression, it is rare for gender dysphoric people to not have a history of depression. The DSM-V notes that "[i]mpairment, … the development of depression and anxiety, may be a consequence of gender dysphoria."

15. Prior to Ms. Eller's transition, she was never diagnosed with PTSD. A review of her medical records and those of her mental health provider clearly document the hostile environment Ms. Eller endured as the genesis of PTSD, and the corresponding treatments prescribed for the disorder. Additionally, I corroborated these findings through psychological testing of Ms. Eller, specific to PTSD. Only clinical psychologists are formally trained and qualified to purchase and administer these types of psychometric instruments. The specific test administered to Ms. Eller is widely used by the military, and normed and standardized on a US sample. It is not a checklist, but rather a sophisticated assessment tool. It consists of two validity scales, (designed to prevent over-reporting or misrepresentation of PTSD), 12 clinical scales, 12 subscales, and four factors. There is high test- retest reliability, internal consistency, and evidence for concurrent discriminant, criterion, factorial and construct validity. There is no doubt that Ms. Eller's current chronic symptomatology and complex PTSD are the predictable result of the prolonged and repetitive assaults she endured while employed at Prince George's County Public Schools.

16. Ms. Eller endured a negative, non-supportive and at times violent workplace. The unremitting stress eroded her resiliency, resulting in PTSD and residual symptomatology. As I stated in my original report, the ceaseless harassment, discrimination and humiliation to which Ms.

Eller was subjected completely eroded her coping strategies and resilience, and resulted in the irremediable damage of what has now become chronic PTSD.

//

//

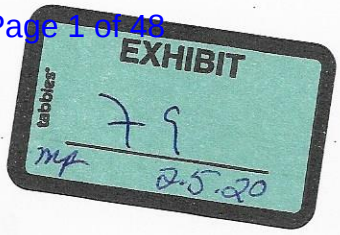
//

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated this 9 day of January, 2020.

Dr Randi C Ettner

Dr. Randi C. Ettner



PRACTICE GUIDELINE FOR THE Treatment of Patients With Acute Stress Disorder and Posttraumatic Stress Disorder

WORK GROUP ON ASD AND PTSD

Robert J. Ursano, M.D., Chair
Carl Bell, M.D.
Spencer Eth, M.D.
Matthew Friedman, M.D., Ph.D.
Ann Norwood, M.D.
Betty Pfefferbaum, M.D., J.D.
Robert S. Pynoos, M.D.
Douglas F. Zatzick, M.D.
David M. Benedek, M.D., Consultant

Originally published in November 2004. This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice. In accordance with national standards, including those of the Agency for Healthcare Research and Quality's National Guideline Clearinghouse (http://www.guideline.gov/), this guideline can no longer be assumed to be current. The March 2009 Guideline Watch associated with this guideline provides additional information that has become available since publication of the guideline, but it is not a formal update of the guideline.

This guideline is dedicated to Rebecca M. Thaler Schwebel (1972–2004), Senior Project Manager at APA when this guideline was initiated. Becca's humor, generous spirit, and optimism will be missed.

AMERICAN PSYCHIATRIC ASSOCIATION STEERING COMMITTEE ON PRACTICE GUIDELINES

John S. McIntyre, M.D.,
Chair
Sara C. Charles, M.D.,
Vice-Chair

Daniel J. Anzia, M.D.
Ian A. Cook, M.D.
Molly T. Finnerty, M.D.
Bradley R. Johnson, M.D.
James E. Nininger, M.D.
Paul Summergrad, M.D.
Sherwyn M. Woods, M.D., Ph.D.
Joel Yager, M.D.

AREA AND COMPONENT LIAISONS

Robert Pyles, M.D. (Area I)
C. Deborah Cross, M.D. (Area II)
Roger Peele, M.D. (Area III)
Daniel J. Anzia, M.D. (Area IV)
John P. D. Shemo, M.D. (Area V)
Lawrence Lurie, M.D. (Area VI)
R. Dale Walker, M.D. (Area VII)
Mary Ann Barnovitz, M.D.
Sheila Hafter Gray, M.D.
Sunil Saxena, M.D.
Tina Tonnu, M.D.

STAFF

Robert Kunkle, M.A., *Senior Program Manager*
Amy B. Albert, B.A., *Assistant Project Manager*
Laura J. Fochtmann, M.D., *Medical Editor*
Claudia Hart, *Director, Department of Quality Improvement and Psychiatric Services*
Darrel A. Regier, M.D., M.P.H., *Director, Division of Research*

CONTENTS

STATEMENT OF INTENT

The American Psychiatric Association (APA) Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities some contributors, including work group members and reviewers, have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. Work group members are selected on the basis of their expertise and integrity. Any work group member or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work is asked to disclose this to the Steering Committee on Practice Guidelines and the work group. Iterative guideline drafts are reviewed by the Steering Committee, other experts, allied organizations, APA members, and the APA Assembly and Board of Trustees; substantial revisions address or integrate the comments of these multiple reviewers. The development of the APA practice guidelines is not financially supported by any commercial organization.

More detail about mechanisms in place to minimize bias is provided in a document available from the APA Department of Quality Improvement and Psychiatric Services, "APA Guideline Development Process."

This practice guideline was approved in June 2004 and published in November 2004.

GUIDE TO USING THIS PRACTICE GUIDELINE

The *Practice Guideline for the Treatment of Patients With Acute Stress Disorder and Posttraumatic Stress Disorder* consists of three parts (Parts A, B, and C) and many sections, not all of which will be equally useful for all readers. The following guide is designed to help readers find the sections that will be most useful to them.

Part A, "Treatment Recommendations," is published as a supplement to *The American Journal of Psychiatry* and contains general and specific treatment recommendations. Section I summarizes the key recommendations of the guideline and codes each recommendation according to the degree of clinical confidence with which the recommendation is made. Section II provides further discussion of the formulation and implementation of a treatment plan as it applies to the individual patient. Section III, "Specific Clinical Features Influencing the Treatment Plan," discusses a range of clinical considerations that could alter the general recommendations discussed in Section I.

Part B, "Background Information and Review of Available Evidence," and Part C, "Future Research Needs," are not included in *The American Journal of Psychiatry* supplement but are provided with Part A in the complete guideline, which is available in print format, in guideline compendiums, from American Psychiatric Publishing, Inc. (http://www.appi.org), and online through the American Psychiatric Association (http://www.psych.org). Part B provides an overview of ASD and PTSD, including general information on natural history, course, and epidemiology. It also provides a structured review and synthesis of the evidence that underlies the recommendations made in Part A. Part C draws from the previous sections and summarizes areas for which more research data are needed to guide clinical decisions.

To share feedback on this or other published APA practice guidelines, a form is available at http://www.psych.org/psych_pract/pg/reviewform.cfm.

DEVELOPMENT PROCESS

This practice guideline was developed under the auspices of the Steering Committee on Practice Guidelines. The development process is detailed in a document available from the APA Department of Quality Improvement and Psychiatric Services: the "APA Guideline Development Process." Key features of this process include the following:

- A comprehensive literature review to identify all relevant randomized clinical trials as well as less rigorously designed clinical trials and case series when evidence from randomized trials was unavailable.
- Development of evidence tables that reviewed the key features of each identified study, including funding source, study design, sample sizes, subject characteristics, treatment characteristics, and treatment outcomes.
- Initial drafting of the guideline by a work group that included psychiatrists with clinical and research expertise in ASD and PTSD.
- Production of multiple revised drafts with widespread review; 11 organizations and 55 individuals submitted significant comments.
- Approval by the APA Assembly and Board of Trustees.
- Planned revisions at regular intervals.

Relevant literature was identified through a computerized search of MEDLINE and the Published International Literature on Traumatic Stress (PILOTS) database, produced by the National Center for Post-Traumatic Stress Disorder and available online (http://www.ncptsd.org//publications/pilots/index.html). An initial search of PubMed was conducted for the period from 1966 to 2002. Key words used were posttraumatic stress, stress disorder, acute stress disorder, posttraumatic stress disorder, and PTSD. Additional citations were identified by using key words emotional trauma, psychic trauma, posttraumatic, disaster, terrorism, rape, assault, physical abuse, sexual abuse, childhood abuse, combat, traumatic event, and traumatic incident and then limited to citations that included the key words stress, psychological sequelae, anxiety, and dissociation. In determining which of the identified citations related to treatment, key words used were treatment, management, therapy, psychotherapy, antidepressive agents, tranquilizing agents, anticonvulsants, debriefing, critical incident, eye movement desensitization, and EMDR. Citations were further limited to clinical trials or meta-analyses published in the English language and accompanied by abstracts. A total of 316 citations were found. When applied to the PILOTS database, this search strategy yielded a total of 587 citations, many of which were duplicates of those obtained in the PubMed search. Additional, less formal literature searches were conducted by APA staff and individual work group members. Other published guidelines for the treatment of ASD and PTSD were also reviewed (1, 2).

This guideline presents recommendations for the evaluation and treatment of adult patients with ASD or PTSD. The *Practice Parameters for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder* of the American Academy of Child and Adolescent Psychiatry (3) may be consulted for guidelines relating to the evaluation and treatment of children and adolescents.

This document represents a synthesis of current scientific knowledge and rational clinical practice. It strives to be as free as possible of bias toward any theoretical approach to treatment. Articles identified in the initial literature search were prioritized for review according to meth-

odological strength. Highest priority was given to randomized, placebo-controlled trials of psychotherapeutic and psychopharmacological interventions for individuals with a diagnosis of ASD or PTSD. The work group review process identified further citations that included randomized and open trials, literature reviews, meta-analyses, and other studies that were incorporated into evidence tables in an iterative manner. In interpreting the conclusions of these studies, consideration was given to factors that could limit the generalizability of the findings, including differences between individuals enrolled in well-controlled efficacy trials and individuals seen in clinical practice. Consequently, the recommendations for any particular clinical decision are based on the best available data and clinical consensus. The summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made. In addition, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence.

INTRODUCTION

It has long been recognized that stressful life events may cause emotional and behavioral effects. In addition, the clinical phenomenon of PTSD has been known by various names, studied, and treated for centuries. In 1980, DSM-III delineated distinct criteria for the diagnosis of PTSD. The diagnosis of ASD was added to DSM-IV in 1995 to distinguish individuals with PTSD-like symptoms that lasted less than 1 month from persons who experienced milder or more transient difficulties following a stressor. The DSM-IV-TR diagnostic criteria for both disorders can be found in Section II.A.2.

Although 50% to 90% of the population may be exposed to traumatic events during their lifetimes (4, 5), most exposed individuals do not develop ASD or PTSD. ASD was introduced into DSM in an effort to prospectively characterize the subpopulation of traumatically exposed persons with early symptoms and identify those at risk for the development of PTSD. Research and clinical experience show that those with high levels of symptoms early on, including those with ASD, are at risk of subsequent PTSD; however, some patients with ASD do not develop PTSD, and a proportion of patients develop PTSD without first having met the criteria for ASD (6–8). Although research shows that individuals who are most highly exposed to a traumatic event are at greatest risk, there is still uncertainty about the patient- or trauma-specific factors that will predict the development of ASD (9) and about interventions that will mitigate against the evolution of ASD into PTSD.

The lifetime prevalence of ASD is unclear, but in the National Comorbidity Survey the estimated lifetime prevalence of PTSD was 7.8% (4). The prevalence of both disorders is considerably higher among patients who seek general medical care (10) and among persons exposed to sexual assault (4, 5) or mass casualties such as those occurring in wars or natural disasters (11–13). The lifetime prevalence of PTSD is also higher in women than in men and is higher in the presence of underlying vulnerabilities such as adverse childhood experiences or comorbid diagnoses (11, 12, 14, 15). Given the prevalence of ASD and PTSD and their associated distress and disability, psychiatrists must be prepared to recognize and treat these disorders.

PART A
TREATMENT RECOMMENDATIONS

I. EXECUTIVE SUMMARY

A. CODING SYSTEM

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence regarding the recommendation:

[I] Recommended with substantial clinical confidence.
[II] Recommended with moderate clinical confidence.
[III] May be recommended on the basis of individual circumstances.

B. SUMMARY OF RECOMMENDATIONS

1. Initial assessment

The initial step in identifying individuals with ASD or PTSD involves screening for recent or remote trauma exposure, although the clinical approach may vary depending on the recency of the traumatic event [I]. If eliciting vivid and detailed recollections of the traumatic event immediately after exposure enhances the patient's distress, the interview may be limited to gathering information that is essential to provide needed medical care [I]. The first interventions in the aftermath of an acute trauma consist of stabilizing and supportive medical care and supportive psychiatric care and assessment [I]. After large-scale catastrophes, initial psychiatric assessment includes differential diagnosis of physical and psychological effects of the traumatic event (e.g., anxiety resulting from hemodynamic compromise, hyperventilation, somatic expressions of psychological distress, fatigue) and identification of persons or groups who are at greatest risk for subsequent psychiatric disorders, including ASD or PTSD [I]. This identification may be accomplished through individual evaluation, group interviews, consultation, and use of surveillance instruments [I].

Diagnostic evaluation may be continued after the initial period has passed and a physically and psychologically safe environment has been established, the individual's medical condition has been stabilized, psychological reassurance has been provided, and, in disaster settings, necessary triage has been accomplished. It is important for this diagnostic assessment to include a complete psychiatric evaluation that specifically assesses for the symptoms of ASD and PTSD, including dissociative, reexperiencing, avoidance/numbing, and hyperarousal symptom clusters and their temporal sequence relative to the trauma (i.e., before versus after 1 month from the traumatic event) [I]. Other important components of the assessment process include functional assessment, determining the availability of basic care resources (e.g., safe housing, social support network, companion care, food, clothing), and identifying previous traumatic experiences and comorbid physical or psychiatric disorders, including depression and substance use disorders [I].

2. Psychiatric management

Psychiatric management for all patients with ASD or PTSD includes instituting interventions and activities to ensure physical and psychological safety, required medical care, and availability of needed resources for self-care and recovery [I]. The patient's level of functioning and safety, including his or her risk for suicide and potential to harm others, are always important to evaluate during initial assessment and may determine the treatment setting [I]. The goals of psychiatric management for patients with ASD and PTSD also include establishing a therapeutic alliance with the patient; providing ongoing assessment of safety and psychiatric status, including possible comorbid disorders and response to treatment; and increasing the patient's understanding of and active adaptive coping with psychosocial effects of exposure to the traumatic event, such as injury, job loss, or loss of loved ones [I]. Additional goals of psychiatric management include providing education regarding ASD and PTSD, enhancing treatment adherence, evaluating and managing physical health and functional impairments, and coordinating care to include collaborating with other clinicians [I].

3. General principles of treatment selection

The goals of treatment for individuals with a diagnosis of ASD or PTSD include reducing the severity of ASD or PTSD symptoms, preventing or treating trauma-related comorbid conditions that may be present or emerge, improving adaptive functioning and restoring a psychological sense of safety and trust, limiting the generalization of the danger experienced as a result of the traumatic situation(s), and protecting against relapse [I].

Patients assessed within hours or days after an acute trauma may present with overwhelming physiological and emotional symptoms (e.g., insomnia, agitation, emotional pain, dissociation). Limited clinical trial evidence is available in this area, as randomized designs are difficult to implement; however, clinical experience suggests that these acutely traumatized individuals may benefit from supportive psychotherapeutic and psychoeducational interventions [II]. Pharmacotherapy may be the first-line intervention for acutely traumatized patients whose degree of distress precludes new verbal learning or nonpharmacological treatment strategies [II]. Research has not consistently identified patient- or trauma-specific factors that predict the development of ASD or interventions that will alter the evolution of ASD into PTSD. However, early after a trauma, once the patient's safety and medical stabilization have been addressed, supportive psychotherapy, psychoeducation, and assistance in obtaining resources such as food and shelter and locating family and friends are useful [II].

Effective treatments for the symptoms of ASD or PTSD encompass psychopharmacology, psychotherapy, and psychoeducation and other supportive measures [I]. Although studies using a combination of these approaches for ASD and PTSD are not presently available, combination treatment is widely used and may offer advantages for some patients [II]. The psychotropic medications used in clinical practice and research for the treatment of ASD and PTSD were not specifically developed for these disorders but have been used in doses similar to those recommended or approved for other psychiatric illnesses.

For patients with ASD or PTSD, choice of treatment includes consideration of age and gender, presence of comorbid medical and psychiatric illnesses, and propensity for aggression or self-injurious behavior [I]. Other factors that may influence treatment choice include the recency of the precipitating traumatic event; the severity and pattern of symptoms; the presence of particularly distressing target symptoms or symptom clusters; the development of interpersonal or family issues or occupational or work-related problems; preexisting developmental or psychological vulnerabilities, including prior trauma exposure; and the patient's preferences [I].

When the patient's symptoms do not respond to a plan of treatment, selection of subsequent interventions will depend on clinical judgment, as there are limited data to guide the clinician. It is important to systematically review factors that may contribute to treatment nonresponse, including the specifics of the initial treatment plan and its goals and rationale, the patient's per-

ceptions of the effects of treatment, the patient's understanding of and adherence to the treatment plan, and the patient's reasons for nonadherence if nonadherence is a factor [I]. Other factors that may need to be addressed in patients who are not responding to treatment include problems in the therapeutic alliance; the presence of psychosocial or environmental difficulties; the effect of earlier life experiences such as childhood abuse or previous trauma exposures; and comorbid psychiatric disorders, including substance-related disorders and personality disorders [I].

4. Specific treatment strategies

(a) Psychopharmacology

Although it has been hypothesized that pharmacological treatment soon after trauma exposure may prevent the development of ASD and PTSD, existing evidence is limited and preliminary. Thus, no specific pharmacological interventions can be recommended as efficacious in preventing the development of ASD or PTSD in at-risk individuals.

For patients with ASD, there are few studies of pharmacological interventions. However, selective serotonin reuptake inhibitors (SSRIs) [II] and other antidepressants [III] represent reasonable clinical interventions that are supported by limited findings in ASD as well as by findings of therapeutic benefits in patients with PTSD.

SSRIs are recommended as first-line medication treatment for PTSD [I]. In both male and female patients, treatment with SSRIs has been associated with relief of core PTSD symptoms in all three symptom clusters (reexperiencing, avoidance/numbing, hyperarousal). Other antidepressants, including tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), may also be beneficial in the treatment of PTSD [II].

Benzodiazepines may be useful in reducing anxiety and improving sleep [III]. Although their efficacy in treating the core symptoms of PTSD has not been established, benzodiazepines are often used in trauma-exposed individuals and patients with PTSD. However, clinical observations include the possibility of dependence, increased incidence of PTSD after early treatment with these medications, or worsening of PTSD symptoms after withdrawal of these medications. Thus, benzodiazepines cannot be recommended as monotherapy in PTSD.

In addition to being indicated in patients with comorbid psychotic disorders, second-generation antipsychotic medications (e.g., olanzapine, quetiapine, risperidone) may be helpful in individual patients with PTSD [III]. Anticonvulsant medications (e.g., divalproex, carbamazepine, topiramate, lamotrigine), α_2-adrenergic agonists, and β-adrenergic blockers may also be helpful in treating specific symptom clusters in individual patients [III].

(b) Psychotherapeutic interventions

Some evidence is available about the effectiveness of psychotherapeutic intervention immediately after trauma in preventing development of ASD or PTSD. Studies of cognitive behavior therapy in motor vehicle and industrial accident survivors as well as in victims of rape and interpersonal violence suggest that cognitive behavior therapies may speed recovery and prevent PTSD when therapy is given over a few sessions beginning 2–3 weeks after trauma exposure [II].

Early supportive interventions, psychoeducation, and case management appear to be helpful in acutely traumatized individuals, because these approaches promote engagement in ongoing care and may facilitate entry into evidence-based psychotherapeutic and psychopharmacological treatments [II]. Encouraging acutely traumatized persons to first rely on their inherent strengths, their existing support networks, and their own judgment may also reduce the need for further intervention [II]. In populations of patients who have experienced multiple recurrent traumas, there is little evidence to suggest that early supportive care delivered as a standalone treatment will result in lasting reductions in PTSD symptoms. However, no evidence suggests that early supportive care is harmful. In contrast, psychological debriefings or single-session techniques are not recommended, as they may increase symptoms in some settings and appear to be ineffective in treating individuals with ASD and in preventing PTSD.

No controlled studies of psychodynamic psychotherapy, eye movement desensitization and reprocessing (EMDR), or hypnosis have been conducted that would establish data-based evidence of their efficacy as an early or preventive intervention for ASD or PTSD.

For patients with a diagnosis of ASD or PTSD, available evidence and clinical experience suggest that a number of psychotherapeutic interventions may be useful. Patients with ASD may be helped by cognitive behavior therapy and other exposure-based therapies [II]. In addition, cognitive behavior therapy is an effective treatment for core symptoms of acute and chronic PTSD [I]. EMDR is also effective [II]. Stress inoculation, imagery rehearsal, and prolonged exposure techniques may also be indicated for treatment of PTSD and PTSD-associated symptoms such as anxiety and avoidance [II]. The shared element of controlled exposure of some kind may be the critical intervention.

Psychodynamic psychotherapy may be useful in addressing developmental, interpersonal, or intrapersonal issues that relate to the nature, severity, symptoms, or treatment of ASD and PTSD and that may be of particular importance to social, occupational, and interpersonal functioning [II].

Case management, psychoeducation, and other supportive interventions may be useful in facilitating entry into ongoing treatment, appear not to exacerbate PTSD symptoms, and in some pilot investigations have been associated with PTSD symptom reduction [II]. Present-centered and trauma-focused group therapies may also reduce PTSD symptom severity [III].

II. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

A. INITIAL ASSESSMENT

1. Initial clinical approach to the patient

The timing and nature of initial assessments will be influenced by the type of the traumatic event (e.g., sexual assault versus natural disaster) and the scope of any destruction caused by the event. In large-scale catastrophes, the initial assessment may be the triage of individuals based on the presence of physical injury or psychological effects of the traumatic event, followed by the identification of individuals at greatest risk for psychiatric sequelae, including ASD or PTSD. Group interviews, consultation, or the administration of surveillance instruments may be part of this process. If local resources are overwhelmed by the catastrophe, psychiatric assessment will need to be prioritized so that the most severely affected individuals are seen first. Several self-rated and observer-based rating scales have been developed and validated to facilitate screening for possible PTSD; however, study of these scales in community-wide disasters with highly diverse populations has been limited. Such rating scales are most likely to be helpful after the acute event, when physical and cognitive functioning allow for a more complex assessment (16–18).

With individual traumas, the timing and nature of the first mental health contact may also vary. For individuals who have been sexually assaulted, for example, supportive psychological interventions may be initiated even before formal psychiatric assessment (e.g., use of educational materials on what to expect in the rape examination). In evaluations that occur shortly after exposure to the traumatic event, particularly in emergency settings, the initial clinical response consists of stabilizing and supportive medical care as well as supportive psychiatric care and assessment, including assessment of potential dangerousness to self or others. Addressing the individual's requirements for medical care, rest, nutrition, and control of injury-related pain is important for assuring the patient's physical health, enhancing the patient's experience

of safety, and initiating the therapeutic relationship. Such interactions with trauma-exposed individuals will always entail sensitivity to the patient's wishes and to the changing symptoms, fears, and interpersonal needs that unfold after trauma exposure.

Whenever possible, care should be given within a safe environment. This may not be feasible after large-scale traumatic events in which there may be additional or ongoing exposures (e.g., earthquakes, war zones, ongoing gang warfare). With other types of traumatic events, further assurances of safety may be possible and necessary. For example, with traumatic events such as domestic violence, specific efforts or engagement of law enforcement or social service agencies may be needed to address the patient's safety and reduce the likelihood of repeat traumatization.

During the first 48–72 hours after a traumatic event, some individuals may be very aroused, anxious, or angry, whereas others may appear minimally affected or "numb" as a result of injury, pain, or dissociative phenomena (19). In triage or emergency department settings, an in-depth exploration of the traumatic event and the patient's experiences may increase distress but may be required for medical or safety reasons. For example, after physical or sexual assault, recounting events in response to the evaluator's questions or the mere gender of the evaluator may have a distressing effect in some individuals. Similarly, after an event involving death or injury to a family member, a clinician may need to obtain or disclose upsetting information, while gauging the patient's response as part of the evaluation. Insensitive or premature exploration of recent life-threatening events or losses can be counterproductive, leading the patient to avoid medical care, whereas other individuals may find in-depth exploration of recent events helpful. Therefore, evaluators must respond to the patient's needs and capabilities. After mass disasters, triage assessments in a group setting may be used effectively to identify those in need of intervention. However, discussion of distressing memories and events in heterogeneously exposed groups may adversely affect those with little or no exposure when they hear of the frightening and terrifying experiences of others.

2. Assessing exposure to a traumatic event and establishing a diagnosis of ASD or PTSD

By definition, ASD and PTSD are psychiatric disorders consisting of physiological and psychological responses resulting from exposure to an event or events involving death, serious injury, or a threat to physical integrity. Events such as natural disasters, explosions, physical or sexual assaults, motor vehicle accidents, or involvement with naturally occurring or terrorist-related disease epidemics are examples of events that may elicit the physiological and psychological response required by the diagnostic criteria of ASD and PTSD. Thus, screening for acute or remote event exposure is a necessary first step in identifying persons with either ASD or PTSD.

Table 1 and Table 2 provide the full criteria for the diagnosis of ASD and PTSD, respectively. For both disorders, DSM-IV-TR defines criterion A as exposure to a traumatic event in which both of the following conditions are present:

1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
2. The person's response involved intense fear, helplessness, or horror.

Thus, for both ASD and PTSD, establishing a diagnosis requires consideration of the individual's response to the event as well as the nature of the event itself. It is important to note that for some individuals, initial assessment may occur in a triage setting immediately after the trauma and before all symptoms related to the trauma exposure are manifest. In addition, the presence of dissociative symptoms may prevent patients from recalling feelings of fear, helplessness, or horror and may require that clinical judgment be used in determining whether criterion A for diagnosis has been satisfied (20–22).

Clinical evaluation for ASD or PTSD requires assessment of symptoms within each of three symptom clusters: reexperiencing, avoidance/numbing, and hyperarousal. In addition, to meet the diagnostic criteria for ASD, a patient must exhibit dissociative symptoms either during or

TABLE 1. DSM-IV-TR Diagnostic Criteria for Acute Stress Disorder (DSM-IV-TR code 308.3)

A. The person has been exposed to a traumatic event in which both of the following were present:
   1. the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   2. the person's response involved intense fear, helplessness, or horror

B. Either while experiencing or after experiencing the distressing event, the individual has three (or more) of the following dissociative symptoms:
   1. a subjective sense of numbing, detachment, or absence of emotional responsiveness
   2. a reduction in awareness of his or her surroundings (e.g., "being in a daze")
   3. derealization
   4. depersonalization
   5. dissociative amnesia (i.e., inability to recall an important aspect of the trauma)

C. The traumatic event is persistently reexperienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event.

D. Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people).

E. Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness).

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or impairs the individual's ability to pursue some necessary task, such as obtaining necessary assistance or mobilizing personal resources by telling family members about the traumatic experience.

G. The disturbance lasts for a minimum of 2 days and a maximum of 4 weeks and occurs within 4 weeks of the traumatic event.

H. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition, is not better accounted for by Brief Psychotic Disorder, and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.

Source. Reprinted from *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Copyright 2000, American Psychiatric Association. Used with permission.

immediately after the traumatic event. In PTSD, dissociative symptoms (e.g., inability to recall important aspects of the trauma) are not necessary to the diagnosis but are often observed.

By definition, ASD occurs within 4 weeks of the trauma and lasts for a minimum of 2 days. Consequently, it can be diagnosed within 2 days after the trauma exposure continuing to 4 weeks after the traumatic event. If symptoms are present 1 month after the trauma exposure, PTSD is diagnosed. Since diagnostic assessment may occur at any time following a traumatic event, the clinician must bear these essential distinctions in mind when evaluating the trauma-exposed individual.

3. Additional features of the initial assessment

After it has been determined that the traumatically exposed individual is able to tolerate more extensive evaluation, it is important to obtain a detailed history of the exposure and the pa-

TABLE 2. DSM-IV-TR Diagnostic Criteria for Posttraumatic Stress Disorder (DSM-IV-TR code 309.81)

A. The person has been exposed to a traumatic event in which both of the following were present:
   1. the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   2. the person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
   1. recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
   2. recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.
   3. acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). Note: In young children, trauma-specific reenactment may occur.
   4. intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
   5. physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
   1. efforts to avoid thoughts, feelings, or conversations associated with the trauma
   2. efforts to avoid activities, places, or people that arouse recollections of the trauma
   3. inability to recall an important aspect of the trauma
   4. markedly diminished interest or participation in significant activities
   5. feeling of detachment or estrangement from others
   6. restricted range of affect (e.g., unable to have loving feelings)
   7. sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
   1. difficulty falling or staying asleep
   2. irritability or outbursts of anger
   3. difficulty concentrating
   4. hypervigilance
   5. exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.

TABLE 2. DSM-IV-TR Diagnostic Criteria for Posttraumatic Stress Disorder (DSM-IV-TR code 309.81) *(continued)*

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: if duration of symptoms is less than 3 months

Chronic: if duration of symptoms is 3 months or more

Specify if:

With Delayed Onset: if onset of symptoms is at least 6 months after the stressor.

Source. Reprinted from *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Copyright 2000, American Psychiatric Association. Used with permission.

tient's early responses to the trauma as well as the responses of significant others. This history can provide important information for treatment and prognosis. Often, individuals provide negative responses to all-inclusive questions (e.g., "Have you ever been abused?"), and responses may also be affected by the timing and context of questioning. Consequently, it is helpful to ask more specific questions (e.g., "Have you ever been hit, beaten, or choked?") and attempt to elicit a history of trauma exposure at various points during the evaluation.

During the evaluation, the clinician obtains a longitudinal history of all traumatic experiences, including age at the time of exposure, duration of exposure (e.g., single episode, recurrent, or ongoing), type of trauma (e.g., motor vehicle accident, natural disaster, physical or sexual assault), relationship between the patient and the perpetrator (in cases of interpersonal violence), and the patient's perception of the effect of these experiences (on self and significant others). Other factors or interventions that may have intensified or mitigated the traumatic response should also be identified.

Clinical interviews may be combined with a variety of validated self-rated measures, including the PTSD Checklist (23), the Impact of Event Scale (24, 25) (available online at www.mardihorowitz.com), and the Davidson Trauma Scale (26), to assess the full range, frequency, and severity of posttraumatic symptoms and the related distress and impairment. Structured diagnostic interviews such as the Clinician-Administered PTSD Scale (27) and the Structured Interview for PTSD (28) have been used extensively in clinical research and are well-validated instruments for the diagnosis of PTSD.

In addition, a complete psychiatric evaluation should be conducted in accordance with the general principles and components outlined in APA's *Practice Guideline for the Psychiatric Evaluation of Adults* (29). These components include a history of the present illness and current symptoms; a psychiatric history, including a substance use history; medical history; review of systems and a review of prescribed and over-the-counter medications (including herbal products and supplements); personal history (e.g., psychological development, response to life transitions and major life events); social, occupational, and family history; history of prior treatments or interventions and their degree of success; mental status examination; physical examination; and diagnostic tests as indicated. Developmental and preexisting psychodynamic issues may make the patient especially vulnerable or reactive to a traumatic event. Old and dormant concerns may resurface and complicate or otherwise intensify the emotional response to a new trauma. Past exposure to traumatic events as well as previous patient and support network responses may affect the evaluation process and choice of and response to treatment. In the context of this complete psychiatric evaluation, certain areas of inquiry should receive additional attention and are described below. Table 3 summarizes the clinical domains relevant to the comprehensive assessment of ASD and PTSD.

a) Military and war-related traumatic event history

Evaluation of exposure to traumatic events during military service or in war-torn areas is an important and often difficult part of clinical assessment. Past exposure to war environments increases the probability of exposure to traumatic events. In addition, past exposures to traumatic events or past PTSD may increase the likelihood of current PTSD from a new exposure (31–34). Persons who come from nations with past or ongoing histories of war and war atrocities may have substantial exposure to traumatic events. Military support troops in rear areas as well as combat troops are vulnerable to attacks and other life-threatening experiences. Those serving in the military or involved in humanitarian assistance may have been massively exposed to death and the dead and can have high rates of ASD and PTSD. Military service members may also be involved in or witness training accidents, including motor vehicle accidents or aircraft crashes.

For those with military service, it is often helpful to begin the evaluation by exploring why the patient joined the military and what he or she hoped to do. Specific data to be gathered that can assist in the evaluation of traumatic event exposures include the length of service (and whether this length of time was broken or unbroken), the presence or absence of any disciplinary charges, and military awards received. The patient should also be asked if he or she was ever referred for alcohol or other substance use counseling, family violence counseling, or a psychiatric evaluation. If the patient had a family while in the service, it is important to explore the frequency and effects of family separation on the service member, the spouse, and the children. With service members or veterans who report having been in combat, a description of the location and the events should be obtained. It is often helpful to obtain copies of service records to verify combat exposures.

Witnessing atrocities, seeing the death of children, seeing friends killed and wounded, and feeling responsible for the death of a friend are especially disturbing elements of some combat and war environments for both military and civilian persons. As in all traumas, the recovery environment (that is, whether family, friends, and the nation are welcoming or ashamed) plays a large role in how the experience is recalled and managed. Some immigrants have previously lived in war zones or have served as members of military, paramilitary, or insurgent units before immigration. Some may also have been victims of torture, maltreatment, or rape as part of a war environment. Immigrants who may have served for regimes that espoused strong anti-American politics may fear repercussions from an unsympathetic country. These contextual issues require clear and supportive discussion in the evaluation and assessment in order to obtain necessary clinical information.

b) Victims of crime and effects of legal system involvement

Individuals with ASD or PTSD may be involved in legal actions either because they are involved in a civil case (e.g., motor vehicle accident) related to their psychiatric condition or because they were a victim of a crime. Some individuals may express distress through a variety of symptoms that may abate after the conclusion of legal proceedings or payment of damages. This pattern may represent the effects of retraumatization resulting from exposure to a perpetrator or recollection of traumatic events during depositions, trial preparation, or testimony, followed by the (at times, only transient) sense of "closure" that these proceedings provide. If the perpetrator is incarcerated as a result of legal proceedings, symptoms may reoccur when the victim learns of the perpetrator's parole or release. Some persons may demonstrate waxing and waning symptoms regardless of the status of legal proceedings. Individuals may also fabricate or embellish symptoms. By raising the possibility that secondary gain, symptom exaggeration, or malingering may be part of the clinical picture, these factors can complicate assessment and treatment planning, as well as research (35). Confidentiality can also be compromised if the treating psychiatrist is in a dual role and is also required to communicate with members of the legal system. Some of the complexity of these cases can be managed by having the treatment and forensic evaluations performed by different psychiatrists, if possible (36, 37). As noted in DSM-IV-TR, the psychiatric assessment should address the possibility of malingering in situ-

TABLE 3. Clinical Domains of Assessment for Acute Stress Disorder (ASD) and Posttraumatic Stress Disorder (PTSD)

Clinical Domain	Component
Trauma history	Type, age, and duration
Safety	Threat of harm from others and dangerousness to self or others
Dissociative symptoms	Necessary for diagnosis of ASD: numbing, detachment, derealization/depersonalization, dissociative amnesia in acute response to trauma
ASD/PTSD symptoms	Reexperiencing, avoidance and numbing, hyperarousal as a consequence of trauma (PTSD is diagnosed if symptom onset is >30 days after the traumatic event; if <30 days and if dissociative symptoms are present, ASD is diagnosed)
Military history	Prior exposure(s), training and preparedness for exposure
Behavioral and health risks	Substance use/abuse, sexually transmitted diseases, preexisting mental illness, nonadherence to treatment, impulsivity, and potential for further exposure to violence
Personal characteristics	Coping skills, resilience, interpersonal relatedness/attachment, history of developmental trauma or psychodynamic conflict(s), motivation for treatment
Psychosocial situation	Home environment, social support, employment status, ongoing violence (e.g., interpersonal, disaster/war), parenting/caregiver skills or burdens
Stressors	Acute and/or chronic trauma, poverty, loss, bereavement
Legal system involvement	Meaning of symptoms, compensation based on disability determination or degree of distress

Source. Adapted with permission from "Posttraumatic Stress Disorder," by Kathryn M. Connor and Marian I. Butterfield. *Focus* 2003; 1:247–262 (30). Copyright © 2003. American Psychiatric Association.

ations in which financial remuneration or benefit eligibility is at issue or when forensic determinations play a role in establishing the diagnosis of PTSD. Determining the temporal course of symptoms relative to the timing of legal initiatives is helpful in this process (38).

c) Identification of ASD and PTSD in the presence of common comorbid conditions

In patients who present for evaluation after a traumatic event, exacerbations or relapse of preexisting comorbid disorders may occur and require evaluation and treatment (see Section III.D, "Medical and Other Psychiatric Comorbidity") (39, 40). Exacerbations or relapse of preexisting PTSD may also occur with subsequent traumas or reminders of trauma.

For many individuals who have experienced a traumatic event but are presenting with other clinical needs, the diagnosis of ASD or PTSD may be missed entirely without a detailed evaluation. For example, individuals hospitalized on medical or surgical services after motor vehicle accidents, severe burns, or other major physical trauma have high rates of symptomatic distress, including ASD or PTSD, that often go unrecognized (34, 41–44). Patients with serious mental illness are exposed to high rates of physical assault and sexual abuse as well as other traumas (45–49). Mental health clinicians may fail to obtain this information unless they specifically inquire (50). Seriously mentally ill persons also have higher rates of PTSD (47–49, 51), compared to the general population (5). Individuals with psychotic disorders (48) and with borderline personality disorder (50, 52–54) are particularly likely to have experienced victimization in childhood and in adulthood. The associated PTSD often goes unrecognized. Histories of victimization and PTSD

are also common among individuals with substance-related disorders (55–58) and eating disorders (59–61). In addition, family members—particularly spouses—who present with symptoms of bereavement after the traumatic loss of a family member should be assessed for PTSD (62).

High rates of comorbid psychiatric and other medical diagnoses are observed in those with ASD and PTSD. For a number of reasons, the medical and neurological effects of traumatic events may not be immediately apparent. Acute psychological responses to trauma such as dissociation may also diminish the initial experience of physical pain. In the presence of overwhelming anxiety and distress, individuals may not be able to describe their mental and physical state to medical professionals in an articulate fashion. Individuals exposed to traumatic events, particularly events that include interpersonal assault and violence, can find the motives of well-intentioned evaluators suspect. Without the establishment of trust, patients may be unwilling or unable to provide a complete medical or psychiatric history.

Patients with PTSD often have comorbid major depressive disorders, anxiety disorders, and substance use disorders (use of alcohol, tobacco, and other substances). Physical complaints, which may result from injury, may also represent comorbid somatization disorder or other somatoform disorders (12, 63). Similarly, patients with preexisting personality disorders or maladaptive character traits, as well as those with unresolved psychodynamic developmental concerns or histories of childhood traumatic events, may be at higher risk for an accentuated response to further traumatic events. In the presence of prominent depressive symptoms, social withdrawal and avoidance may be increased, and suicide risk may be heightened. Thus, identification and treatment of comorbid psychiatric and other medical illnesses are important to an integrated treatment plan that addresses all of the patient's needs and contributes to recovery from PTSD.

B. PRINCIPLES OF PSYCHIATRIC MANAGEMENT

Psychiatric management consists of a broad array of interventions and activities that may be instituted by psychiatrists for patients who have been exposed to extreme trauma. The specific components of psychiatric management that appear to mitigate the sequelae of trauma exposure and that are important to the treatment of patients with ASD or PTSD are described in more detail below.

1. Evaluating the safety of the patient and others

As with all psychiatric patients, for patients exposed to trauma it is crucial to assess the risk for suicide and nonlethal self-injurious behavior as well as the risk for harm to others. Details of suicide assessment and estimation of suicide risk are described in APA's *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors* (64). Although many factors have been associated with an increased risk of suicide attempts and suicide in groups of individuals, it is not possible to predict suicide in a given individual at a given point in time. Nonetheless, a number of factors should be taken into consideration in evaluating and estimating the patient's potential for self-injury or suicide.

In assessing suicide risk, it is essential to determine whether the patient has had thoughts of death, self-harm, or suicide and the degree to which the patient intends to act on any suicidal ideation, the extent of planning or preparation for suicide, and the relative lethality of any suicide methods that the patient has considered. The availability of the means for suicide, including firearms, should also be explored, and a judgment should be made concerning the lethality of those means.

Risk for suicide and for suicide attempts is also increased by the presence of previous suicide attempts, including aborted attempts. Thus, if a patient has a history of previous suicide attempts, the nature of those attempts should be determined. Individuals who experienced childhood abuse and who may have PTSD as a result of that experience sometimes exhibit self-harming behavior that is often repetitive but occurs in the absence of suicidal intent (65, 66).

Such behavior may progress to more serious forms of nonlethal self-harm but also confers an increased risk of suicidal behaviors. Patients should also be asked about suicide in their family and recent exposure to suicide or suicide attempts by others.

Depression, substance use, panic attacks, and severe anxiety are commonly present in individuals with ASD or PTSD and are associated with increased risk for suicide and suicidal behaviors. Other factors that deserve specific attention in individuals with ASD or PTSD include the presence of dissociative symptoms; high levels of shame or stigma (e.g., after rape); loss of family, friends, or employment as a result of the traumatic event; specific neurovegetative symptoms, including insomnia or weight/appetite loss; social withdrawal; social or cultural isolation with relocation or immigration; and preexisting psychological issues, personality traits, or patterns of coping that may indicate a heightened response to a specific trauma. Individuals who feel trapped within an inescapable and abusive relationship (e.g., situations involving domestic violence, marital rape, or child abuse) or who anticipate continued, imminent exposure to traumatic experiences or stimuli may be more likely to act on suicidal ideas. An association has also been observed between the number of previous traumatic events and the likelihood that an individual will attempt suicide (67, 68). Thus, a complete assessment of suicide risk should be individualized to the particular circumstances of the patient and should also include an evaluation of the patient's strengths, social support, and motivation to seek help (69–71).

Less is known about the risk factors for harm to others in the context of PTSD. Nonetheless, it is important to assess thoughts, plans, or intentions of harming others as part of the psychiatric evaluation. As with assessment of suicide risk, it is important to determine whether firearms or other lethal weapons are available that could be used for harming others. The presence of hallucinations, persecutory delusions about a particular individual or group, or the feeling of being trapped in a dangerous, abusive, and inescapable situation may augment risk of dangerousness to others.

2. Determining a treatment setting

Treatment settings for patients with ASD or PTSD include the full continuum of levels of care. Treatment should be delivered in the setting that is least restrictive, yet most likely to prove safe and effective. In determining the appropriate treatment setting, multiple patient-specific factors are considered: symptom severity, comorbidity, suicidal ideation or behavior, homicidal ideation or behavior, level of functioning, and available support system. The determination of a treatment setting should also include consideration of the patient's personal safety, ability to adequately care for him- or herself, ability to provide reliable feedback to the psychiatrist, and willingness to participate in treatment. Here also, an important consideration is the patient's ability to trust clinicians and the treatment process; this ability may be limited as a consequence of traumatic events themselves, cultural barriers, or other factors. The choice of treatment setting and the patient's ability to benefit from a different level of care should be reevaluated on an ongoing basis throughout the course of treatment, as efficacy does not necessarily increase with increasing duration of treatment in a specific setting or level of care (72).

For the majority of individuals with ASD or PTSD, treatment on an outpatient basis is the most appropriate treatment setting. However, some patients, particularly those with comorbid psychiatric and other medical diagnoses, may require treatment on an inpatient basis. Patients who exhibit suicidal or homicidal ideation, plans, or intent require close assessment and monitoring. Hospitalization is generally indicated for patients who are considered to pose a serious threat of harm to themselves or others. If such patients refuse admission, they may be hospitalized involuntarily when their condition meets local jurisdictional criteria for emergency detention or involuntary hospitalization. Severely ill patients who lack adequate social support outside a hospital setting should also be considered for hospital admission, residential treatment, or participation in an intensive outpatient or day treatment program. For severely ill patients with repeated hospitalizations related to nonadherence, assertive community treatment may also be considered.

3. Establishing and maintaining a therapeutic alliance

The therapeutic alliance is important and at times challenging to establish with patients who have experienced traumatic events.

Attention to the physician-patient interaction is important, even in settings such as emergency departments where the clinician may have only a single contact with the patient. Although more than 80% of victims of recent sexual or physical assault surveyed in an emergency department setting indicated interest in further mental health treatment (73), other studies have indicated that those with PTSD underuse or avoid mental health services (74). A positive experience may also make the patient more receptive to future evaluation or follow-up.

Evaluation and treatment should always be conducted with sensitivity and in a safe environment that facilitates the development of trust. The presence of ASD or PTSD may challenge the clinician's ability to ensure that the patient feels safe in the therapeutic relationship. Clinicians must acknowledge the patient's worst fears about reexposure to intolerable traumatic memories and recognize that treatment itself may be perceived as threatening or overly intrusive. The patient is often relieved when the therapist indicates that talking about traumatic life events can be distressing and that the patient will decide how deeply to explore the difficult events and feelings. This suggestion of flexibility helps the patient to maintain or restore a sense of control, which is often lost after exposure to traumatic events. In chronic PTSD, avoidant/numbing behaviors may have been present for many years or decades. Therefore, clinicians must be patient and ensure that therapy proceeds at a tolerable pace.

Many other components of the treatment of ASD and PTSD also require trust in the doctor-patient relationship as well as particular attention to the therapeutic alliance. Effective treatment of both of these disorders requires that patients understand educational or treatment plans and return for follow-up assessment and treatment. In addition, successful treatment may require patients to tolerate intense affect and/or disruptive or unpleasant medication side effects. To establish and maintain a therapeutic alliance, it is important for the psychiatrist to address the patient's concerns as well as treatment preferences. Developing a therapeutic alliance with a patient who has experienced significant traumatic events—particularly in childhood—may require considerable psychotherapeutic effort and require lengthening of treatment. Cultural factors may also impose barriers to developing a therapeutic relationship, since many non-Western cultures do not value traditional Western psychiatric interventions. Management of the therapeutic alliance also includes awareness of transference and countertransference issues, even if these issues are not directly addressed in treatment (75).

4. Coordinating the treatment effort

Providing optimal treatment for patients with ASD and PTSD may require a team approach involving the coordinated effort of several clinicians. Patients may have a wide variety of comorbid psychiatric and/or physical disorders that need to be addressed. Family intervention or coordination of support services is often needed. One team member must assume the primary overall responsibility for the patient's treatment. This individual serves as the coordinator of the treatment plan, advocates for the appropriate level of care, oversees the family involvement, makes decisions regarding which potential treatment modalities are useful and which should be discontinued, helps assess the effects of medications, and monitors the patient's safety. Because of the diversity and depth of medical knowledge and expertise required for this oversight function, a psychiatrist may be optimal for this role, although this staffing pattern may not be possible in some health care settings. Ongoing coordination of the overall treatment plan is enhanced by clear role definitions, plans for the management of crises, and regular communication among the clinicians who are involved in the treatment. If team members work collaboratively with each other, with the patient, and with the patient's family and other social supports, the treatment has a better chance of helping the patient distinguish safe from dangerous and potentially retraumatizing situations, develop self-monitoring skills and coping strategies for anx-

iety states related to reminders of his or her trauma, avoid abusive relationships, minimize alcohol and other drug misuse, and control impulsive, aggressive, or self-destructive behaviors.

Those who have experienced an acute traumatic injury or assault often require ongoing medical attention. Collaborating with physicians who are providing additional medical treatment to the patient is an important part of psychiatric treatment. Individuals with PTSD also often have high rates of somatic and somatoform (i.e., medically unexplained) symptoms that are not directly related to the traumatic event but that prompt visits to primary care physicians (76–79). In such settings, collaboration between the psychiatrist and the primary caregiver may facilitate appropriate medical assessment and management.

5. Monitoring treatment response

During treatment, different features and symptoms of the patient's illness may emerge or subside. Monitoring the patient's status for the emergence of changes in destructive impulses toward self or others is especially crucial. For patients whose risk of such behaviors is found to be increased, additional measures such as hospitalization or more intensive treatment should be considered. Emergence of new symptoms, significant deterioration in functional status, or significant periods without response to treatment may suggest a need for diagnostic reevaluation. The psychiatrist should be particularly vigilant for comorbid medical conditions or substance-related disorders, for the emergence of symptoms such as interpersonal withdrawal or avoidance, and for the development or progression of symptoms of other disorders, including anxiety disorders or major depression.

6. Providing education

For persons who seek care after traumatic events, it is helpful to provide education concerning the natural course of and interventions for ASD and PTSD as well as for the broad range of normal stress-related reactions. The APA Disaster Psychiatry web site (http://www.psych.org/disasterpsych/) provides educational materials and links to other online resources. Education should also be given to involved family members or significant members of the patient's support network. It is important to help patients understand that their symptoms may be exacerbated by reexposure to traumatic stimuli, perceiving themselves to be in unsafe situations, or remaining in abusive relationships and that they can learn methods for better managing their feelings when they are reminded of the traumatic event. Emphasizing that ASD and PTSD are conditions for which effective treatments are available may be crucial in educating patients who attribute their illness to a moral defect or in educating family members who are convinced that nothing is wrong with the patient. Education regarding available treatment options can also help patients (and family members) make informed decisions, anticipate side effects, and adhere to treatment regimens.

For individuals or groups whose occupation entails likely exposure to traumatic events (e.g., military personnel, police, firefighters, emergency medical personnel, journalists), ongoing educational efforts may decrease exposure to trauma (by reducing risk behaviors) or improve the likelihood that an individual in need will seek care. Awareness of the predictable initial psychological and physiological responses to traumatic events may also be reassuring when these responses occur and may vitiate new fears or expectations of disability. Such education can also aid in the accurate identification and support of colleagues who develop symptoms of ASD or PTSD (80, 81).

7. Enhancing adherence to treatment

For patients who develop chronic PTSD, a long or indefinite duration of treatment may be needed. During acute exacerbations, patients with chronic PTSD may be easily discouraged and unduly pessimistic about their chances of recovery. In addition, the side effects or requirements of treatments may lead to nonadherence. Patients with PTSD who appear to have achieved

a stable and positive clinical response and those who appear to have recovered from ASD may exhibit sudden relapse when new events reactivate traumatic concerns and fears about the safety of their families or themselves. For patients involved in ongoing litigation related to the traumatic event and subsequent impairment, legal proceedings may similarly reactivate concerns or emotions surrounding the event and its aftermath. The patient's motivation for participating in PTSD treatment may also be altered by ongoing legal actions. Psychiatrists should recognize these possibilities, address them in therapy, and encourage the patient to discuss any concerns regarding adherence, personal safety, or reexposure to traumatic reminders.

Medication adherence may be improved by emphasizing to the patient 1) when and how often to take the medicine, 2) the expected time interval before beneficial effects of treatment may be noticed, 3) the necessity to take medication even after feeling better, 4) the need to consult with the physician before discontinuing medication, and 5) steps to take if problems or questions arise (82). Some patients, particularly those who are elderly, have achieved improved adherence when both the complexity of the medication regimen and the cost of treatments are minimized. Severe or persistent problems of nonadherence may represent psychological concerns, psychopathology, or disruptions in the doctor-patient relationship, for which additional psychotherapy should be considered. Family members who are supportive of medication and/or other treatment can also play an important role in improving adherence. Although models of care such as assertive community treatment have not been specifically studied in individuals with PTSD, they have demonstrated efficacy in decreasing symptom severity, reducing length of hospitalization, and improving living conditions in individuals with serious and persistent mental illness (83–86). Consequently, such approaches may be useful in improving adherence in individuals with PTSD who have repeated hospitalizations related to nonadherence, particularly in the presence of significant psychiatric comorbidity.

8. Increasing understanding of and adaptation to the psychosocial effects of the disorder

While trauma itself often results in detrimental social, familial, academic, occupational, and financial phenomena, further effects may also stem from the symptoms of ASD or PTSD and may perpetuate these illnesses. For example, if one loses employment as a result of a disaster or because of missed work secondary to symptoms of ASD, the additional stressor of unemployment may increase the risk of developing PTSD (87). Consequently, the psychiatrist should assist the patient in addressing issues that may arise in various life domains, including family and social relationships, living conditions, general health, and academic and occupational performance, and help the patient to consider options that may be available to address such problems (e.g., consideration of alternative school or work schedules, other vocational options, financial or social supports). Working in collaboration with patients to set realistic and achievable short- and long-term goals can be useful. Patients can increase their sense of self-worth through achieving these goals, thereby reducing the demoralization that exacerbates or perpetuates illness. It may also be important to help the patient with ASD or PTSD obtain clinical assistance for family problems or for family members who may themselves require clinical intervention. Patients who have children may need help in assessing and meeting their children's needs, both during and in the wake of acute episodes.

Resilience has been alternately defined (by various researchers) as an individual trait or quality, an outcome, or a process. The concept of resilience may also encompass the ability to negotiate psychosocial and emotional changes after trauma exposure and in this way increase recovery possibilities. However, studies to date have identified no universal resilience factor or outcome (88, 89). Barnes and Bell (90) suggested that factors involved in resilience include 1) biological factors (intellectual and physical ability, toughness), 2) psychological factors (adaptive mechanisms such as ego resilience, motivation, humor, hardiness, and perceptions of self; emotional attributes such as emotional well-being, hope, life satisfaction, optimism, happiness, and trust; cognitive attributes such as cognitive styles, causal attribution such as an internal locus

of control and blame, world view or philosophy of life, and wisdom), 3) spiritual attributes, 4) atributes of posttraumatic growth, 5) social attributes (interpersonal skills, interpersonal relationships, connectedness, and social support), and 6) environmental factors such as positive life events and socioeconomic status. Some studies show that optimism can buffer the effects of life stress (91–97) and enable some individuals to mobilize protective factors such as adaptive coping skills, increased self-efficacy, ways of reinterpreting adverse experiences in a positive manner, and strategies for seeking social support (98–101). Although no published studies have assessed the effect of optimism training on the development or outcome of ASD or PTSD, a school-based community-wide screening followed by psychosocial intervention was able to effectively identify and reduce disaster-related trauma symptoms and facilitate psychological recovery in children (102). Thus, efforts to improve psychosocial functioning and resilience may help to minimize symptoms and enhance recovery and remission.

9. Evaluating and managing physical health and functional impairments

Because ASD and PTSD are often the result of physically traumatic events, they are frequently associated with physical health problems and with functional impairments. Other mechanisms (e.g., hyperarousal, hypothalamic-pituitary-adrenal [HPA] axis dysregulation, poor self-care) may contribute to this association (103). In those who have experienced a trauma, medical problems may affect many aspects of health. Consequently, the presence, type(s), and severity of medical symptoms should be monitored continuously. Medical symptoms, symptoms of ASD or PTSD, and psychosocial or interpersonal relationship problems are each associated with impairments in a patient's ability to function. For such impairments to be addressed, level of functioning should also be assessed on an ongoing basis. For example, some patients may require assistance in scheduling absences from work or other responsibilities, whereas others may require encouragement to avoid major life changes during intensification of symptoms.

C. PRINCIPLES OF TREATMENT SELECTION

1. Goals of treatment

The goals of treatment for individuals who have experienced a traumatic event and have received a diagnosis of ASD or PTSD include the following.

a) Reduce the severity of ASD or PTSD symptoms

Treatment aims include reducing the patient's overall level of emotional distress as well as reducing specific target symptoms that may impair social or occupational function. In general, the clinician attempts to assist the patient to better tolerate and manage the immediate distress of the memories of the traumatic experience(s) and to decrease distress over time. In addition, the clinician works to enhance the patient's ability to discriminate trauma cues and reminders from the original traumatic experience(s) by promoting adaptive coping with reexperiencing states and instilling the belief that the current response to triggers results from recall of a past danger that is no longer present. Thus, the aim of treatment is to prevent, ameliorate, and promote recovery from the presumed neurobiological alterations associated with ASD and PTSD. Symptom-specific goals include helping the patient reduce intrusive reexperiencing, psychological and physiological reactivity to reminders, trauma-related avoidant behaviors, nightmares and sleep disturbance, and anxieties related to fears of recurrence. Other targeted goals include reducing behaviors that unduly restrict daily life, impair functioning, interfere with decision making, and contribute to engagement in high-risk behavior.

b) Prevent or reduce trauma-related comorbid conditions

Little is known about the effects of comorbid disorders on the course of ASD. Depression, substance abuse, and other conditions can impede recovery in PTSD and carry additional risks for

psychiatric morbidity and functional impairment (4, 104). Medical disorders and somatic complaints are also common in war veterans (79, 105, 106) and persons with a history of sexual abuse (107–114). Thus, a major goal of treatment is to prevent secondary disorders and to appropriately diagnose and treat other concurrent conditions when present.

c) Improve adaptive functioning and restore or promote normal developmental progression

ASD and particularly PTSD are associated with a range of functional impairments in various areas of daily life (10, 12, 115–122). In addition to interventions that may be needed to address such impairments, related goals are to foster resilience and assist patients in adaptively coping with trauma-related stresses and adversities.

Traumatic experiences at any stage in the life cycle may impede the normal developmental progression. Posttraumatic stress symptoms can curtail current developmental achievements (for example, in dating, friendship, marriage, parenthood, educational achievement, occupational advancement, and retirement). Fears of event or symptom recurrence, avoidant behaviors, and restrictions on interpersonal life can also lead to lost developmental opportunities. As patients recover from PTSD, a therapeutic goal is to help identify and develop strategies to restore and promote normal developmental progression.

d) Protect against relapse

The course of acute and posttraumatic stress reactions can vary with symptomatic exacerbation relating to reminders of trauma or loss, additional life stresses or adversities, subsequent encounters with situations of danger or trauma, or discontinuation of psychotropic medication (123). Relapse prevention assists patients in anticipating such situations and in developing skills such as problem solving, emotional regulation, and the appropriate use of interpersonal support and professional help.

e) Integrate the danger experienced as a result of the traumatic situation(s) into a constructive schema of risk, safety, prevention, and protection

The danger or consequences associated with the original traumatic experience can skew personal beliefs, expectations, and constructs about the future, the risks of life, and safety. In addition, patients often search for the meaning of their life experience. The treatment of PTSD may include strategies to assist patients to constructively address these issues. As PTSD often evolves into a chronic illness, the meaning of the precipitating trauma in terms of its connections to past experience and its effects on subsequent perceptions of self-worth and interpersonal relationships may need to be addressed. Psychodynamic approaches and other psychotherapies may facilitate this integration (124–127).

2. Choice of initial treatment modality

Patients assessed within hours or days after an acute trauma may present with overwhelming posttraumatic physiological and emotional symptoms that would appear to prevent or severely limit psychotherapeutic interchanges. Such presentations do not necessarily indicate impending development of ASD or PTSD. However, pharmacological intervention to relieve overwhelming physical or psychological pain, impairing insomnia, or extremes of agitation, rage, or dissociation may restore baseline function or may be a useful temporizing measure as the clinician monitors for the development of additional symptoms and considers additional psychotherapeutic intervention and/or medication treatment.

Treatment of ASD or PTSD symptoms includes three broad categories of intervention: pharmacological treatment, psychotherapeutic intervention, and education and supportive measures. While cognitive and behavior therapies and pharmacological intervention (particularly with SSRIs) have reasonable clinical evidence to support their efficacy in treating the core symptoms of PTSD (see Section II.D, "Specific Treatment Strategies"), few direct comparisons of specific interventions or studies of combinations of support/education, pharmacological intervention,

and psychotherapies are available. Nonetheless, consensus suggests that several factors, including the presence of specific target symptoms and individual patient characteristics, may guide decisions regarding initial treatment; these factors are reviewed in Section II.D, "Specific Treatment Strategies."

For patients with ASD as well as for those without overt symptoms, single-session individual debriefing does not prevent PTSD and may impede recovery (128, 129). In ASD, early after a trauma, once the patient's safety and medical stabilization have been addressed, supportive psychotherapy, case management, and assistance in obtaining resources such as food or shelter are useful (130, 131). Furthermore, in contrast to the findings for debriefing, there is no evidence to suggest that early supportive care is harmful (131–134). Preliminary evidence also suggests that ASD patients may be helped by cognitive behavior psychotherapy that incorporates exposure (135–137). Although there are few studies of pharmacological interventions in patients with ASD, treatment with SSRIs and possibly other antidepressants may represent reasonable initial clinical interventions.

In individuals with PTSD, evidence from randomized, controlled trials supports both psychotherapeutic and medication-based approaches to initial treatment. SSRIs are recommended as first-line medication treatment for PTSD, and other antidepressants may also be beneficial. In terms of psychotherapies, cognitive behavior therapy is an effective treatment for core symptoms of acute and chronic PTSD. EMDR is also effective. Stress inoculation, imagery rehearsal, and prolonged exposure techniques may also be employed in treating PTSD as well as associated symptoms such as anxiety and avoidance. The use of psychodynamic psychotherapy in treating PTSD is supported by a considerable number of descriptive studies and process-to-outcome analyses as well as substantial clinical experience. It may be useful in addressing developmental, interpersonal, or intrapersonal issues that may be of particular importance to social, occupational, and interpersonal functioning. It also appears to be useful in addressing the patient's changes in beliefs, world expectations, generalization of threat experiences to other life events, and attempts to find meaning in her or his experience. Interpersonal issues that develop as a result of ASD or PTSD, including changes in interpersonal relationships, fears, avoidance, loss of trust, anger and aggression, and increasing generalization of fears and threat, should also be addressed psychotherapeutically.

The presence of a comorbid psychiatric disorder may also guide initial intervention. For example, substance misuse is a common concomitant of ASD or PTSD and signals a need for specific treatment for substance use disorder. In addition, individuals who are depressed may be at greater risk for further exposures to trauma. For example, when domestic partner violence is ongoing, low self-esteem or decreased energy accompanying depression may produce increased violence in the abusive partner or inadequate self-protective efforts in the patient. Thus, direct and vigorous treatment of underlying depression with psychotherapy and/or specific antidepressant pharmacotherapy may minimize the risk for additional trauma and development or prolongation of PTSD.

3. Approaches for patients who do not respond to initial treatment

Because of the paucity of high-quality evidence-based studies of interventions for patients with treatment-resistant PTSD, treatment nonresponse cannot be addressed algorithmically. However, a systematic review of the factors that may be contributing to treatment nonresponse is possible. Since the initial treatment plan will have detailed each selected treatment, the rationale for its use, and the goals for treatment outcome, a review of this initial plan of care should help determine the extent to which therapeutic goals have been met. If interventions have been introduced sequentially, it will be easier to discern their individual effects. In reviewing the original plan, the clinician should explore with the patient which (if any) symptoms have improved, worsened, or remained the same. It is also important to determine whether the patient understands the plan and is adhering to it and, if nonadherence is present, the reasons for non-

adherence. For example, has the patient failed to do homework assignments or discontinued medications or skipped doses because of side effects or financial difficulties? The potential of other psychological disorders or underlying personality traits to interfere with the treatment should be reconsidered and addressed as needed. The therapist should inquire about any new psychosocial or other environmental factors that may be hindering therapy, such as a conflict at work or with family members.

If it appears that the therapist-patient relationship is not at issue and that the patient is adhering to the treatment, the therapist should explore other options. One strategy for nonresponse is to augment the initial treatment with another—for example, adding pharmacotherapy to psychotherapy, psychotherapy to a pharmacological intervention, or couples therapy to an individual psychotherapy. Generally, the therapist should first exhaust the treatments for which there is the best evidence of efficacy before trying more novel treatments. In some cases, the original treatment may need to be discontinued and a different modality selected, as in the case of a patient who is too overwhelmed by anxiety to tolerate exposure therapy. Because most therapies used for the treatment of PTSD or ASD are also indicated for other psychiatric conditions, a review of the literature on strategies for improving response in those situations may also be helpful. However, there are limited data to guide the clinician in the treatment of patients with treatment-resistant PTSD and ASD, and, at present, clinical judgment must prompt the selection of one path rather than another.

D. SPECIFIC TREATMENT STRATEGIES

Since patients with a diagnosis of ASD or PTSD experience a broad and complex range of symptoms, caring for patients with these disorders involves an array of approaches and should include consideration of the biopsychosocial diversity of the patient's clinical presentation. When choosing a specific strategy to treat ASD or PTSD, it is important to consider the weight of scientific evidence supporting each treatment option as well as the limitations of the current evidence base. There have been relatively few double-blind, randomized, controlled trials of treatments for patients with PTSD and even fewer such trials for patients with ASD. Many promising results still require replication, and some interventions that are commonly used; based on extensive clinical experience and consensus, have yet to be examined in more methodologically rigorous studies. In the studies that are available, treatment and follow-up durations are typically short, sample sizes are frequently small, and the possibility of a placebo response is often inadequately addressed (138). Furthermore, measured outcomes have often concentrated on more readily quantifiable changes in specific symptoms rather than focusing on the diagnosis of ASD and PTSD per se or on important short- and long-term outcomes such as social, occupational, and interpersonal functioning.

It is also likely that responses to specific treatments may differ depending on the type of trauma experienced (e.g., acute versus ongoing or cumulative, natural disaster versus interpersonal violence, community-wide versus individual traumatic event, presence versus absence of simultaneous physical injury) and the timing of treatment relative to the occurrence of the traumatic event. Since ASD, by definition, occurs in the 4 weeks immediately after a traumatic event, studies of treatment interventions during this period should be considered as treatment of ASD and potentially as preventive strategies for PTSD. Treatment strategies for symptoms occurring between 1 and 3 months after trauma exposure (acute PTSD) may be different than those for symptoms occurring (or reoccurring) more than 3 months after the traumatic event(s) (chronic PTSD), although the differential efficacies of specific strategies for treating acute versus chronic PTSD have not been well studied. Throughout the first 3 months after a traumatic event, recovery is the general rule (139), and this natural recovery period may extend up to 6 months (34, 140). Here, the clinician is guided by the expectation of recovery, the relief of suffering, and the use of interventions to speed recovery and to prevent additional exposure to the traumatic event, chronicity of symptoms, and relapse.

In choosing a specific treatment strategy, consideration should also be given to the patient's age, gender, and previous history (e.g., developmental history, past traumatic experiences, substance use disorders, other psychiatric diagnoses), current comorbid medical and psychiatric illnesses, propensity for aggression or self-injurious behavior (see Section III, "Specific Clinical Features Influencing the Treatment Plan"), or other factors that may vary widely across individuals. Although systematic study of these factors is rare, clinical experience suggests that these factors may also necessitate modification of the individual treatment plan. Specific treatment strategies should be selected to target the symptoms or symptom clusters (i.e., reexperiencing, avoidance/numbing, or hyperarousal) that are most disruptive for the patient and to take into account the time interval between trauma exposure and symptom development. Personality style and family interactions may affect symptom expression, persistence, or exacerbation.

Treatment for the symptoms of ASD or PTSD involves three approaches either alone or in combination: psychopharmacology, psychotherapy, and education and supportive measures. To date, no psychotropic medications have been developed specifically for use in ASD or PTSD. Therefore, in clinical practice and in pharmacotherapy research, medications have been used in doses similar to those recommended or approved for other psychiatric illnesses. While the clinical evidence to date for each of these interventions is limited, the efficacy of combinations of education/support, psychotherapy, and psychopharmacology has been even less well characterized. Clinical practice and consensus support combinations of these approaches based on several factors, such as specifically identified target symptoms, psychiatric and other medical comorbidity, and the patient's preferences. Medication therapy may also be initiated to address symptoms (e.g., physical pain, agitation, severe insomnia, or psychosis) that might otherwise limit the efficacy of psychotherapy. The sections that follow summarize specific psychopharmacological, psychotherapeutic, and educational and supportive approaches to the treatment of ASD and PTSD. Where efficacy has been established to a greater degree with regard to particular symptoms or clinical features or at particular time intervals after the trauma exposure, these findings are highlighted.

1. Psychopharmacology

a) SSRIs

Evidence from several large randomized, double-blind controlled trials suggests that SSRIs are first-line medication treatment for both men and women with PTSD (123, 141–147). There are four reasons that SSRIs are the current medications of choice for PTSD: 1) they ameliorate all three PTSD symptom clusters (i.e., reexperiencing, avoidance/numbing, and hyperarousal), 2) they are effective treatments for psychiatric disorders that are frequently comorbid with PTSD (e.g., depression, panic disorder, social phobia, and obsessive-compulsive disorder), 3) they may reduce clinical symptoms (such as suicidal, impulsive, and aggressive behaviors) that often complicate management of PTSD, and 4) they have relatively few side effects.

Reductions in the severity of core PTSD symptoms have been shown with fluoxetine, sertraline, and paroxetine in studies that were of relatively short duration (8–12 weeks) and included predominantly women with chronic PTSD resulting from rape or assault (123, 141–146, 148). While symptom reduction was generally observed within 2–4 weeks of treatment, symptoms of anger and irritability were reduced within the first week (149). In studies of fluoxetine, improvement in arousal, numbing, and avoidance (but not reexperiencing) and overall response were greater in women than in men. Other studies have demonstrated efficacy for these agents in intrusive, avoidance/numbing, and arousal symptoms. Smaller open-label studies of fluvoxamine have shown efficacy in sleep-related symptoms (including nightmares) in combat veterans (147, 150). Head-to-head comparisons between any of the SSRIs for ASD or PTSD symptoms have not been published; however, clinical consensus holds that these agents differ primarily in their pharmacokinetics, metabolic effects on other medications, and side effects rather than in their efficacy in treating ASD or PTSD.

b) Tricyclic antidepressants and MAOIs

Studies of tricyclic antidepressants demonstrated efficacy for amitriptyline and imipramine (151, 152) but not desipramine (153). With the MAOIs, limited data suggest the efficacy of phenelzine and brofaromine (an MAOI available in Europe) (154, 155). In all of the trials, subjects were primarily male combat veterans, which limits the generalizability of findings. There do not appear to be studies of the effects of either MAOIs or tricyclic antidepressants specifically in women with PTSD or ASD.

c) Benzodiazepines

While benzodiazepines can reduce anxiety and improve sleep, their efficacy in preventing PTSD or treating the core symptoms of PTSD has been neither established nor adequately evaluated (156, 157). Concerns about addictive potential in individuals with comorbid substance use disorders may prompt additional caution regarding the use of benzodiazepines. Worsening of symptoms with benzodiazepine discontinuation has also been reported (158). However, in a naturalistic study of more than 300 veterans with PTSD and comorbid substance abuse, treatment with benzodiazepines was not associated with adverse effects on outcome (159).

d) Anticonvulsants

Open-label studies of divalproex, carbamazepine, and topiramate have demonstrated mixed or limited efficacy with regard to specific symptom clusters of PTSD (160–162), but these studies, as well as a single controlled trial of lamotrigine (163), have indicated benefit with regard to the reexperiencing symptoms.

e) Antipsychotics

Psychotic symptoms are not included in the diagnostic criteria for either ASD or PTSD. Nonetheless, patients with these illnesses may also experience psychotic symptoms as part of a comorbid disorder. Before initiating antipsychotic treatment, careful diagnostic evaluation is required to appropriately address the potential contributions of delirium, dementia, primary thought disorders, brief psychotic reactions, delusional disorder, substance abuse, closed head injury, or other comorbid general medical conditions. Preliminary studies of the second-generation antipsychotic agents olanzapine (164–166), quetiapine (167), and risperidone (168) in patients with PTSD suggest a potential role for these medications in pharmacological treatment, particularly when concomitant psychotic symptoms are present or when first-line approaches have been ineffective in controlling symptoms.

f) Adrenergic inhibitors

Agents acting on adrenergic receptors have also been proposed for the treatment of PTSD. Preliminary evidence has shown possible benefits with the α_1 antagonist prazosin (169) and with the α_2 agonist clonidine in combination with imipramine (170). However, there have been no large controlled studies of these agents to date.

While β-adrenergic blockers are at times prescribed for PTSD (171) and have been used in the treatment of performance anxiety, there have been no controlled studies of these agents for PTSD. Preliminary results suggest that acute administration of propranolol after trauma may reduce some later symptoms of PTSD (137, 172). Further controlled studies are necessary to evaluate this practice before it can be considered a part of the therapeutic armamentarium.

2. Psychotherapeutic interventions

a) Cognitive and behavior therapies

Cognitive behavior therapy in ASD or PTSD targets the distorted threat appraisal process (in some instances through repeated exposure and in others through techniques focusing on infor-

mation processing without repeated exposure) in an effort to desensitize the patient to trauma-related triggers. Distinctions may be drawn between psychotherapies that focus principally on aspects of cognitive processing and those that emphasize behavioral techniques. However, aspects of both are frequently combined, and studies that identify the effective components of these therapies or that distinguish one from another are not available. A course of cognitive behavior therapy generally begins with education about the symptoms of the disorder, as well as a rationale for asking the patient to recall painful experiences and relaxation training. After the therapist assesses the patient's ability to tolerate within-session anxiety and temporary exacerbations of symptoms, the patient is led through a series of sessions in which the traumatic event and its aftermath are imagined and described, and the patient is asked to focus on the negative affect and arousal until they subside. Reassurance and relaxation exercises aid the patient in progressing through these sessions, and homework assignments allow the patient to practice outside the sessions or while confronting triggers of anxiety (specific places or activities) in vivo (125, 173, 174). A limited number of well-designed studies demonstrate some success not only in speeding recovery but also in preventing PTSD when cognitive behavior therapy is given over a few sessions beginning 2–3 weeks after trauma exposure (135, 173, 175–178). Both stress inoculation and prolonged exposure techniques have demonstrated efficacy in women with PTSD resulting from assault or rape (179–181). Prolonged exposure (through imaginal and in vivo exposure to avoided situations associated with previous trauma) has been shown to be effective, particularly in the PTSD-associated symptoms of anxiety and avoidance (179, 182). However, several studies have noted that exposure may increase rather than decrease symptoms in some individuals (178, 183). Stress inoculation training involving breathing exercises, relaxation training, thought stopping, role playing, and cognitive restructuring has also proven effective alone and in combination with prolonged exposure in reducing PTSD symptoms (179). Survivors of rape, crime victims, and combat veterans have demonstrated improvement in overall PTSD symptoms and nightmares in response to imagery rehearsal (i.e., imaginal prolonged exposure) (184, 185). Clinical improvement (but not recovery) was also demonstrated in a group of PTSD patients with diverse trauma exposures who received either imaginal exposure or cognitive behavior therapy (186, 187). In group settings, cognitive processing therapy designed to correct distortions related to threat appraisal and safety through a facilitated study of the patient's written narrative of his or her traumatic experience has shown promise (188). Most of these trials have been short-term, and the extent to which improvement is maintained over time has not been assessed through follow-up study.

b) Eye movement desensitization and reprocessing (EMDR)

EMDR is a form of psychotherapy that includes an exposure-based therapy (with multiple brief, interrupted exposures to traumatic material), eye movement, and recall and verbalization of traumatic memories of an event or events. It therefore combines multiple theoretical perspectives and techniques, including cognitive behavior therapy. Some point to the use of directed eye movements as a feature markedly distinguishing this form of therapy from other cognitive behavior approaches. Others point to the fact that traumatic material need not be verbalized; instead, patients are directed to think about their traumatic experiences without having to discuss them. Like many of the studies of other cognitive behavior and exposure therapies, most of the well-designed EMDR studies have been small, but several meta-analyses have demonstrated efficacy similar to that of other forms of cognitive and behavior therapy (189–192). Studies also suggest that the eye movements are neither necessary nor sufficient to the outcome (193–195), but these findings remain controversial (196, 197). Although it appears that efficacy may be related to the components of the technique common to other exposure-based cognitive therapies, as in the previously described cognitive behavior therapies, further study is necessary to clearly identify the effective subcomponents of combined techniques. Follow-up studies are also needed to determine whether observed improvements are maintained over time.

c) Psychodynamic psychotherapy

Psychodynamic therapy has, from its beginnings, been concerned with responses to traumatic events (198–200). There is an extensive body of research that includes descriptive designs, process-to-outcome correlational studies, and case studies. However, randomized, controlled research on psychodynamic psychotherapy in patients with ASD or PTSD is extremely limited. One controlled trial of psychodynamic therapy versus hypnotherapy or desensitization versus no therapy showed all interventions were superior to the control condition (no treatment) in decreasing avoidance and intrusive symptoms (201). Other controlled trials of hypnotherapy for ASD or PTSD have not been published, but descriptive studies and clinical consensus support its use—by appropriately trained individuals—in reducing symptoms of anxiety associated with acute distress and traumatic event cues and as a nonpharmacological adjunctive approach to anxiety reduction (202). A meta-analysis of controlled psychotherapy trials (including the study by Brom et al. [201]) also suggested the efficacy of hypnosis—particularly at the end of therapy (203).

The clinical research and narrative-based literatures on psychodynamic psychotherapy outline two major approaches to the treatment of traumatic stress disorders. The first views an individual's defenses and coping skills as a product of his or her biopsychosocial development and focuses on the meaning of the trauma for the individual in terms of prior psychological conflicts and developmental experience and relationships, as well as the particular developmental time of the traumatic occurrence(s). This approach examines the person's overall capacity to cope with memories of traumatic event(s) and their triggers and the coping style he or she uses to manage these memories (204, 205). The second approach focuses on the effect of traumatic experience on the individual's prior self-object experiences, overwhelmed self-esteem, altered experience of safety, and loss of self-cohesiveness and self-observing functions and helps the person identify and maintain a functional sense of self in the face of trauma (206, 207). Both approaches appear to be useful in addressing the subjective and interpersonal sustaining factors of the illness (e.g., shattered assumptions about attachments, issues of trust), as well as the changes in beliefs and world view and the widely altered threat perceptions often seen in chronic PTSD (21, 208, 209). Psychodynamic psychotherapists employ a mixture of supportive and insight-oriented interventions based on an assessment of the individual patient's symptoms, developmental history, personality, and available social supports as well as an ongoing assessment of the patient's ability to tolerate exploration of the trauma (210, 211). In chronic PTSD, issues of transference are often explored to help the patient understand conscious and unconscious concerns surrounding the meaning of recent and more remote traumatic events in his or her life as they appear in the treatment (212). Awareness of countertransference is a central component of treatment of traumatic experience in psychodynamic psychotherapy and in other therapies. The therapist's emotional response on hearing the patient describe the traumatic events can either facilitate or disrupt the therapeutic alliance, making ongoing attention to countertransference of particular importance in treating patients with ASD and PTSD.

d) Psychological debriefing

Psychological debriefing was developed as an intervention aimed at preventing the development of the negative emotional sequelae of traumatic events, including ASD and PTSD. This staged, semistructured group (or, as often administered, individual) interview and educational process includes education about trauma experiences in general and about the chronological facts of the recently experienced traumatic event and exploration of the emotions associated with the event. Since debriefing has received considerable publicity, it may be expected (or specifically requested) by leaders or managers when a group confronts disaster. In the military, for example, group debriefings have been used as a means for describing normative responses to trauma exposures and educating individuals about pursuing further assistance if symptoms persist or cause significant dysfunction or distress. However, well-controlled studies of debriefing that have used single-session, individual, and group debriefing have not demonstrated efficacy

(128, 129, 213–216). Although some trauma survivors have reported that they experienced such debriefings as helpful, there is no evidence at present that establishes psychological debriefing as effective in preventing PTSD or improving social and occupational functioning. In some settings, it has been shown to increase symptoms (217–219). Its use may be most problematic with groups of unknown individuals who have widely varying trauma exposures or when it is administered early after trauma exposure, before safety and decreased arousal are established. Immediately after exposure, persons may not be able to listen attentively, absorb new information, or appreciate the nuances of the demands ahead in a manner that promotes recovery (220, 221). Also, in heterogeneous groups, some individuals will be increasing their exposure through group participation and obtain no added support after the group session, thereby potentially increasing their likelihood of later distress (19).

3. Psychoeducation and support

Supportive interventions are often used as the control intervention in studies of more specific treatments. However, clinical experience indicates that both support and psychoeducation appear to be helpful as early interventions to reduce the psychological sequelae of exposure to mass violence or disaster. When access to expert care is limited by environmental conditions or reduced availability of medical resources, rapid dissemination of educational materials may help many persons to deal effectively with subsyndromal manifestations of trauma exposure. Such educational materials often focus on 1) the expected physiological and emotional response to traumatic events, 2) strategies for decreasing secondary or continuous exposure to the traumatic event, 3) stress-reduction techniques such as breathing exercises and physical exercise, 4) the importance of remaining mentally active, 5) the need to concentrate on self-care tasks in the aftermath of trauma, and 6) recommendations for early referral if symptoms persist. Encouraging persons who are acutely traumatized to first rely on their inherent strengths, their existing support networks, and their own judgment may reduce the need for further intervention. Although the efficacy of these measures alone in prevention of ASD or PTSD is unproven, emphasis on self-reliance and self-care should augment other strategies when and if they become necessary.

III. SPECIFIC CLINICAL FEATURES INFLUENCING THE TREATMENT PLAN

A. AGE

Trauma exposure, and therefore ASD and PTSD, occurs in individuals of all ages, including infants. For all types of trauma, exposure varies with age (5), peaking in late adolescence. Although findings on the relationship between age and risk for developing PTSD are inconsistent (4, 33, 222), age and developmental stage may be important considerations in treatment. The meaning of the exposure to a traumatic event will differ depending on the developmental stage as well as the extent of any preexisting emotional problems or age-specific concerns of the patient. For example, an injury that causes a loss of a limb in early adulthood can raise issues of how to establish long-term intimate relations with a disability, while a similar injury late in life may raise fears of dependency, loss of mobility, and needs for care that may not be available in the family. Confrontation with the threat of the loss of one's life will also raise different concerns depending on the time of life. Since these meanings affect the patient in life planning, they should be addressed in psychotherapy or supportive treatment. Advancing age increases the probability of comorbid medical disorders (e.g., hypertension, renal failure, heart disease) and concomitant medication use that will influence psychopharmacological decisions.

B. GENDER

Although overall exposure to trauma may be somewhat greater in men than in women (4, 5, 223), men and women differ in the types of traumatic events to which they are most likely to be exposed (4, 5, 223–226). That men are more likely to be exposed to combat and physical violence, whereas women are more likely to be exposed to rape and sexual assault, only partly accounts for the significantly higher lifetime prevalence rates of PTSD among women in the general population (4, 5, 222, 223, 226) as well as the longer duration of PTSD among women (5, 226). Differences in trauma exposures between men and women may also affect treatment considerations.

Initial assessment after sexual assault or rape requires a willingness to listen to the patient with an open mind to obtain necessary medical and investigative information and establish trust. Early attention to the therapeutic alliance may enhance the degree to which support and psychotherapy may be helpful in addressing later difficulties such as sexually transmitted diseases, pregnancy, difficult contraceptive choices, and feelings of loss of self-esteem, anger, rage, or guilt. Research neither supports nor refutes the prevalent notion that a treating clinician who is experienced as "different" from the perpetrator will more rapidly be accepted early on after the traumatic event. However, the gender of the treating clinician may be an issue for a specific patient under specific circumstances; therefore, the potential influence of the clinician's gender on treatment response should be considered.

C. ETHNIC AND CROSS-CULTURAL FACTORS

The likelihood of being exposed to traumatic events, as well as the likelihood of receiving a lifetime diagnosis of PTSD, differs by ethnic group. In general, clinicians who understand the importance of social and cultural dynamics will be sensitive to the need to treat patients with ASD and PTSD in such a manner as to not alienate them from their families and communities. Treatment must be knowledgeable and respectful of the culture, the cultural meaning of symptoms or illness, and cultural values of the patient and the patient's family. Treatment must also recognize that the "cultural context" in which treatment occurs may affect the development of symptoms. That Central American refugees are viewed as immigrants rather than persons escaping combat and that Vietnam veterans were viewed with disdain rather than welcomed as heroes may help explain different aspects of these traumatized populations or their response to treatment, compared to others entering the United States in the aftermath of war. Clinicians must be sensitive to the idea that such societal views may also shape treatment response. An individual's culture may be protective and contain a supportive system of values, roles, lifestyles, and knowledge that may buffer some of the effects of traumatic events (227). Protective influences of culture and social systems occur in part through provision of an acceptable context in which social support can be experienced and the traumatic event interpreted. The social and cultural context has the potential to provide a positive evaluation of the self, as well as to provide social support, both of which buffer the negative effects of stressful events (228). In other situations, cultural norms may contribute to the perception of an experience as traumatic (e.g., a rape victim may be shunned by family members for having "shamed" them). In addition, a disruption of social and cultural foundations can result in drastic changes in people's expectations and views of the meaning of life, thus making individuals potentially more vulnerable to traumatic events. Consequently, therapy must be conducted in a manner that does not estrange the individual from his or her family and community (229). Thus, while psychosocial treatments that attempt to identify and process traumatic experiences may be effective for individuals from Western cultures, they may be contraindicated for some Southeast Asian populations and persons from other non-Western cultures (229).

No controlled studies have explored the extent to which specific religious groups or subgroups within the United States may be more or less likely to seek care for psychiatric symptoms related to trauma exposure. However, African American veterans may be less likely than European Amer-

ican veterans to use psychosocial care outside Department of Veterans Affairs (VA) clinical programs, even though both ethnic groups appear to respond similarly to treatment for PTSD (230).

Ethnicity is also relevant to the pharmacological treatment of patients with ASD or PTSD. Cultural values may affect a patient's decision to take medication or a patient's adherence to medication regimens. Moreover, genetic polymorphisms in hepatic cytochrome P450 (CYP) enzymes occur at varying frequencies across ethnic groups (231–234). Since most psychotropic medications are metabolized through the CYP system, polymorphisms will affect the likelihood that an individual patient will experience therapeutic benefits or adverse effects at a given dose of medication. For example, about 7% of Caucasians are poor metabolizers of CYP 2D6 substrates, and 3%–6% are poor metabolizers of CYP 2C19 substrates (233, 234). These patients would be expected to have disproportionately high blood levels of medications that are metabolized through these routes. In contrast, ultrarapid metabolism by means of CYP 2D6 enzymes is observed in 1%–3% of Middle Europeans but up to 29% of Ethiopians (232). Finally, because ethnic groups also differ in genetic polymorphisms affecting sites of psychotropic action (e.g., serotonin transporters), a drug's pharmacodynamic properties may also vary with ethnicity (235, 236). These findings emphasize the need to take ethnic and cultural factors into consideration in developing a plan of therapy with the patient.

D. MEDICAL AND OTHER PSYCHIATRIC COMORBIDITY

Individuals with ASD or PTSD present with a complex array of symptoms and comorbid conditions. Physical injury is common as a result of the exposure to traumatic events. Patients with PTSD may present with medical or somatic concerns. Indeed, a history of childhood physical and/or sexual abuse has been associated with a greater number of hospital admissions and surgical procedures, somatization, and hypochondriasis in adulthood (237). Victimization, particularly exposure to chronic trauma, has also been associated with chronic gastrointestinal symptoms (111, 114, 238–242), chronic pain syndromes (107–114), and fibromyalgia (243, 244). Thus, gender differences in the rates of childhood physical and/or sexual victimization may contribute to gender differences in associated medical comorbidity. In addition, physical disorders such as cardiac or neurological illnesses may mimic symptoms of traumatic stress (229), resulting in underdiagnosis of either ASD or PTSD. This confusion may result in inadequate treatment of posttraumatic anxiety disorders but may also result in inappropriate provision of medical or surgical care, including unnecessary prescribing of potentially addictive substances. Thus, in treating individuals with ASD or PTSD, coordination of care with other physicians is important in developing an appropriate plan of diagnostic assessment and therapy for concomitant somatic symptoms and medical disorders.

In intensive care and rehabilitation settings, ASD and later PTSD may be part of the complex medical picture of patients recovering from injuries ranging from burns and amputations to traumatic brain injury. Consideration of the patient's physical function, concurrent medications, and need for medical intervention is required for appropriate pharmacological management and psychotherapy. In the emergency department, life-sustaining measures as well as hydration, sleep, and nutrition must take precedence over psychosocial treatments. However, the longer the stay in the hospital, the more likely that ASD or PTSD symptoms will become a focus for treatment, as sleep disturbances, anxiety, depression, or fears of planning for the future become evident. Family members may also have substantial reactions to the traumatic events their loved ones have experienced. Family members should be afforded opportunities to discuss their concerns in an environment that fosters trust. They should receive available information about the condition or prognosis of loved ones, including discussion of the range of behavioral and emotional responses that may arise in the injured person(s) and in other family members. Often, indirectly affected family members will request advice about how to discuss or whether to discuss certain topics with the patient (e.g., death of a husband or wife in the same motor vehicle collision). These issues may further complicate the evaluation and manage-

ment of traumatized patients and must be taken into consideration when developing a treatment plan. Complicated evaluations may, by necessity, be initiated in an inpatient (intensive care or rehabilitative) setting but continue into outpatient care.

Patients who develop ASD or PTSD are also more likely to have other comorbid psychiatric disorders, including mood, dissociative, anxiety, substance-related, and personality disorders (171, 242, 245–254). Somatization disorder may also co-occur with ASD or PTSD, and in some individuals posttraumatic symptoms may represent somatization disorder psychopathology rather than ASD or PTSD (12). Thus, integrated treatment of ASD or PTSD and other psychiatric disorders is often required.

Among individuals with ASD or PTSD, depression and suicidal ideation or behavior require particular attention both pharmacologically and psychotherapeutically. Associated symptoms of depression, such as interpersonal withdrawal, survivor guilt, or shame, may be more amenable to psychosocial interventions than psychopharmacological interventions. Suicide risk may increase as the individual adjusts to physical losses or experiences guilt, shame, anger, or grief related to the loss of loved ones who may have been injured or may have died in the same traumatic event. While treatment targeted to specific symptoms of ASD or PTSD may also address these associated depressive features, such treatment may need to be continued beyond the time frame necessary to address ASD or PTSD alone.

Substance use may have a complex relation to ASD or PTSD after trauma. At times, substance use may contribute to the traumatic event itself (e.g., industrial or motor vehicle accident). Substance use may also be part of a preexisting substance use disorder or may reflect the patient's attempt to treat posttraumatic symptoms (e.g., sleep disturbance or anxiety). In fact, a period of increased substance (alcohol, tobacco, or drug of abuse) use often occurs early in ASD or PTSD, even when no substance use disorder existed before the trauma. In studies of large populations that have been exposed to trauma, higher rates of alcohol and tobacco use are observed after the event (255). Other studies of traumatized adults have reported high rates of alcohol and substance use (247, 250, 256, 257). Although increased usage does not equate to the presence of a substance use disorder, it remains a potential health concern and risk factor for other medical comorbidity. Substance misuse may also complicate psychiatric treatment of ASD or PTSD by producing symptoms that decrease the patient's ability to make use of psychotherapeutic treatments. Substance use also complicates pharmacological management and increases the risk of inadvertent patient overdose, somnolence, and behavioral problems. Thus, after a traumatic event, increased use of substances should be addressed as part of the treatment of ASD or PTSD, regardless of whether the criteria for a substance use disorder are met.

Patients with a large number of comorbid psychiatric and medical disorders are likely to have a greater severity of symptoms and a higher likelihood of developing a chronic course. It is prudent to realize that such individuals will often require long periods of treatment related to comorbid conditions and situational crises generated from these other illnesses. In addition, as a result of debilitation from both physical and mental conditions, these patients may require high levels of management and support to accomplish activities of daily living. They may be fragile, and some treatment interventions may prove either too exhausting or more disabling. Consequently, patients with chronic PTSD accompanied by comorbid medical and other psychiatric disorders need a graduated plan of treatment that begins with a primarily supportive approach and evolves into treatment that is more directed at restoring previous function. Very fragile patients may need hospitalization if they become dangerous to themselves or others or if they become so affectively labile that they experience significant functional impairment (229).

E. HISTORY OF PREVIOUS TRAUMAS

Exposure to previous trauma may modify vulnerability to subsequent trauma (32, 33), influence the development of PTSD (32, 33, 223), and complicate treatment and recovery. Recent

loss—particularly if sudden or unexpected—is also associated with an increased prevalence of PTSD and may also complicate treatment (62). Although immediate illness may be precipitated by a recent trauma, symptoms of ASD or PTSD (sleep disturbance, irritability, hyperarousal) may in fact be directly related to the more remote traumatic experience(s), including childhood sexual abuse. Psychotherapeutic interventions aimed at integrating traumatic experience and diminishing the effect of intrusive recollections must therefore target not only the precipitating trauma but the remote trauma as well.

F. AGGRESSIVE BEHAVIOR

More than a half-century ago, Kardiner (198) noted that some patients with PTSD had problems with aggressive behavior that was frequently impulsive and episodic. More recent studies have documented increases in domestic violence, child abuse, and delinquency after disasters (15, 258–260). It has been postulated that with the development of PTSD, an increased expectation of danger and potential trauma occurs and results in an "anticipatory bias" (261) or an increased readiness for "flight, fight, or freeze." This increased readiness for aggression, as well as decreased sleep associated with PTSD, may produce a reduced ability to tolerate mild or moderate slights, resulting in acts of aggression that are disproportionate to the level of provocation (262).

Little evidence addresses the treatment of heightened aggressiveness in individuals with PTSD. Based on the use of SSRI antidepressants in treating PTSD, there is reason to suggest use of these medications in patients with aggression in the context of PTSD. Observation for symptomatic exacerbations is warranted in the early phases of treatment, before the therapeutic benefits of pharmacotherapy are manifest. Anticonvulsants are sometimes suggested for management of irritability and aggression, but evidence for their efficacy is similarly sparse, with only a single small-scale open-label trial that found a modest effect of carbamazepine on irritability/aggression (160).

To the extent that aggressive behavior occurs in the context of reexperiencing symptoms (e.g., flashbacks), treatment approaches targeting this symptom cluster may also reduce aggression. Since aggressive behaviors are associated with states of both intoxication and withdrawal, concurrent treatment of comorbid substance use disorders may also reduce the likelihood of aggressive behavior.

G. SELF-INJURIOUS AND SUICIDAL BEHAVIORS

Both acute and chronic response to trauma exposure may include self-harming behaviors that range from self-mutilation to disordered eating behaviors to abuse of alcohol and other substances (256, 257, 263–270). This response may occur particularly when the trauma induces stigma, shame, or guilt. Children and adults who have been traumatized are likely to redirect onto themselves the feelings of aggression they have toward others (267, 271, 272). Furthermore, studies consistently show a significant relationship between childhood sexual abuse and various forms of self-injury later in life, particularly self-starving, cutting, and suicide attempts (267). In fact, PTSD has demonstrated the strongest association with suicidal behaviors of any of the anxiety disorders (273, 274). Specifically, PTSD is associated with a sixfold increase in the likelihood of an initial suicide attempt, an odds ratio that is double that for other anxiety disorders and about half that for mood disorders (275). In addition, individuals with PTSD appear to have an equal or greater odds ratio for making a suicide plan and for making impulsive suicide attempts, compared to those with mood disorders or other anxiety disorders (275). Anxiety disorders including PTSD are also associated with an increased risk for suicide per se (276, 277). Thus, it is apparent that patients with PTSD are at increased risk for developing self-harming and suicidal behaviors (269).

The possible utility of SSRI antidepressants in treating self-harming or suicidal behaviors in individuals with PTSD is suggested by the utility of SSRIs in treating PTSD in general (123, 141, 144–146, 148, 150, 278–280). Observation for symptomatic exacerbations is warranted

in the early phases of treatment, before the therapeutic benefits of pharmacotherapy are manifest. Other pharmacotherapies may also be useful, although evidence for their efficacy is sparse. For example, one study showed carbamazepine to be effective for treatment of self-destructive behaviors (281), and a single, relatively small study suggested that lithium carbonate may also be helpful (282). Finally, although opiate receptor blockers have not been studied specifically in patients with ASD or PTSD, limited evidence suggests that such agents may decrease self-destructive behaviors in other populations (283).

Regarding psychological treatments for suicidal behavior in patients with PTSD, few studies are available. In addition, most studies of PTSD specifically exclude acutely suicidal patients; therefore, clinical judgment must augment the research to date. Thus, although many studies show that cognitive behavior therapy is effective in treating psychiatric disorders such as depression and PTSD, which can increase the risk for suicide, few studies have shown cognitive behavior therapy to be effective for reducing actual suicidal behavior and intent (284). As in other mental disorders associated with suicidal behavior, involving the patient's family members and other sources of support in the treatment plan may increase awareness of and vigilance for indications of the potential for deliberate self-harm or suicide.

PART B
BACKGROUND INFORMATION AND REVIEW OF AVAILABLE EVIDENCE

IV. DISEASE DEFINITION, EPIDEMIOLOGY, AND NATURAL HISTORY

A. CORE CLINICAL FEATURES

The DSM-IV-TR criteria for ASD and PTSD are shown in Table 1 and Table 2, respectively. Table 4 compares the specific criteria used in making these diagnoses. For both ASD and PTSD, essential features are exposure to a traumatic event that need not be outside the normal range of human experience but that arouses "intense fear, helplessness, or horror" (DSM-IV-TR, p. 463), followed by development of characteristic symptoms. Exposure can occur through direct experience or through witnessing or learning about a traumatic event that caused "actual or threatened death," "serious injury," or "threat to the physical integrity" of oneself or others (DSM-IV-TR, p. 463). Both natural and human-made traumatic events have the potential to evoke these symptoms. Naturally occurring stressors include, for example, tornadoes, earthquakes, and medical illnesses. Human-made events include accidents, domestic and community violence, rape, assault, terrorism, and war. Some of these are singular events; others involve chronic or repeated exposure. In general, human-made events have been believed to cause more frequent and more persistent psychiatric symptoms and distress.

TABLE 4. Comparison of DSM-IV-TR Diagnostic Criteria for Acute Stress Disorder (ASD) and Posttraumatic Stress Disorder (PTSD)

Description of Criterion	ASD Criterion	PTSD Criterion
Characteristics of traumatic exposure	Criterion A	Criterion A
Exposure to a traumatic event in which both of the following conditions were present: 1. the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others 2. the person's response involved intense fear, helplessness, or horror		
Dissociative symptom cluster	Criterion B	—[a]
Either while experiencing or after experiencing the distressing event, the individual has three (or more) of the following symptoms: 1. a subjective sense of numbing, detachment, or absence of emotional responsiveness 2. a reduction in awareness of his or her surroundings (e.g., "being in a daze") 3. derealization 4. depersonalization 5. dissociative amnesia (i.e., inability to recall an important aspect of the trauma)		
Reexperiencing cluster	Criterion C (except item 5)	Criterion B
The traumatic event is persistently reexperienced in one (or more) of the following ways: 1. recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions 2. recurrent distressing dreams of the event 3. acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated) 4. intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event 5. physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event		

TABLE 4. Comparison of DSM-IV-TR Diagnostic Criteria for Acute Stress Disorder (ASD) and Posttraumatic Stress Disorder (PTSD) *(continued)*

Description of Criterion	ASD Criterion	PTSD Criterion
Avoidance/numbing of response cluster	Criterion D (requires only marked avoidance of stimuli that arouse recollections of the trauma)	Criterion C
Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following characteristics: 1. efforts to avoid thoughts, feelings, or conversations associated with the trauma 2. efforts to avoid activities, places, or people that arouse recollections of the trauma 3. inability to recall an important aspect of the trauma 4. markedly diminished interest or participation in significant activities 5. feeling of detachment or estrangement from others 6. restricted range of affect (e.g., unable to have loving feelings) 7. sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)		
Arousal cluster	Criterion E (requires only marked symptoms of anxiety or increased arousal)	Criterion D
Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following symptoms: 1. difficulty falling or staying asleep 2. irritability or outbursts of anger 3. difficulty concentrating 4. hypervigilance 5. exaggerated startle response		

TABLE 4. Comparison of DSM-IV-TR Diagnostic Criteria for Acute Stress Disorder (ASD) and Posttraumatic Stress Disorder (PTSD) *(continued)*

Description of Criterion	ASD Criterion	PTSD Criterion
Duration of disturbance	Minimum of 2 days, maximum of 4 weeks	Greater than 1 month (acute PTSD is diagnosed if duration is less than 3 months; chronic PTSD if duration is 3 months or greater)
Temporal relationship to traumatic event	Occurs within 4 weeks	Usually occurs within 3 months (if onset occurs more than 6 months after stressor, delayed onset is specified)
Distress or impairment in functioning: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (or inability to pursue some necessary task in ASD)	Criterion F	Criterion F
Exclusion of other conditions	Criterion H	—[a]
Not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition		
Not better accounted for by brief psychotic disorder		
Not an exacerbation of a preexisting axis I or axis II disorder		

[a]Not included in PTSD criteria.

The criteria for ASD overlap substantially with but are not identical to those for PTSD (Table 4). Although core symptoms fall into characteristic symptom clusters for both diagnoses, ASD and PTSD differ in the numbers of symptoms from each cluster that are required to establish a diagnosis. For example, in addition to three or more dissociative symptoms and "marked avoidance of stimuli that arouse recollections of the trauma," the diagnosis of ASD requires at least one reexperiencing symptom as well as "marked" anxiety or increased arousal. On the other hand, for a diagnosis of PTSD to be made, DSM-IV-TR stipulates that there be at least one reexperiencing symptom, two arousal symptoms, and three avoidance/numbing symptoms and that these symptoms be temporally related to the stressor. Symptoms in the reexperiencing cluster include "recurrent and intrusive recollections" of the event, recurrent distressing trauma-related dreams, acting or feeling as if the event were reoccurring, "intense psychological distress" with exposure to trauma cues, and physiological reactivity to traumatic cues (DSM-IV-TR, p. 464). Within the avoidance/numbing cluster, purposeful actions as well as unconscious mechanisms may be present and may include efforts to avoid trauma-related thoughts, feelings, or conversations; efforts to avoid activities, places, or people reminiscent of the trauma; inability to recall important aspects of the trauma; greatly decreased "interest or participation in previously enjoyed activities"; feeling detached or estranged; restricted range of affect; and a "sense of a foreshortened future" (DSM-IV-TR, p. 464). Increased arousal includes sleep disturbance, "irritability or outbursts of anger," difficulty concentrating, hypervigilance, and exaggerated startle response (DSM-IV-TR, p. 464), all of which are generalized arousal responses and are not precipitated by reminders of the stressor.

The two disorders also differ in the duration of the disturbance and its temporal relationship to the traumatic stressor. For ASD, the disturbance occurs within 4 weeks of the traumatic event and is from 2 days to 4 weeks in duration. To qualify for a diagnosis of PTSD, symptoms must be present for more than 1 month. If symptom duration is less than 3 months, acute PTSD is diagnosed, whereas chronic PTSD is diagnosed when symptoms persist for 3 months or longer. Although symptoms of PTSD usually begin within 3 months of exposure, DSM-IV-TR also allows for delayed onset with symptoms that appear months or even years after the event. Finally, for both ASD and PTSD, the severity of symptoms must be sufficient to cause "clinically significant distress" or impaired functioning (DSM-IV-TR, pp. 468, 472).

B. ASSOCIATED FEATURES

A number of additional features may be associated with PTSD. According to DSM-IV-TR, these features include somatic complaints, shame, despair, hopelessness, impaired affect modulation, social withdrawal, survivor guilt, anger, impulsive and self-destructive behavior, difficulties in interpersonal relationships, changed beliefs, and changed personality. Difficulty seeking and sustaining medical care has also been observed (285). Symptoms such as inappropriate guilt, shame, or hopelessness may be indicative of comorbid depression that requires separate intervention, and other symptoms, such as somatic complaints, may represent common phenomena that are associated with anxiety disorders but are not necessary for the diagnosis of either ASD or PTSD. Finally, symptoms of trauma-related dissociation are essential to the diagnosis of ASD but are not necessary for the diagnosis of PTSD. Nonetheless, a previous history of peritraumatic dissociation (and ASD) may be of clinical significance in patients with PTSD, as studies have demonstrated that such a history predicts greater severity and chronicity of PTSD (7, 286, 287).

C. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ASD and PTSD includes a broad range of psychiatric and physical diagnoses as well as normative responses to traumatic events. Individuals who are exposed to events that fulfill criterion A for ASD or PTSD often experience some transient symptoms that

differ from those of ASD or PTSD only in their duration or in the associated level of dysfunction or distress. In some professions (e.g., military, firefighters, police, emergency medical personnel), exposure to criterion A events is inevitable. If symptoms do not meet the criteria for ASD or PTSD but are persistent or associated with dysfunction or distress, a V code diagnosis (e.g., V62.2, occupational problem) may be appropriate.

Establishing a differential diagnosis also requires that ASD be differentiated from PTSD. For a single discrete traumatic event, ASD and PTSD can be readily distinguished from one another based on the time that has passed since the trauma. However, for less discrete or reoccurring traumas such as repetitive domestic violence, the distinctions between ASD and PTSD may be less clear. Although no convention or consensus exists regarding the classification of recurrent symptoms (for more than 1 month) during the course of repetitive episodic trauma, it may be best to conceptualize this symptom presentation as PTSD rather than as recurrent episodes of ASD. Clearly, eliminating the source or threat of continued violence and injury is critical to ultimate resolution of posttraumatic symptoms, regardless of diagnostic classification. As noted earlier, beyond duration of symptoms, the major distinguishing feature between ASD and PTSD is the emphasis in the former on dissociative symptoms. Although persons with ASD often develop PTSD, this is not invariably true. PTSD may also occur in persons who manifest few or even no symptoms of ASD in the period immediately after trauma (6, 7, 9). In patients with subthreshold or full symptoms of PTSD for less than 1 month who do not experience dissociative symptoms sufficient to meet the DSM-IV-TR criteria for ASD, the illness would be best characterized as an adjustment disorder in DSM terms. Such patients would also meet the diagnostic criteria for acute stress reaction, as defined by ICD-10. The differential diagnosis also includes medical disorders as well as a number of other psychiatric disorders (Table 5).

The fact that many of these disorders occur comorbidly with ASD or PTSD further complicates diagnosis. For example, a substantial proportion of trauma-exposed veterans (20, 247), refugees (292), and civilians (12, 293) develop symptoms consistent with major depressive disorder. Mood disorders are also an established risk factor for the development of PTSD in newly exposed individuals (12, 14, 34). Symptoms such as insomnia, poor concentration, and diminished interest in activities may be present with ASD and PTSD as well as with major depression. In addition, the restricted affective range that may accompany the numbing of responses with PTSD may resemble the restricted affect seen in depressed patients. It is important to note that if the DSM-IV-TR criteria are met, a major depressive episode can be diagnosed in conjunction with ASD or PTSD.

Trauma-exposed populations and patients with PTSD frequently experience comorbid substance-related disorders (256, 257, 294–299). Patients with PTSD also manifest increased physical complaints (76–79, 300, 301) and comorbid medical conditions (302). Although DSM-IV excluded complicated or prolonged grief as an axis I diagnosis (because of a lack of empirical evidence regarding symptoms), some investigators have proposed criteria for a diagnosis of complicated grief disorder based on patterns of prolonged bereavement characterized by persistence, intensity, intrusive recollections or images of the death, preoccupation with the loss, and avoidance of reminders (303). Furthermore, there is evidence that these symptoms may be more distressing after an unnatural or violent death. Such symptoms overlap with both major depressive disorder and PTSD, but persons may acknowledge these symptoms without meeting the criteria for either diagnosis. Here, preoccupation with the suddenness, violence, or catastrophic aspects of traumatic loss may be independent from and may interfere with the normal bereavement process (304). Consensus criteria for "traumatic grief" have been developed; these criteria overlap with those of complicated grief but incorporate additional symptoms of distress related to cognitive reenactment of the death, terror, and avoidance of reminders (289). Once again, studies that address treatment for these phenomena distinct from treatment for PTSD or depression are presently lacking. Nonetheless, complicated or traumatic grief as well as bereavement must be considered in the differential diagnosis for persons who have experienced a traumatic loss.

Finally, since childhood trauma may be a common antecedent to the development of personality (particularly cluster B) disorders in adulthood, and associated features of personality disorders and PTSD overlap (e.g., difficulty with affect modulation, impulsivity, irritability, comorbid substance abuse), PTSD symptoms may be "masked" by an underlying personality disorder. Numerous reports describe childhood trauma in adults with borderline personality disorder, and other reports describe childhood trauma as a root cause of adult PTSD. However, the extent to which symptoms may be misattributed to either PTSD or a personality disorder has not been well studied. Therefore, personality disorders must be considered in the differential diagnosis either as the primary etiology for symptoms or as comorbid illnesses.

D. EPIDEMIOLOGY

Exposure to a traumatic event, the essential element for development of ASD or PSTD, is a relatively common experience, although the specific rates of such experiences within a population sample will vary with the criteria used to define a potential trauma as well as with the sample characteristics and the interviewing method (e.g., telephone survey versus face-to-face interview, clinician versus lay interviewer, structured versus unstructured interview), as reviewed by Brewin and colleagues (222). For example, using DSM-III-R criteria, which required that the event be outside the range of normal human experience, researchers in the National Comorbidity Survey (4) assessed 5,877 individuals ages 15–54 years with the Diagnostic Interview Schedule (DIS) and the Composite International Diagnostic Interview, administered by experienced nonclinician interviewers. They found that more than one-half of the subjects had experienced a traumatic event during their lifetime, with most people having experienced more than one. Giaconia and colleagues (305) also used the DSM-III-R version of the DIS and found that by age 18 years, more than two-fifths of youths in a community sample had been exposed to an event that was severe enough to qualify for a diagnosis of PTSD. Using structured telephone interviews in a national sample of 4,008 adult women, Resnick and colleagues (306) found a lifetime rate of exposure to any type of traumatic event of 69%. Using the DSM-IV version of the DIS, Breslau and colleagues (5) examined trauma exposure and the diagnosis of PTSD in a telephoned community sample of 2,181 individuals in the Detroit area and found that the lifetime prevalence of trauma exposure was 89.6%. The most prevalent types of events were the sudden unexpected death of a close relative or friend (60.0%) or learning of trauma to a close relative or friend (62.4%).

Overall exposure to traumatic events may be somewhat greater in men than in women (4, 5), although the gender difference in the lifetime prevalence of such exposure is relatively small (60.7% for men versus 51.2% for women in the study of Kessler and colleagues [4], and 92.2% for men versus 87.1% for women in the study of Breslau and colleagues [5]). In addition, men and women differ in the types of events to which they are exposed. For example, in the National Comorbidity Survey, 0.7% of men versus 9.2% of women had a lifetime experience of being raped, whereas 19.0% of men but only 6.8% of women had been threatened with a weapon and 6.6% of men but no women had experienced combat (4). In the Detroit Area Survey of Trauma (5), a similar pattern was noted, with women being more likely than men to report rape (9.4% versus 1.1%) or other sexual assault (9.4% versus 2.8%) and men being more likely than women to report other types of assaultive violence, including being mugged or threatened with a weapon (34.0% versus 16.4%) and being shot or stabbed (8.2% versus 1.8%).

Exposure to traumatic events also varies with age, showing consistent declines with age across multiple studies. For example, Norris (307) found a strong trend for decreases in both past-year and lifetime exposure with increasing age in a nonrandom sample of 1,000 individuals from four cities in southeastern states. Bromet and colleagues (14) analyzed data from the National Comorbidity Survey and found that the risk of experiencing a traumatic event was greatest in the 15- to 24-year-old cohort and decreased in subsequent age cohorts. Similarly, Breslau and colleagues (5)

TABLE 5. Psychiatric Diagnoses Often Applicable to Injured Trauma Survivors Treated in the Acute Care Medical Setting

	Diagnostic Considerations			
Diagnosis[a]	**Symptomatic Criteria**	**Functional Criteria**	**Time Course**	**Acute Care Considerations**
Acute stress disorder (ASD)	A. Exposure to a traumatic event in which the person experienced or witnessed a life-threatening event that was associated with intense emotions (e.g., physical injury) B. Either while experiencing the event or after, the person experiences three or more dissociative symptoms. C. The event is reexperienced. D. Avoidance of reminders of the event E. Symptoms of arousal	Symptoms are associated with clinically significant impairments in social, occupational, or physical function.	Diagnosis can be made between 2 and 30 days after the event.	Not all injured patients with immediate distress will experience three dissociative symptoms.
Posttraumatic stress disorder (PTSD)	A. Exposure to a traumatic event in which the person experienced or witnessed a life-threatening event that was associated with intense emotions (e.g., physical injury) B. The event is persistently reexperienced C. Persistent avoidance of reminders of the event D. Persistent arousal symptoms	Symptoms are associated with clinically significant impairments in social, occupational, or physical function.	Diagnosis must be made at least 1 month after the event.	Patient's symptoms frequently appear before the 1-month point.
Major depressive episode	Five or more of the following symptoms: depressed mood,[b] diminished interest in pleasurable activities,[b] weight loss or gain, insomnia or hypersomnia, agitation or retardation, fatigue or energy loss, feelings of worthlessness, poor concentration, and suicidal ideation	Symptoms are associated with clinically significant impairment in social, occupational, or physical function.	Symptoms must be present for 2 weeks.	Major depressive episode can be diagnosed in conjunction with ASD or PTSD. Injured trauma survivors frequently present with multiple symptoms of a depressive episode early on (i.e., before 2 weeks after the traumatic injury).

TABLE 5. Psychiatric Diagnoses Often Applicable to Injured Trauma Survivors Treated in the Acute Care Medical Setting *(continued)*

	Diagnostic Considerations			
Diagnosis[a]	**Symptomatic Criteria**	**Functional Criteria**	**Time Course**	**Acute Care Considerations**
Traumatic grief	This evolving diagnostic category can be used when the events that lead to a patient's or relative's visit to the acute care setting involve sudden unanticipated loss. The symptoms of traumatic grief involve distressing thoughts and experiences related to reunion, longing, and searching for the deceased loved one (289–291).	The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.	Duration of disturbance is at least 2 months.	Traumatic grief is applicable to patients who have experienced the death of a significant other.
Adjustment disorder	A. Development of emotional or behavioral symptoms in response to an identifiable stressor. Symptoms can include depression, anxiety, conduct disturbance, or other emotional disturbance. B. The symptoms or behaviors are clinically significant, as evidenced by marked distress.	Emotional or behavioral symptoms are associated with marked impairment in social, role, or physical function.	Onset occurs within 3 months after the traumatic injury.	DSM-IV-TR suggests that the adjustment disorder diagnosis be used for patients who develop a symptom pattern that is not entirely consistent with the criteria for ASD/PTSD. Nonspecific symptomatic requirements make adjustment disorder a useful diagnosis for the many patients who experience posttraumatic behavioral and emotional disturbances that include symptoms that do not fit into other diagnostic rubrics (e.g., patients who present with marked somatic symptom amplification).

Source. Adapted with permission from *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Copyright 2000. American Psychiatric Association; and from *Seminars in Clinical Neuropsychiatry*, vol. 8, Zatzick D., "Posttraumatic stress, functional impairment, and service utilization after injury: a public health approach," pp. 149–157, Copyright 2003, with permission from Elsevier.

[a]Often, posttraumatic symptoms may be present that are insufficient to meet criteria for the diagnoses listed in this table. In such cases, V code diagnoses would be indicated, as would supportive therapy, psychoeducation, and continued monitoring for the development of further psychiatric disorder(s). [b]At least one of the five symptoms must be either depressed mood or diminished interest in pleasurable activities and shall not be due to a general medical condition or mood-incongruent delusions or hallucinations.

found that in all classes of traumas studied, peak exposures to traumatic events occurred in persons ages 16–20 years, with subsequent declines in exposure rates with age.

The lifetime prevalence of ASD is unclear, but a number of community-based studies have examined the prevalence of PTSD. Here, too, the reported rates vary with the specific diagnostic criteria employed, the interviewing method, and the sample characteristics. For example, in a study of the data for 2,985 participants from a central North Carolina community who were assessed as part of the Epidemiologic Catchment Area (ECA) survey, Davidson and colleagues (242) found a lifetime prevalence for DSM-III PTSD of 1.3%. Helzer and colleagues (308) found a lifetime PTSD prevalence of 1% in the St. Louis ECA sample. Using DSM-III-R criteria, Kessler and colleagues (4) found an estimated lifetime prevalence of PTSD of 7.8% in the National Comorbidity Survey, whereas Giaconia and colleagues (305) found that more than 6% of youths in a community sample met the criteria for a lifetime diagnosis of PTSD.

The likelihood of developing PTSD after having been exposed to a traumatic event (i.e., the conditional risk of PTSD) varies widely with the specific experience. Overall in the Detroit Area Survey of Trauma, for example, 9.2% of trauma-exposed persons developed PTSD, but PTSD developed in about half of those who were raped or held captive, tortured, or kidnapped, compared to only 2.2% of those who learned of the rape, attack, or injury of a close relative (5). In the women studied by Resnick and colleagues (306), rates of PTSD were significantly greater in crime victims that in noncrime victims (25.8% versus 9.4%).

General population studies typically find a significantly higher lifetime prevalence of PTSD in women, with rates that are consistently about twice those seen in men (4, 5, 222, 242, 308). The absolute rates for a lifetime diagnosis of PTSD again vary with the definition and severity of the traumatic stressor. Using the DSM-III criteria as part of the ECA survey, Helzer and colleagues (308) found that 1.3% of women and 0.5% of men met the criteria for a lifetime diagnosis of PTSD, and Davidson and colleagues (242) found lifetime rates of PTSD of 1.8% in women and 0.9% in men. In contrast, using the DSM-III-R criteria in the National Comorbidity Survey, Kessler and colleagues (4) found a lifetime prevalence for PTSD of 10.4% in women and 5.0% in men, and Breslau and colleagues (5, 223), using the DSM-IV criteria, found the lifetime prevalence of PTSD to be 13.0% in women, compared to 6.2% in men. In terms of the relative likelihood of developing PTSD after having experienced a traumatic event, Kessler and colleagues (4) found more than a twofold increase in the conditional risk of PTSD in women, compared with men (20.4% versus 8.1%). These gender differences in rates of PTSD do not necessarily imply that women are more likely to develop PTSD, per se; the differences may be explained by other factors that increase risk for women (15), such as the greater likelihood of women's experiencing rape and other sexual assaults, which carry a high conditional risk of developing PTSD. In addition, since a history of mood disorder increases the subsequent risk of developing PTSD in response to a stressor (14), the greater prevalence of such disorders among women may influence their likelihood of developing PTSD. Furthermore, specific aspects of the traumatic event, such as fear, threat, surprise, and meaning, may influence the victim's response (309).

The literature provides inconsistent information on the relationship between age and the risk of developing PTSD. Breslau and colleagues (33), in a representative community sample in southeast Michigan, found no relationship between age and risk of PTSD. In the National Comorbidity Survey, Kessler and colleagues (4) found some variations in the lifetime prevalence of PTSD by birth cohort, but men had the highest rates in the 45- to 54-year-old cohort, whereas women had the highest rates in the 25- to 34-year-old cohort. In terms of the conditional risk of developing PTSD after adjustment for the type of trauma exposure, a subsequent analysis of the National Comorbidity Survey data also showed variations in risk with age among men but a greater risk for PTSD among women in younger age cohorts (14). Brewin and colleagues (222) found weak effects of age in a meta-analysis of risk factors for PTSD but suggested that the differences may reflect confounding factors.

The prevalence of exposure to traumatic events as well as the development of PTSD also varies across racial and ethnic groups, with high rates of exposure to violence among African Americans, American Indians, and Alaska Natives, compared to members of more economically advantaged groups (310, 311). For example, in one study, 82% of American Indians and Alaska Natives had been exposed to one traumatic event, and the prevalence of PTSD was 22% (4). American Indians have a rate of violent victimization that is more than twice the national average (312), whereas rates of PTSD among American Indians and Alaska Natives are about threefold higher than in the general population. An investigation of Northern Plains Indian youths in grades 8 through 11 found that 61% had been exposed to some kind of traumatic event (313). These adolescents were reported to have more trauma-related symptoms but not substantially higher rates of diagnosable PTSD (3%), compared to the general population (313). A study of a Southwestern American Indian community found even higher rates of experience of one or more traumatic events but also noted a higher prevalence of lifetime PTSD in this community, compared with the general U.S. population (314).

Because members of some racial and ethnic groups are more likely to have lower socioeconomic status, live in an inner-city area, or be U.S. combat veterans (315), and because such status is associated with an increased likelihood of experiencing undesirable life events (316), some racial and ethnic groups are more likely to experience ASD and PTSD (4, 314). Among veterans, an increased likelihood of traumatic early experiences (310–312, 317) may contribute to the increased rates of PTSD seen in African Americans, Hispanics, and American Indian/Alaska Natives after combat-related trauma (247, 310).

Differences in the rates of previous exposure to traumas may account, in part, for differences observed in rates of PTSD among U.S. veterans of differing ethnic and racial backgrounds. However, greater war zone exposure to traumatic experiences among African Americans (315) and American Indians (318, 319) is likely to play a large role as well. In terms of racial differences in rates of PTSD among U.S. veterans, the National Vietnam Veterans Readjustment Study found that although 10% of U.S. soldiers in Vietnam were black and 85% were white, more African American (21%) than European American (14%) veterans experienced PTSD (247). In the American Indian Vietnam Veterans Project (319), evaluation of random samples of Vietnam combat veterans from three Northwestern Plains reservations and one Southwest reservation between 1992 and 1995 showed that approximately one-third of the Northern Plains (31%) and Southwestern (27%) American Indian participants had PTSD at the time of the study. Approximately one-half had experienced the disorder in their lifetime (57% and 45%, respectively). This rate was far in excess of rates of current PTSD observed in the European American or African American veterans (247).

Hispanics also have been found to be at higher risk for war-related PTSD than their European American counterparts (247). Because the risk for Hispanics was higher than that for black veterans, minority status must not be the only risk factor (320). Of the Hispanic subgroups, Puerto Rican veterans have been found to have a higher probability of experiencing PTSD than others with similar levels of war zone stressor exposure (321). Because these differences in prevalence were not explained by exposure to stressors or acculturation and were not accompanied by significant reductions in levels of functioning, it has been proposed that differences in symptom reporting may reflect features of expressive style rather than different levels of illness (320).

National variations in rates of PTSD development have been reported across populations exposed to traumatic events. For instance, less than 5% of hospitalized European survivors of unintentional injuries (e.g., motor vehicle crashes, job-related injuries) appear to develop PTSD (322, 323). However, between 10% and 40% of survivors of both intentional (e.g., injuries associated with human malice, such as physical assaults) and unintentional injuries treated within acute care settings in the United States, England, and Australia appear to develop symptoms consistent with the disorder (34, 117, 293, 324–328). The explanations for these different rates include methodological differences, cultural differences, and diagnostic accuracy (329).

The prevalence of PTSD in countries where war and disease are endemic is substantially higher and has been reported to range between 9.4% and 37.0% of the population. For example, Bleich and colleagues (330), in a telephone survey of a representative sample of 512 Israeli adults, found that after 19 months of ongoing terrorist attacks, 16.4% had been directly exposed to a terrorist attack, 37.3% had an exposed family member or friend, and 9.4% of the sample met the symptom criteria for PTSD. Sabin and colleagues (331) found similar rates in a cross-sectional survey of Mayan refugees living in Mexico, of whom 11.8% met the symptom criteria for PTSD, as measured by the Harvard Trauma Questionnaire and Hopkins Symptom Checklist-25, 20 years after fleeing the civil conflict in Guatemala. De Jong et al. (332) used the Composite International Diagnostic Interview to assess for PTSD in community populations of four postconflict low-income countries and found a prevalence rate of PTSD of 37.4% in Algeria, 28.4% in Cambodia, 15.8% in Ethiopia, and 17.8% in Gaza.

Treatment-seeking refugees may have even higher rates of PTSD, ranging from 55% to 90% (333). Studies have revealed alarming rates of PTSD in immigrant communities with a high degree of preimmigration exposure to potentially traumatic experiences (e.g., Asian Americans and Hispanic Americans). For example, in some samples, up to 70% of refugees from Vietnam, Cambodia, and Laos met the diagnostic criteria for PTSD, in contrast to prevalence rates of about 4% for the U.S. population as a whole (334).

Studies of Southeast Asian refugees receiving mental health care have uniformly found high rates of PTSD. One study found that 70% of the subjects met the diagnostic criteria for PTSD, with Mien from the highlands of Laos and Cambodians having the highest rates (333). Another mental health study of Southeast Asian refugees (Hmong, Laotian, Cambodian, and Vietnamese) in Minnesota found that 73% had major depression, 14% had PTSD, and 6% had anxiety or somatoform disorders (335). A random community sample of Cambodian adults revealed that 45% had PTSD, and 81% experienced five or more symptoms of PTSD (336). Similarly, 43% of parents recruited from a community of resettled Cambodian refugees in Massachusetts reported the death of between one and six of their children (337). Child loss was associated with an increased likelihood of health-related concerns, a variety of somatic symptoms, and culture-bound conditions of emotional distress such as deep worrying and sadness not visible to others (337). Finally, Kinzie et al. (338) found that nearly one-half of a sample of Cambodian adolescents who survived Pol Pot's concentration camps as children had PTSD approximately 10 years after this traumatic period. Thus, many Southeast Asian refugees are at risk for PTSD associated with the events they experienced before they immigrated to the United States (311). A large community sample of Southeast Asian refugees in the United States found that preimmigration and refugee camp experiences were significant predictors of psychological distress even 5 or more years after migration (339). In this study, significant subgroup differences were found: Cambodians reported the highest levels of distress, Laotians were next, then Vietnamese. While trauma treatments may be effective for persons from Western cultures, in some Southeast Asian populations, it may be contraindicated to attempt to identify and process traumatic experiences (229).

Central American immigrants to the United States may be at risk for PTSD as a result of their preimmigration exposure to war-related trauma (340), even though they are not recognized as political refugees (311). For example, a study of Los Angeles adults who were examined for symptoms of PTSD and depression found that one-half of the Central American participants reported symptoms that were consistent with a diagnosis of PTSD (341). In comparison with recent Mexican immigrants, a greater proportion of Central American refugees reported symptoms of PTSD (50% versus 25%) (341). In another study, 60% of adult Central American refugee patients received a diagnosis of PTSD (342). Central American immigrant children seeking care at refugee service centers also had high rates of PTSD (33%) (343). In a more recent study of a systematic sample of 638 adult Latino primary care patients living in Los Angeles, Eisenman and colleagues (344) found that 54% of the sample had experienced political

violence before migration, and of these, 18% had symptoms of PTSD. Those who had experienced political violence had a 3.4-fold greater risk of meeting the criteria for a PTSD diagnosis, compared to those who had not experienced political violence.

E. NATURAL HISTORY AND COURSE

Prospective studies suggest that symptomatic distress peaks in the days and weeks after a trauma and then gradually declines over the course of the year after injury (139). In the National Comorbidity Survey, symptoms also decreased most rapidly in the first 12 months after trauma exposure (4). However, approximately one-third of persons who developed PTSD had chronic symptoms that did not remit. Although this issue is not settled (309), rates of recovery from PTSD may vary by gender. Although gender differences in the duration of PTSD are in part explained by gender differences in the type of trauma experienced, Breslau and colleagues (5, 226) found a median time to remission of symptoms of 12 months in men and 48 months in women. However, studies of motor vehicle accident victims have shown initial rates of approximately 35%, decreasing nearly 50% by 12 months postaccident (34, 345).

The responses of traumatized patients fall on a continuum, and the natural course of ASD and PTSD may vary with personality and other individual characteristics. Some individuals are relatively resistant to developing posttraumatic symptoms or report interpersonal growth experiences as a result of their traumatic exposure (229, 346). For other individuals with PTSD, however, long-lasting personality change may occur (252, 347–349). Problems of impaired affect modulation; self-destructive and impulsive behavior; dissociative symptoms; somatic complaints; feelings of ineffectiveness, shame, and despair or hopelessness; feelings of being permanently damaged; a loss of previously supportive beliefs; hostility; social withdrawal; feeling constantly threatened and being in an alert status; and impaired relationships with others all portend personality change from the individual's previous characteristics.

Investigations have also shown symptoms of PTSD to be associated with functional impairment and diminished quality of life (115, 117, 122, 293, 327, 350–353). Across veteran (122), refugee (292), and injured civilian (117, 293, 327) populations, PTSD makes an independent contribution to diminished functioning and quality of life above and beyond the effects of comorbid medical conditions and injury severity. Posttraumatic stress is also coupled with a spectrum of physical health problems and medical disorders (103, 354, 355). These considerations make the treatment of PTSD important not just from the standpoint of individual suffering but also from the perspective of the potential societal costs associated with the disorder (273, 356).

Individuals who have been exposed to trauma may also be vulnerable to subsequent traumas and have an increased likelihood of developing PTSD with repeated traumatic experiences (32, 33, 223). In individuals with a first hospitalization for psychosis, a similar pattern was observed, with exposure to multiple traumatic events being associated with greater rates of PTSD than exposure to a single trauma (48). These findings suggest that in trauma-exposed individuals, interventions should include efforts to decrease the risk for subsequent exposures to traumatic events.

V. REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE

A. ISSUES IN INTERPRETING THE LITERATURE

The empirical research on the efficacy of treatments for ASD and PTSD is not as extensive at present as that for other disorders such as major depressive disorder, schizophrenia, or bipolar

disorder. Most of the randomized clinical trials of ASD and PTSD treatments have a relatively small number of subjects, and their inclusion in the study is often determined by their having experienced one type of index trauma. In addition, exact replications of methods are the exception rather than the rule. Further study is needed to better establish the generalizability of findings across populations and various traumatic event exposures. For example, many studies are limited to combat veterans with chronic PTSD or to rape victims. Treatment for ASD has only just begun to be examined. Effectiveness studies of ASD and PTSD treatments are also limited.

The rapid recovery rate of patients with ASD and acute PTSD means that outcomes studies need to examine closely the timing of treatment administration and the rates of recovery as well as remission and relapse. Treatment studies that specifically examine critical symptoms (such as sleep disturbance or withdrawal or arousal) are also needed. Gender differences in the rates of PTSD suggest that close attention should be paid to gender differences in treatment outcomes. The widespread nature of traumatic exposures in some subpopulations, including persons living in urban environments in major cities, also means that PTSD may have gone undetected but may have existed long before the index disorder is diagnosed.

The high comorbidity of PTSD with major depression and substance abuse also complicates the interpretation of efficacy studies.

With psychosocial interventions, measuring the efficacy of one treatment may be confounded by the effects of other simultaneous treatments.

B. PSYCHOSOCIAL INTERVENTIONS

1. Individual psychotherapies

In general, psychotherapy, examined across all types of interventions and for different types of victims, is an effective intervention for PTSD. Sherman (203) conducted a meta-analysis of 17 controlled clinical trials of psychotherapy for PTSD that included behavioral, cognitive, and psychodynamic individual and group therapy with veterans, female assault victims, and victims of other traumatic events. Psychotherapy was found to have a significant beneficial effect on PTSD.

Prediction of success in psychotherapy of PTSD, however, is in its infancy. For instance, beliefs about mistrust, helplessness, meaninglessness, and unjustness of the world predict baseline PTSD symptom severity but not treatment outcome (357). Little is known about the relationship of the type of traumatic event to the type or duration of psychotherapy likely to be effective.

a) Psychodynamic psychotherapy

Psychodynamic psychotherapy for either ASD or PTSD has not been well studied by means of randomized, controlled trials. Given the fact that ASD, by definition, is an illness of relatively brief duration, long-term therapy would seem unnecessary. However, ASD may be associated with or may aggravate preexisting psychological problems, and a remote history of repeated trauma (including childhood abuse) predicts the development of PTSD. In the face of an acute trauma, dormant issues may at times become more apparent or more amenable to treatment. Considerable clinical literature and case studies comment on this phenomenon, but the extent to which such intervention might prevent the development of PTSD remains untested. For PTSD, one controlled trial by Brom et al. (201) compared psychodynamic therapy to trauma desensitization, hypnotherapy, and a control condition. All three treatments were significantly effective in reducing intrusive and avoidance symptoms. A meta-analysis of psychotherapies—including psychodynamic psychotherapy—also supports this mode of treatment (203). Other less rigorous studies and reviews also suggest the efficacy of psychodynamic therapy in PTSD (21, 208, 358). Again, despite a lack of randomized, controlled trials, clinical consensus reflects the idea that a psychodynamic approach is useful in helping the patient integrate past traumatic experience(s) into a more adaptive or constructive schema of risk, safety, prevention, and protection (359, 360), thereby reducing core symptoms of PTSD.

b) Cognitive and behavior therapies

The cognitive and behavior therapies are applied in the individual, family, or group treatment forms. Although particular behavior therapies have been used as stand-alone treatment, it is more common for behavior therapy to be used in conjunction with other forms of therapy, such as cognitive approaches (e.g., cognitive behavior therapy). These complex treatments may have more than one efficacious component, and in many studies it is somewhat difficult to "dismantle" the specific contributions of the various elements of such combined treatments. Cognitive approaches to the treatment of ASD or PTSD target the distorted threat appraisal process in an effort to desensitize the patient to trauma-related triggers. These approaches often include a component of repeated exposure, either in talking about the trauma or in processing the traumatic experience.

Behavior therapy is derived from psychological models of learning that emphasize the role of environmental cues and consequences in patterning behavior. A behavioral assessment of the PTSD patient would focus on the traumatic event, the reexperiencing symptoms, the maladaptive avoidance and numbing strategies, and the pathological arousal responses that drive the disorder.

Systematic desensitization has been used to reduce anxiety associated with the traumatic stressor. The essential ingredient of systematic desensitization is the gradual and progressive exposure of the patient to feared stimuli while steps are taken to reduce elicited anxiety by displacing it with a sense of relaxation (reciprocal inhibition of the fear response). Improvements in active coping and reductions in traumatic anxiety can occur both inside and outside the sessions through the learning of relaxation techniques such as progressive muscle relaxation, diaphragmatic or meditative breathing, and guided imagery. Progressive muscle relaxation involves alternating the tensing and releasing of muscle groups throughout the body, sometimes proceeding in a head-to-toe direction. Breathing exercises concentrate on exhaling in order to generalize a calming effect, while guided imagery promotes relaxation though visualizing enjoyable places or activities. Biofeedback may be used to augment relaxation by providing the patient with instantaneous feedback on physiological variables, such as blood flow and muscle contraction. These phenomena are not normally sensed, but their continuous presentation permits the patient to exert some degree of voluntary control over variables related to tension and anxiety.

Therapeutic use of prolonged and repeated exposure to traumatic cues, either in a gradual fashion or intensively through flooding or implosion, is based on the principle that traumatic anxiety will decrease in the absence of real danger. Direct therapeutic exposure can be accomplished in vivo (directly) or in imagination. Typically, a course of exposure-based treatment begins with relaxation training and education about the symptoms of PTSD and about the rationale for having participants reexpose themselves to painful experiences. The therapist assesses the patient's ability to tolerate within-session emotion and temporary exacerbations of symptoms before implementing further treatment. If these experiences are acceptable, the patient is then led through a series of sessions in which the traumatic event and its aftermath are imagined and described and patients are asked to focus on the intense negative affects and arousal that are elicited, until they subside. Relaxation exercises and reassurance permit the patient to continue without feeling overwhelmed and abandoning the therapy. Homework assignments allow the patient to practice outside the session. In addition, the treatment may be enhanced if the patient is encouraged to confront specific places or activities in vivo. Success can be measured as complete or partial extinction of PTSD symptoms (173, 174).

Early exposure research was frequently conducted with Vietnam veterans with chronic, combat-related PTSD. Peniston's 1986 randomized, controlled study of biofeedback-assisted systematic desensitization (361) provided preliminary evidence for the potential effectiveness of high-frequency exposure therapy. In one of the early studies, which used flooding, Keane et al. (362) randomly assigned 24 combat veterans with PTSD to 14–16 sessions of flooding (N=11) or to a waiting list (N=13). Assessments at pretreatment, posttreatment, and 6-month follow-up showed improvement in reexperiencing symptoms, startle response, and memory/concentra-

tion. No improvement was seen in numbing or social avoidance. Cooper and Clum (363) studied imaginal flooding as a supplementary treatment to standard VA care. All 26 subjects completed the study, which showed that exposure increased the effectiveness of the usual treatment. Boudewyns et al. (364, 365) compared 58 Vietnam veteran inpatients with severe PTSD randomly assigned to either direct therapeutic exposure (flooding) or standard therapy. At 3-month follow-up, significantly more successes than failures were in the exposure group. In a review of the limited clinical literature on flooding, implosion, and direct therapeutic exposure for PTSD in Vietnam combat veterans, Foy et al. (183) noted the significant reductions in symptoms of intrusion and arousal but did register concern regarding reports of decompensation, distress, depletion of emotional reserves, and symptom exacerbation in some patients.

Richards et al. (366) tested four weekly sessions of imaginal exposure followed by four weekly sessions of real-life exposure (or vice versa) in 14 civilian patients with PTSD. Both groups showed a 65%–80% reduction in symptoms, with only a few differences noted, suggesting the salience of imaginal and in vivo forms of exposure. Rothbaum and Hodges (367) published a single case study of the use of a virtual reality mode of exposure for PTSD in a Vietnam veteran. The patient showed a 34% reduction in clinician-rated PTSD symptoms, which was maintained at 6-month follow-up. An open clinical trial also showed promise (368). Thus, imaginal, virtual, and in vivo exposures may each represent useful methods of delivering exposure therapy to PTSD patients.

Imagery rehearsal is another behavior therapy designed to ameliorate traumatic nightmares by having the patient recall the distressing content of recurring nightmares and repetitively envision (rehearse) a different outcome. Krakow et al. (184, 369) published two reports of a controlled study of imagery rehearsal for chronic nightmares in 168 sexual assault survivors with moderate to severe PTSD. The subjects were randomly assigned to an imagery rehearsal treatment group or to a waiting-list control group. A total of 114 subjects completed follow-up at 3 and/or 6 months. The treatment groups experienced significant reductions in the number of nightmares per week and significant improvement in sleep, relative to the control group. These improvements were noted at the 3-month follow-up and were sustained without further intervention or contact between 3 and 6 months. Furthermore, PTSD symptoms decreased in a majority of treated subjects but remained the same or worsened in a majority of control subjects. Forbes et al. (185) employed the same intervention for combat-related nightmares in 12 Vietnam veterans with PTSD and found significant reductions in targeted nightmares and improvements in PTSD symptoms. These changes persisted at 12-month follow-up (370). Similar success in female rape victims with chronic PTSD was reported in a study comparing cognitive processing therapy (another non-exposure-based cognitive therapy) to prolonged exposure and a waiting-list condition (181).

Group exposure therapy has also been found to be more effective than minimal attention groups. Falsetti et al. (371) reported on the results of a pilot study of a manualized treatment that included multiple cognitive and behavioral strategies, which they called multiple channel exposure therapy (M-CET), for patients with PTSD and comorbid panic disorder. They compared M-CET with a minimal attention group. Subjects recruited from an outpatient department and a local rape crisis center were randomly assigned to either 12 weeks of once-weekly M-CET group therapy or to a minimal attention group that received bimonthly supportive telephone counseling. Women in the control condition were offered free treatment after completing their participation in that condition. Posttreatment, only 8.3% of the subjects in the M-CET condition met the Clinician-Administered PTSD Scale diagnostic criteria for PTSD, compared with 66.7% of the control subjects. Ninety-three percent of the control group reported at least one panic attack in the past month, compared with only 50% of the treatment group. Glynn et al. (372) examined a behavioral family therapy for 42 Vietnam veterans with combat-related PTSD and a family member for each veteran (typically the veteran's wife). Three conditions were used: a course of twice-weekly direct exposure therapy, the same course of exposure followed by 16 sessions of behavioral family therapy, or a waiting-list condition.

Participation in exposure therapy was associated with a decrease in positive (e.g., intrusive and hyperarousal) symptoms of PTSD but not negative (e.g., avoidance/numbing) symptoms. There were no additional therapeutic gains from the family sessions.

Cognitive behavior therapy has often been combined with exposure therapy and shown to be effective. In a randomized, controlled study by Fecteau and Nicki (373) of cognitive behavior therapy (N=10) versus a waiting-list condition (N=10), adults (14 women) with PTSD were treated approximately 18 months after motor vehicle accidents with physical injury. The treatment consisted of four weekly 2-hour sessions of cognitive behavior therapy, including education, relaxation training, imaginal exposure, self-directed in vivo practice, and cognitive restructuring. Five of the 10 cognitive behavior therapy subjects no longer had diagnosable PTSD after treatment, while all 10 of the waiting-list group continued to meet the criteria for PTSD. PTSD symptoms improved significantly, with the Clinician-Administered PTSD Scale (CAPS-2) score decreasing from an average of 70.9 (high/PTSD present) to 37.5 (moderate). In contrast, the subjects' Beck Depression Inventory scores did not show significant improvement, suggesting a specific effect on PTSD rather than merely a nonspecific improvement in comorbid depression. The weak response in depression measures may also have been related to chronic pain and disability status. Follow-up at 3 and 6 months showed persistent improvements in PTSD symptoms.

Cognitive therapy techniques have not always been combined with exposure techniques, allowing for some comparison of these techniques. Foa et al. (374) randomly assigned 55 female rape victims with PTSD to one of four conditions: 17 were assigned to stress inoculation training, 14 to prolonged exposure, 14 to supportive counseling (to control for nonspecific therapy effects), and 10 to a waiting-list control group. PTSD diagnoses were made by an outside clinician who used DSM-III-R criteria. The range of time since the assault varied from 3 months to 12 years, with a mean of 6.2 years (SD=6.7). Treatment consisted of nine biweekly 90-minute individual sessions conducted by a female therapist. PTSD symptoms, rape-related distress, general anxiety, and depression were measured pretreatment, posttreatment, and at follow-up (mean=3.5 months posttreatment). Of the 55 patients who started the study, 10 dropped out, with no significant differences in dropout rates across the three treatment groups. However, the 10 noncompleters differed from the completers on three variables: a greater percentage of the noncompleters earned an annual income of less than $10,000, a greater percentage were blue-collar workers, and they scored higher on the Rape Aftermath Symptom Test. Immediately after treatment, stress inoculation therapy was the most effective treatment in reducing PTSD symptoms, and prolonged exposure was also an effective treatment. The supportive counseling and waiting-list conditions improved arousal symptoms of PTSD but not the intrusion and avoidance symptoms. Three and one-half months after treatment, however, prolonged exposure appeared to be the superior treatment. Thus, although stress inoculation therapy appeared to be the most effective treatment in the short term, prolonged exposure appeared to be the most effective treatment in the long term. Furthermore, the superiority of stress inoculation therapy and prolonged exposure over supportive counseling and waiting-list placement was found only for PTSD symptoms.

Marks et al. (177) showed that cognitive therapy, exposure therapy, and exposure plus cognitive therapy were better than relaxation treatment in 87 subjects randomly assigned to ten 90-minute sessions of the four treatment groups. It is important to note that all three cognitive behavior therapy approaches were markedly better than relaxation at 1, 3, and 6 months but no better than each other in decreasing PTSD symptoms or symptom severity, producing remission of PTSD, or improving functioning at the end of the study. Similarly, Echeburua et al. (375) tested progressive relaxation training versus cognitive restructuring and self-exposure in 20 victims of sexual aggression. Most treated patients improved, but the cognitive restructuring and exposure treatment was more successful on all measures than relaxation alone. In contrast, Silver et al. (376) treated inpatient Vietnam veterans with additional EMDR, biofeedback, or relaxation training and found no statistically significant differences between cognitive restructuring and exposure treatment.

Given the similarities between cognitive behavior therapy and exposure therapy, it is not surprising that comparisons of these two modalities have shown similar treatment outcomes. In a randomized, double-blind trial of cognitive behavior therapy versus exposure therapy for chronic PTSD, Tarrier et al. (178) found that the two treatments were equally effective in reducing symptoms in a diverse group of 72 trauma patients but that neither therapy produced complete symptom remission. It is important to note that nine patients in the exposure condition versus three patients in the cognitive behavior therapy condition showed worsening symptoms. Subsequent studies showed that improvements were maintained at 6 months (186) and 12 months (187), again with no significant differences between therapies.

Similarly, in a small, randomized study of 16 refugee outpatients with PTSD, both cognitive behavior therapy and exposure therapy resulted in large improvement on all measures, and this improvement was maintained at follow-up (377). The two treatments did not differ on any measure, but cognitive behavior therapy required relatively more and longer sessions to obtain significant results.

Studies of cognitive behavior therapy for PTSD have also examined outcomes for factors other than PTSD symptoms, such as anger. In a randomized trial, Chemtob et al. (378) assigned 15 Vietnam combat veterans with PTSD to routine VA care or to routine VA care plus 12 sessions of cognitive behavior therapy focused on anger. The 1-hour individual cognitive behavior therapy sessions involved self-monitoring of anger, devising an anger hierarchy, relaxation, cognitive restructuring skills training, and skills practice (role playing in anger-provoking situations). The anger therapy subjects had increased capacity to control anger at completion and 18-month follow-up, although there were no differences between groups on measures of psychophysiological reactions to anger provocation at treatment end. This study showed the specific clinical utility of a cognitive behavior treatment for anger as an adjunct to routine care, although no information was given on PTSD symptoms.

A few studies have indicated that a brief cognitive behavior therapy intervention in the acute posttraumatic phase can prevent PTSD while simultaneously treating ASD. Although these studies are few and included only a small number of subjects, the measured outcome of prevention of PTSD makes them very important, and their findings should be replicated. Bryant et al. (135) examined 45 civilian trauma survivors with ASD treated with five sessions of either prolonged exposure, prolonged exposure plus anxiety management, or supportive counseling begun within 2 weeks of the traumatic event. After treatment, the criteria for PTSD were met by significantly fewer of the patients who received prolonged exposure (14%) and prolonged exposure plus anxiety management (20%) than of those who received supportive counseling (56%). The effect of the two active treatments was maintained at 6-month follow-up after the traumatic event. In contrast to previous reports that 80% of patients who initially meet the criteria for ASD will have chronic PTSD 6 months after the trauma, this study found that patients who received supportive counseling had a rate of PTSD of 67%, indicating that supportive counseling may be somewhat helpful in ameliorating symptoms of PTSD. However, substantially fewer individuals met the criteria for PTSD after either prolonged exposure plus anxiety management (23%) or prolonged exposure (15%), suggesting even greater efficacy of these treatments. There were no differences in outcome between the prolonged exposure and prolonged exposure plus anxiety management interventions, indicating that anxiety management did not contribute to treatment efficacy.

Similarly, Foa et al. (379) treated female victims of recent rape or aggravated assault with a brief prevention program consisting of four 2-hour sessions of cognitive behavior therapy and education, compared with a matched assessment control group. Two months after the assault, only 10% of the brief prevention group met the PTSD criteria, in contrast to 70% of the control group. The brief prevention group did significantly better on measures of depression and reexperiencing symptoms than did the control group members, with an effect size for brief prevention of 1.22.

Gillespie et al. (380) found a similar effect size in a case series treated with cognitive therapy. In this study, a consecutive series of 91 patients were treated within 2 weeks after exposure to a car bomb in Omagh, Northern Ireland, with cognitive therapy along the lines advocated by Ehlers and Clark (381). Neither comorbidity nor the presence or absence of a supportive relationship predicted treatment response. Those who were physically injured improved less significantly than witnesses or those who were not injured. Witnesses and emergency personnel did not differ in their degree of improvement. It is interesting to note that there was a nonsignificant trend for patients who were treated later to improve more than those who were treated earlier, which highlights a need to better understand the timing of treatment interventions. Generalization from these findings is limited by the fact that patients received varying numbers of sessions, there was no control group, and the therapy was not manualized.

c) Eye movement desensitization and reprocessing (EMDR)

EMDR is generally seen as a combination of elements of cognitive behavior therapy, exposure therapy (albeit brief and interrupted exposures), and a unique attention to eye movements. Since cognitive behavior therapy and exposure therapy have been shown to have efficacy in treatment of PTSD, a major question about EMDR has been whether the eye movements contribute to therapy outcome. A number of factors have contributed to the difficulty in establishing whether EMDR effects are distinct from those of cognitive behavior therapy and exposure therapy. Studies of EMDR have included a range of trauma types, weighted toward persons with combat exposure but also including adults with histories of childhood sexual abuse, adults with adult sexual assault, adults after a major hurricane, and (for a few studies) adults with mixed civilian traumas. There is great variation in the protocols, from one 90-minute session to 8–10 sessions. The number of subjects in the studies has also varied widely. Several studies compared EMDR to waiting-list, supportive counseling, or active listening control groups. Others compared EMDR to different forms of prolonged exposure, while several employed dismantling designs that compared EMDR with or without eye movement or finger tapping procedures. Outcome variables primarily included self-report PTSD scales (often, the Impact of Event Scale), with a few using more general symptom checklists or depression inventories. No study has included structured or systematic functional outcome measures. Thus, because of the substantial variability in study design and other methodological shortcomings, it is difficult to draw firm conclusions about the independent effective elements of EMDR.

EMDR appears to be effective in ameliorating symptoms of both acute and chronic PTSD. For example, Marcus (382) compared EMDR to standard care for 67 demographically diverse patients at a health maintenance organization who had developed PTSD after assault, rape, incest, accidents, or witnessing of a trauma. Subjects were randomly assigned to a treatment condition, but evaluations were not conducted in a fully blinded fashion, and standard care differed from therapist to therapist. Treatment sessions continued until PTSD symptoms had remitted or until the end of the study, at which point 75% of the EMDR-treated subjects and 50% of subjects who received standard care no longer met the criteria for PTSD. Significant improvements, which were more rapid in the EMDR-treated group, were also noted in PTSD symptoms as measured by the Mississippi PTSD Rating Scale and the Impact of Event Scale as well as in depressive symptoms as measured by the Beck Depression Inventory.

Rothbaum (383) randomly assigned 20 female rape victims either to three weekly 90-minute sessions of EMDR or to a waiting-list control group. The subjects all met the DSM-III-R criteria for PTSD, and most had had symptoms for years. At 4 weeks after the completion of treatment, 90% of the EMDR-treated subjects no longer met the criteria for PTSD. Unblinded symptom ratings for PTSD and depression showed significant improvements, although the duration of these benefits was unclear, since the waiting-list subjects were subsequently treated.

Scheck et al. (384) randomly assigned women (ages 16–25 years) with a self-reported traumatic memory to either EMDR or active listening, which was delivered in two 90-minute sessions

1 week apart. Although immediately after the intervention both groups showed improvements on measures of depression and anxiety, including symptoms of PTSD, greater effect sizes were noted for the EMDR group. However, the study was limited by the fact that only one-half of those eligible to participate enrolled in the study, and of those who enrolled, only 70% completed the study. In addition, only 77% of subjects met the criteria for a diagnosis of PTSD at study entry.

Wilson et al. (385) randomly assigned 80 subjects to receive either EMDR or delayed treatment with EMDR. Subjects included equal numbers of men and women who had experienced a variety of traumas that occurred from 3 months to 54 years before treatment. Only one-half of the subjects met the DSM-IV criteria for PTSD, and only one-third of the sample had not received previous therapy for their symptoms. EMDR treatment consisted of three 90-minute sessions, and follow-up assessments were conducted. The subjects who received delayed treatment showed no change in symptoms in the 30 days before EMDR was begun, whereas the subjects who received EMDR showed significant improvements on measures of PTSD symptoms, somatization, interpersonal sensitivity, depression, and anxiety. Similar improvements were seen in the delayed-treatment EMDR group after treatment initiation, with improvements in both groups maintained at 90-day follow-up and again at 15-month follow-up (386).

Ironson et al. (387) compared the efficacy of EMDR and prolonged exposure in 22 civilian patients. Both approaches produced a significant reduction in PTSD and depression symptoms that was maintained at a 3-month follow-up. Successful treatment was faster, better tolerated, and more complete in the EMDR group (387). EMDR also resulted in reduced anxiety on process measures that was disproportionate to overall symptom improvement on outcome measures, with some evidence for sustainable symptom improvement for up to 3 months.

One study with a more extended follow-up period found that treatment gains were lost by 6 months (388). In this EMDR dismantling study, 51 Australian male combat veterans with PTSD were assigned to one of three conditions. Subjects were assigned to groups that received two sessions of EMDR, two sessions of reactive eye dilation desensitization and reprocessing (REDDR), or no intervention. REDDR was the same method as EMDR, except "eye movement" was replaced by "eye dilation," and a black box with a flashing light (opticator) was substituted for the eye movement stimuli. All subjects continued to receive standard care. No statistically significant changes were found from pre- to posttreatment on any of the outcome measures for the three conditions. At 3 months, all three treatment groups had improved somewhat, but there was no statistically significant difference among them. By 6 months, changes from pretreatment were no longer statistically significant for trait anxiety, depression, or PTSD (effect sizes at 6-month follow-up for EMDR plus standard care versus REDDR plus standard care=0.25). However, these findings must be interpreted in light of the brevity of both the EMDR and REDDR conditions. In a 5-year follow-up that compared 13 Vietnam combat veterans who received EMDR to a demographically matched control group of 14 combat veterans with PTSD who did not receive EMDR, both groups showed an overall worsening of PTSD symptoms over the 5-year period and loss of the modest to moderate early benefit of EMDR (389).

In another study, Devilly and Spence (35) compared nine sessions of a cognitive behavior therapy variant with up to eight sessions of EMDR in a total of 23 subjects with mixed trauma histories. The trauma treatment protocol (TTP) used prolonged exposure, in-depth cognitive therapy, and a variant of Foa's stress inoculation training. Compared to EMDR, TTP was more effective from pre- to posttreatment and had a reasonable effect size and high power. TTP's superiority became more pronounced at 3-month follow-up, at which time 83% of the TTP patients no longer met the PTSD criteria, compared to 36% of the EMDR subjects. However, in interpreting these data, it should be noted that the study was not randomized in a conventional manner, as most of the non-EMDR subjects were grouped in an initial block and EMDR was administered in a second block.

Cusack and Spates (390) randomly assigned 38 subjects to three 90-minute sessions of either standard EMDR or eye movement desensitization, which included all components of EMDR ex-

cept the cognitive reprocessing elements. Of the 27 individuals (23 women and four men) who completed the study, two-thirds had met the criteria for a DSM-IV diagnosis of PTSD at study entry and half had experienced either a physical or sexual assault. At posttreatment, both groups showed statistically significant decreases in symptoms as measured by the revised SCL-90, the Impact of Event Scale, the Structured Interview for PTSD, a behavioral assessment of speech anxiety, and a subjective unit-of-discomfort scale. However, both treatment groups showed comparable levels of improvement, suggesting that the imaginal exposure component of EMDR and not the cognitive reprocessing element is important to clinical efficacy.

Meta-analyses of the various controlled trials have generally concluded that EMDR represents an effective treatment. A 1997 review by Foa and Meadows (190) included studies of persons exposed to highly stressful events as well as those who met the criteria for PTSD. Many of the reviewed studies indicated no difference between EMDR and no-treatment or waiting-list control conditions, but one study indicated superiority of EMDR. The authors noted that because of methodological problems, further research to determine effectiveness was needed. Davidson and Parker (194) compared EMDR with no treatment, cognitive behavior therapy, exposure approaches (not involving in vivo exposure), variants of EMDR (e.g., dismantling studies), and "nonspecific" treatments. EMDR was more effective than no treatment and comparable to other active treatments. In this analysis, the dismantling studies appeared to provide comparable effectiveness across variant EMDR protocols. Maxfield and Hyer's meta-analysis (193) compared EMDR to waiting-list conditions, cognitive behavior therapy, and other treatments. EMDR was superior to the waiting-list conditions and either comparable or superior to other treatments (with considerable variability across studies). Although the meta-analysis by Shepherd et al. (191) included traumatized patients who did not all meet the DSM-IV or DSM-III-R criteria for PTSD, the researchers found that EMDR was comparable to a variety of psychotherapies and antidepressant therapy.

In summary, EMDR belongs within a continuum of exposure-related and cognitive behavior treatments. EMDR employs techniques that may give the patient more control over the exposure experience (since EMDR is less reliant on a verbal account) and provides techniques to regulate anxiety in the apprehensive circumstance of exposure treatment. Consequently, it may prove advantageous for patients who cannot tolerate prolonged exposure as well as for patients who have difficulty verbalizing their traumatic experiences. Comparisons of EMDR with other treatments in larger samples are needed to clarify such differences. The dismantling studies, in general, show no incremental effect from the use of eye movement or other proxies during the treatment sessions. Despite the demonstrable efficacy of EMDR, these studies call into question EMDR's theoretical rationale. It would therefore appear that it is the common sharing of trauma exposure techniques and emotional reprocessing that is principally responsible for treatment gains. Thus, EMDR is better than no treatment or supportive counseling and may be as effective as cognitive behavior therapy and other exposure-based techniques. As with the other therapies, the extent to which gains are maintained over the long term requires further evaluation.

2. Group psychotherapy for PTSD

There is a paucity of randomized, controlled treatment outcome studies for group treatment approaches among adults. The studies that have been done have not included groups that receive control or comparison treatments. Drawing conclusions across studies is difficult, since group protocols vary widely and include supportive therapy, psychoeducation, psychodynamic therapy, and various types of cognitive behavior therapy, including anxiety management, stress inoculation, assertiveness training, prolonged exposure, and cognitive restructuring. The patients treated in group psychotherapy studies have predominately been combat veterans and women with histories of childhood sexual abuse. Length of treatment has varied from 10 to 24 sessions that extend over 3 to 6 months. Some treatments have included booster sessions that extend over a year. Most studies have lacked sufficiently structured protocols, specific PTSD diagnostic assessments, and functional outcome measures.

Of five randomized, controlled trials, one showed modest improvement (combining trauma-focused and present-focused group data) in 64 women who received supportive-expressive group therapy, compared to 61 women in a waiting-list condition, decades after the trauma occurred (391). In another randomized, controlled trial of individuals who experienced childhood trauma and abuse, group therapy as an adjunct to individual therapy produced a decrease in PTSD symptoms (392). Schnurr et al. (393), in a well-designed multisite study of combat veterans with chronic PTSD, used methods that blended efficacy and effectiveness designs and found modest effects of both trauma-focused and present-focused group therapy but no difference between the two treatments (although the dropout rate for the trauma-focused therapy was about twice that for the present-centered treatment). The higher dropout rate highlights a concern that exposure-based therapies—whether group or individual—may prove intolerable for some patients (394, 395). A randomized study of a two-stage group therapy for incarcerated women showed reductions in PTSD, mood, and interpersonal symptoms in subjects who received dialectical behavior therapy skills training and writing assignments, although participants were not all identified as having PTSD before study entry (396). The only randomized, controlled trial that involved more recent trauma investigated group treatment among Serbian concentration camp survivors within 3 months of release from the camps (397). At study entry, 44% of the 120 men in the study met the DSM-III-R criteria for PTSD and were randomly assigned to receive group therapy, group therapy plus medication (anxiolytics and tricyclic antidepressants, but no SSRIs), or medication alone over a 6-month treatment course. The study also followed subjects who refused treatment. Although there were significant differences between treated and untreated groups at 6 months (with a much greater percentage of resolution of PTSD among the treated subjects), a 3-year follow-up among randomly selected subjects revealed the paradoxical finding that the untreated group was improved, relative to the treatment groups, in scores on the Watson Questionnaire for PTSD.

Of the six nonrandomized studies, four related to treatment of women with histories of childhood sexual abuse (180, 398–400), one was a structured inpatient group treatment of Gulf War veterans (401), and one targeted adults after the traumatic loss of an adolescent or young adult child (402). In three of the four group interventions for individuals who had experienced childhood sexual abuse, no measurements of PTSD were used. Group interventions were associated with improvement in various global symptom measures, including measures of self-concept and social adjustment. The one study that examined effects of a psychoeducation group for multiply traumatized women reported mixed and conflicting outcome findings regarding PTSD. Thus, these studies do not provide sufficient strength, in methods or outcomes, to adequately judge the usefulness of group interventions with adults who have been sexually abused in childhood.

The British Gulf War veteran group study, which examined a treatment format that was markedly different from other group interventions, provided an intensive 12-day structured inpatient group therapy, with day-group follow-up sessions for 1 year (401). The intervention included some form of ongoing psychological debriefing. There was a robust decrease in the percentage of patients who met the criteria for PTSD (from 100% to 14.7%) 1 year posttreatment. It is noteworthy that there was no reported use of drugs of abuse or increased alcohol use during the follow-up period. These findings suggest that an intensive, structured 2-week group intervention with extended booster follow-up sessions may provide a useful modality for treatment of combat-related PTSD.

The only group intervention study for traumatic bereavement in adults combined problem solving and emotional support over 12 weeks and found that mothers improved somewhat in PTSD-related reactions, while fathers worsened (402). Those with lower levels of initial PTSD symptoms worsened, while there was mild improvement among those with higher levels of initial PTSD symptoms. This study strongly points to the need for caution in selecting group membership, even among spouses, where there may be varying degrees of exposure and pretreatment levels of PTSD symptoms.

An additional nonrandomized comparison study compared two cognitive behavior approaches—stress inoculation and assertiveness training—to supportive group therapy in a group of 24 rape victims (180). Relative to 13 subjects in a waiting-list control group, all three treatments, each of which included six 2-hour sessions, did equally well in producing moderate improvements in PTSD, depression, anxiety, and self-esteem. In addition, in the active treatment groups, therapeutic benefits were maintained at 3- and 6-month follow-up.

As discussed by Foy et al. (403), the supportive groups tend to place primary emphasis on addressing current life issues, while psychodynamic or cognitive behavior-oriented groups are primarily "trauma-focused," with major work directed at specific traumatic experiences and memories. In group psychotherapy, there is the advantage of being able to provide services to large numbers of individuals in response to a shared traumatic experience or because of shared PTSD symptoms. In regard to trauma-focused group psychotherapy, most of the evidence for efficacy and effectiveness is in the treatment of children and adolescents (304, 404–407). In a study of adults, Schnurr et al. (393) randomly assigned 360 combat veterans into groups of six and compared trauma-focused group therapy in 30 weekly sessions followed by five monthly boosters to a present-centered comparison treatment. Relative to baseline, significant improvements were noted on posttreatment measures of PTSD severity in both groups, but intent-to-treat analysis showed no differences between therapy groups on any outcome measure. These studies together provide evidence that group sessions in conjunction with assigned homework can achieve sufficient prolonged trauma-focused exposure to be a bona fide treatment approach.

The trauma-focused group psychotherapies just described typically share certain principles. The first sessions provide general psychoeducation regarding PTSD, coping skills for trauma reminders and posttraumatic stress reactions, and either anxiety-regulating or emotion-regulating techniques. They also provide group process exercises to improve group cohesion, openness, and tolerance. The trauma exposure sessions utilize different versions of prolonged narrative or imaginal exposure, moving from more general accounts to the most intense traumatic moments. They rely on group members' assisting each other in this difficult task. These sessions are generally followed by problem-solving sessions that address avoidant and aggressive behavior, secondary or current adversities, and developmental hindrances. Group studies would suggest that the group format is especially effective in addressing this latter group of functional impairments.

There are as yet no clear guidelines regarding the contribution of group process to group psychotherapy outcomes in PTSD. Davies et al. (408) provided general guidelines that will need to be specifically adapted for this work. In a study that has important implications for group process, Cloitre and Koenen (398) examined the effects of interpersonal therapy groups for women who had experienced childhood sexual abuse. In mixed groups that included at least one individual with a diagnosis of borderline personality disorder, the group therapy process was no different from a waiting-list control group in symptom diminution but did induce a significant increase in posttreatment anger. In contrast, in groups that did not contain patients with borderline personality disorder, there were significant reductions in anger, depression, and symptoms of PTSD. Thus, the study results raise caution about the diagnostic composition of interpersonal therapy groups.

3. Other early psychosocial intervention strategies

There is substantial evidence that single-session, individual psychological debriefing in the immediate aftermath of a broad range of traumatic exposures (e.g., motor vehicle crashes, combat, physical assaults, burn injury) does not reduce psychological distress or prevent the onset of chronic PTSD (128–130). A series of randomized, controlled trials have assessed the efficacy of debriefing across trauma-exposed populations (213, 217–219, 409). Bisson et al. (217) randomly assigned 43 hospitalized burn survivors to 30–120 minutes of single-session debriefing versus control conditions 2–19 days after traumatic injury. Sixteen percent of the debriefed group versus 9% of the intervention group had PTSD at 13-month follow-up, a difference that

was statistically significant. It is noteworthy that the subjects who were randomly assigned to debriefing had significantly greater injury severity and had more frequent involvement of others in the injury event. Carlier et al. (410) debriefed police officers within 24 hours after exposure to a variety of traumas and found no symptomatic improvement in debriefed subjects, compared with control subjects. Conlon et al. (213) performed a 30-minute debriefing with motor vehicle crash victims and found no PTSD symptom improvement in the intervention group, compared with control subjects who received an advice leaflet and follow-up telephone contact number. Hobbs et al. (218) performed a 1-hour critical incident stress debriefing in randomly selected, symptomatic subjects 24–48 hours after motor vehicle crashes. Patients who received the debriefing demonstrated either similar or worsened symptomatic outcomes, compared to control subjects at 4 months (218) and 36 months (219) posttrauma. Rose et al. (409) delivered a 1-hour critical incident stress debriefing to victims of violent crime within 1 month after the trauma and found no significant differences in PTSD symptoms in intervention patients, relative to control subjects, at the 11-month follow-up assessment.

A handful of randomized and open trials of debriefing suggest limited benefit of group debriefing. In an open trial, Shalev et al. (20) performed group debriefings (emphasizing clarification of individuals' roles, time sequences, and facts surrounding the traumatic event, without exploring emotions) with soldiers 48–72 hours after exposure to combat and found reductions in anxiety, improvement in self-efficacy, and increased homogeneity of the group immediately after the debriefing. Deahl et al. (411) randomly assigned soldiers to a postdeployment debriefing/predeployment stress prevention intervention or to predeployment stress intervention alone. Although PTSD symptoms across the two groups showed no significant differences at 6- and 12-month follow-up, there was evidence of significantly reduced alcohol use in soldiers who received the debriefing. Campfield and Hills (412) randomly assigned robbery victims to immediate (<10 hour) versus delayed (>48 hour) critical incident stress debriefing group conditions. Victims in the immediate debriefing condition demonstrated improved symptom outcomes 2 weeks after the debriefing.

Although the debriefing models that have been investigated generally do not appear to be efficacious, there is only preliminary evidence that other psychosocial interventions with established efficacy for the treatment of PTSD can be effectively delivered as early interventions in complex real-world settings such as postdisaster environments and acute care medical settings. One study suggests that cognitive behavior interventions can be effectively delivered after mass attack, although the number of treatment sessions may need to be extended and high-risk groups of trauma survivors such as the physically injured may be less responsive (380). Preliminary evidence suggests that early psychosocial intervention strategies such as in-person/telephone case management may be effective in both engaging trauma survivors in treatment and reducing acute distress (131–134). Gidron et al. (133) randomly assigned 17 patients who had had motor vehicle crash injuries and elevated heart rates during acute care to receive a telephone-based memory restructuring intervention or a supportive listening control intervention within several days of the accident. Patients who received the active telephone-based intervention demonstrated significantly decreased PTSD symptoms. Zatzick et al. (134) delivered a collaborative care intervention that included posttraumatic concern elicitation and support to 34 randomly selected survivors of intentional and unintentional injuries. At 1-month postinjury, the patients receiving the intervention had significantly diminished PTSD and depressive symptoms, compared with control patients, yet treatment gains were not maintained at the 4-month assessment. In a follow-up randomized effectiveness trial with 120 injured trauma survivors, Zatzick et al. (131) extended the stepped care procedure to include case management and evidence-based cognitive behavior therapy and medication treatment targeting PTSD. Compared with control subjects who received usual care, patients who received the combined intervention demonstrated modest and statistically significant prevention of PTSD, which coincided with the initiation of the evidence-based treatments. In a nonrandomized design, Bor-

dow and Porritt (132) delivered a case management intervention to 70 male motor vehicle crash survivors. Intervention patients demonstrated less symptomatic distress than control groups of patients who received no intervention, immediate intervention, or delayed contact 3 months after the injury. More research is needed to determine if these initial engagement interventions will require augmentation with other proven psychotherapeutic and psychopharmacological interventions to prevent development of chronic PTSD.

4. Other psychotherapies

New psychotherapeutic approaches continue to be developed and applied to the treatment of trauma survivors with PTSD. As with previously developed interventions, it is essential that initial small-scale trials be followed by larger-scale randomized, controlled trials to establish efficacy. Recent small-scale trials of Internet-based therapies (413, 414) and Outward Bound group recreational therapies (415, 416) suggest potential beneficial effects on symptoms and functional outcomes.

In a pilot study, Gidron et al. (417) assessed the effects of written emotional disclosure on mental and physical health in Israeli patients with PTSD. One to 3 years after their trauma, subjects were randomly assigned either to the disclosure condition or to a casual writing control condition. Disclosure condition patients were asked to write for 20 minutes for 3 consecutive days about their most traumatic experiences and then, in a brief structured format, to talk about the most severe events about which they had written. Control subjects wrote about their daily agenda without affective content and then discussed one daily activity. The investigators found that a brief return to traumatic narrative may be counterproductive. Disclosure patients reported higher levels of negative affect immediately after writing than did the control patients and also reported larger increases in avoidance symptoms. The proportion of emotional words in the trauma narratives was associated with intrusive and avoidance symptoms of PTSD. The proportion of words on physical health predicted a greater number of health care visits at follow-up.

Monitoring of intrusions has also been suggested as a treatment intervention (418) and was studied in six individuals, all with PTSD. The subjects were given instructions to monitor intrusions—e.g., "try to not think of it," "think your way through," "cope with it"—over a 2-month period; then they were followed up immediately thereafter and again 3 months afterward. Of the six individuals treated with this approach, only one still met the criteria for PTSD at the end of the study, whereas four recovered. Although the small sample size limited the authors' ability to evaluate differences statistically, this innovative treatment of specific symptoms highlights future directions for possible public health interventions that may limit the need for specialty care.

With regard to novel techniques, a key question is whether they contain active components of efficacy-proven PTSD interventions. For instance, a review of case studies of Native American healing rituals that have been applied to the treatment of trauma survivors, such as sweat lodge and shamanic healing ceremonies, suggests that these interventions may contain an imaginal exposure component (419, 420). These "culturally sensitive" interventions may therefore combine "active" PTSD intervention components with socially accepted service delivery modalities that enhance adherence and reduce dropout.

C. PHARMACOTHERAPIES

1. Antidepressants

a) SSRIs

SSRIs are the most extensively studied medications in PTSD treatment research. Eight randomized, controlled trials have investigated SSRIs. These trials were often large, industry-sponsored clinical studies with hundreds of subjects. The general finding is that SSRIs are significantly

more effective than placebo. In a 12-week randomized, controlled trial of sertraline, Davidson et al. (421) randomly assigned 208 civilian men and women to receive either medication or placebo. Subjects treated with the SSRI were more likely to show a significant clinical response consisting of at least a 30% reduction in PTSD symptoms and were also more likely to experience a global improvement in symptoms (improvement was found in 60% of sertraline-treated subjects, compared to 38% of the placebo group subjects). In a similarly designed study, in which a separate sample of 187 civilian subjects were randomly assigned to receive sertraline or placebo, responder rates were 55% in the SSRI group, in contrast to 35% for the placebo subjects (144). Two randomized clinical trials with the SSRI paroxetine have also had favorable results. In one, 551 civilian men and women were randomly assigned to receive 20 mg/day of paroxetine (N=183), 40 mg/day of paroxetine (N=182), or placebo (N=186). Subjects in the two medication groups did not differ from one another but demonstrated significant improvement on all three PTSD symptom clusters, global improvement, and improvement in social and occupational functioning (141). In the second large paroxetine study, 307 civilian subjects were randomly assigned to receive medication or placebo with similar positive results; the medication group showed significantly greater improvement with regard to all three clusters of PTSD symptoms, global improvement, and improvement of functional capacity (e.g., in work, social interactions, and family life) (145). Unlike the sertraline results, which were positive for women but not for men (possibly because so few men participated in these trials), paroxetine was equally effective for men and women. As a result of these large-scale multisite randomized, clinical trials, SSRIs are currently considered first-line pharmacotherapeutic treatment for PTSD, and both sertraline and paroxetine have received the approval of the U.S. Food and Drug Administration as indicated treatments for PTSD. A randomized clinical trial with fluoxetine has also had favorable results. In this study, in which 301 mostly white, male non-American veterans of United Nations peacekeeping deployments were randomly assigned to receive medication or placebo, the SSRI subjects exhibited significantly greater improvement in PTSD symptom severity and global functioning than did the placebo group (146). Open-label trials with two other SSRIs—citalopram (278) and fluvoxamine (150)—were also promising.

A few long-term continuation and discontinuation studies with sertraline are also noteworthy. Fifty-five percent of patients who failed to respond positively to sertraline after 12 weeks of treatment did exhibit a favorable response when treatment was extended for an additional 24 weeks (279). Discontinuation of sertraline treatment in patients who had previously responded favorably was six times more likely to lead to clinical relapse than was continuation of sertraline treatment (123).

In addition to finding reduction of PTSD symptoms, studies with sertraline and fluoxetine have suggested that SSRI treatment also promotes improvement in functional status and quality of life and that discontinuation of medication is associated with decreased quality of life and functional measures in addition to symptom relapse (148, 280).

To summarize, in short- and intermediate-term trials, SSRIs have proven efficacy for PTSD symptoms and related functional problems. Patients who respond favorably will generally need to continue taking medication in order to maintain clinical gains.

b) Other second-generation antidepressants

Despite high utilization of second-generation antidepressants to treat depression and other anxiety disorders, no randomized, controlled trials of these medications have been carried out in patients with PTSD. The most extensively tested medication, nefazodone, might be expected to have a favorable effect on PTSD symptoms since, like the SSRIs, it promotes serotonergic activity. Indeed, several open-label trials with nefazodone suggest that this medication may have efficacy for treatment of all three PTSD symptom clusters, especially for patients with treatment-resistant symptoms (422–426). Nefazodone is also an attractive possibility because it is often better tolerated than SSRIs, although caution must be taken given its association with irreversible and life-threatening hepatic failure.

Positive reports from small open-label trials with trazodone (427), bupropion (428), venlafaxine (429), and mirtazapine (430) do not provide sufficient evidence to justify endorsing any of these medications for PTSD patients at this time; one double-blind, placebo-controlled pilot study with mirtazapine also suggests efficacy (431). Trazodone may have a unique niche in treatment because its serotonergic action is synergistic with SSRIs while its sedative properties are often an effective antidote to SSRI-induced insomnia, and sleep disturbance is often central to the clinical picture in ASD and PTSD. Efficacy of such agents in ASD or in acutely traumatized individuals who do not meet the full diagnostic criteria for PTSD warrants further investigation.

c) Tricyclic antidepressants

In three randomized, controlled trials conducted with tricyclic antidepressants, all subjects were Vietnam veterans seeking PTSD treatment in VA hospital settings. In a study in which 60 veterans in a VA setting were randomly assigned to receive the tricyclic antidepressant imipramine (N=23, mean dose=225 mg/day), the MAOI phenelzine (N=19, mean dose=68 mg/day), or placebo (N=18), imipramine produced significantly more improvement than placebo but not as much as phenelzine (151) (see further details in the next section, Section V.C.1.d, "MAOIs"). In an 8-week trial in which 40 veterans in a VA setting were randomly assigned to receive either the tricyclic antidepressant amitriptyline (N=22, mean dose=169 mg/day) or placebo (N=18), the response rate was 47% for the patients who received amitriptyline, compared to 19% for placebo subjects; this difference was statistically significant (152). Taken together, both studies indicated that tricyclic antidepressant treatment produced global improvement and reduction of reexperiencing symptoms. It should be noted, however, that in the third published randomized, controlled trial, which included only 18 veterans randomly assigned to receive the tricyclic antidepressant desipramine (mean dose=165 mg/day) or placebo for 4 weeks, no response by either group was found (153). A quantitative analysis of all trials (randomized, controlled trials and open-label trials) with these medications indicated that tricyclic antidepressants in general produce global improvement and reductions in reexperiencing symptoms (432). Thus, although clinical management with tricyclic antidepressants may be more complicated than that with newer agents, the tricyclic antidepressants are effective medications that still have a potential role in PTSD treatment.

Robert et al. (433) compared imipramine with chloral hydrate as treatment in a randomized clinical trial. Twenty-five children, ages 2–19 years, with symptoms of ASD and hospitalized on a burn unit for severe injury (with a mean total burn surface area of 45%), received either imipramine (1 mg/kg, with a maximum dose of 100 mg/day) or chloral hydrate (25 mg/kg, with a maximum dose of 500 mg/day). After 7 days of treatment, ASD symptoms remitted in 83% of the patients treated with imipramine, compared with 38% of those treated with chloral hydrate. Stated differently, 10 of the 12 children who received imipramine were considered to have a positive treatment response. Unfortunately, there was no long-term follow-up, so it is unclear whether this early tricyclic antidepressant treatment prevented later development of PTSD. This study stands as the best demonstration that acute pharmacotherapy can be an effective treatment for acutely traumatized subjects.

d) MAOIs

Two randomized, controlled trials have been carried out with the MAOI phenelzine. In the 8-week study with American Vietnam veterans in a VA setting mentioned in the previous section, 60 subjects were randomly assigned to receive the MAOI phenelzine (N=19), the tricyclic antidepressant imipramine (N=23), or placebo (N=18) (151). In assessments with the Impact of Event Scale, both medication groups did significantly better than the placebo group, with 44% improvement among the phenelzine subjects, compared with 25% improvement among the imipramine subjects. The difference between the MAOI and tricyclic antidepressant groups was statistically significant (151). A single report of a successful open trial of the reversible

monoamine oxidase type A inhibitor moclobemide (434) also supported the use of MAOIs as a class in treatment of PTSD. Moclobemide, which is not presently available in the United States, was tested in a 12-week open trial with 20 subjects and yielded promising results (434). At the end of the trial, 11 subjects no longer met the PTSD diagnostic criteria, and there was a significant reduction in PTSD symptom severity and significant improvement in global function. In addition to studies with phenelzine, two randomized, controlled trials that used brofaromine, a unique MAOI/SSRI medication that is not available commercially, showed some improvement in PTSD symptoms (155, 435). Finally, there are two reports of meta-analyses that synthesized results from a number of published reports (432, 436). Although there have been some negative reports, MAOIs have generally been shown to produce global clinical improvement and reductions in PTSD symptom severity, with specific effectiveness for reexperiencing symptoms. In the only head-to-head comparison of an MAOI (phenelzine) and a tricyclic antidepressant (imipramine), as noted earlier, the MAOI was more effective, although the tricyclic antidepressant was still more effective than placebo (151). Clinicians' reluctance to prescribe MAOIs generally relates to concerns about the capacity of patients to adhere to tyramine-free diets or to abstain from alcohol, certain drugs of abuse, and contraindicated prescription medications (e.g., SSRIs, CNS stimulants, decongestants, and meperidine). However, it must be emphasized that MAOIs are clinically effective and that many patients can adhere to such constraints. Finally, reversible monoamine oxidase type A inhibitors are much easier to manage clinically because patients need not observe such dietary or pharmacological restrictions.

2. Benzodiazepines

Benzodiazepines cannot be recommended as monotherapy for PTSD patients, despite their proven efficacy in generalized anxiety disorder. Despite widespread use in treatment of PTSD, their utility in PTSD has not been adequately evaluated. In the only pertinent randomized, controlled trial, alprazolam was tested with 10 civilians and veterans who received treatment for 5 weeks (437). The benzodiazepine was ineffective against PTSD reexperiencing and avoidant/numbing symptoms, although it did improve sleep and general anxiety. Rebound anxiety related to alprazolam treatment was also observed during this trial. In addition, a postdiscontinuation benzodiazepine withdrawal syndrome has been described that was characterized by a profound exacerbation of PTSD symptoms (158). Although a limited open-label case series also suggested improvement in insomnia and core PTSD symptoms in acutely traumatized individuals (438), positive long-term outcome data have not been reported, and a controlled study did not show advantage over placebo (156). Indeed, early administration of benzodiazepines was associated with a higher incidence of PTSD at 1- and 6-month follow-up in one study (157).

3. Miscellaneous medications

A variety of classes of psychopharmacological agents have been tested for the treatment of PTSD. Initial open and randomized trials of carbamazepine (160), valproic acid (161, 162), and lamotrigine (163) suggested that these agents may be efficacious in targeting discrete PTSD symptom clusters. Two small open-label trials showed promising results with the serotonergic anxiolytic buspirone (439, 440), but the data are insufficient to recommend it for use at this time. Two studies (169, 441) suggested that prazosin may be effective in treating nightmares and other PTSD symptoms in male combat veterans.

Olanzapine, a second-generation antipsychotic agent, when prescribed to augment ongoing sertraline treatment, was shown to produce improvement in PTSD, depressive, and sleep-related symptoms in Vietnam veterans (166). Open-label studies of adjunctive olanzapine and quetiapine have demonstrated symptom reduction in veterans with PTSD (165, 167). However, olanzapine alone did not show an effect in a small randomized, double-blind, placebo-controlled trial in female veterans (164). A small controlled study of risperidone in chronic combat-related PTSD was similarly disappointing for core PTSD symptoms, although reexperiencing and global psychotic symptoms were reduced (168).

Early case reports suggested that cyproheptadine, a serotonin antagonist, might ameliorate PTSD flashbacks and traumatic nightmares, but a randomized, controlled trial by Jacobs-Rebhun et al. (442) and a large open-label trial by Clark et al. (443) disconfirmed these findings. In the randomized trial by Jacobs-Rebhun et al., 69 veteran subjects in a VA setting were randomly assigned to receive either cyproheptadine or placebo. After 2 weeks of treatment, the cyproheptadine subjects exhibited a (nonsignificant) worsening of PTSD symptom severity, sleep quality, and traumatic nightmare severity (442). The large open-label trial of cyproheptadine by Clark et al. (443) also failed to produce positive results. Therefore, cyproheptadine cannot be recommended for PTSD treatment.

Inositol is a second messenger with limited evidence supporting efficacy in treating depression and panic disorder. However, in a small randomized, crossover study, with 13 subjects randomly assigned to receive medication or placebo for a 4-week trial, inositol was ineffective in alleviating PTSD symptom severity (444).

A number of agents have been pilot tested in the secondary prevention of PTSD. There is preliminary evidence from two studies that steroid administration during inpatient medical/surgical hospitalization may diminish PTSD symptom development in patients with critical medical illness (445, 446). One observational study among youths hospitalized after burn injury suggested that patients who received the highest doses of opiate analgesics exhibited the lowest PTSD symptom severity after discharge from the hospital (447). As mentioned previously, another randomized investigation on a pediatric burn unit suggested that imipramine is efficacious in ameliorating ASD (433). A single investigation pilot tested the use of propranolol among injured patients seen in an emergency department after a motor vehicle accident and had interesting findings; although no significant improvement in PTSD was detected and high dropout rates were observed in the intervention group, subjects who received propranolol had a significant reduction in physiological reactivity that persisted for 3 months after acute treatment (137). In addition, a recent controlled but nonblind, nonrandomized study reported that acute administration of propranolol posttrauma reduced subsequent PTSD symptoms (172). These findings will also be important to pursue further in larger randomized trials.

PART C
FUTURE RESEARCH NEEDS

Research over the past decade has led to considerable advances in our understanding of the epidemiology of the acute and long-term neurobiological and psychological changes that occur after highly stressful experiences. Research has also identified a variety of treatment approaches for pathological responses to traumatic events, including ASD and PTSD. Although much has been accomplished, future study is required to expand current understanding and inform future assessment, prevention, and treatment strategies. The following future research needs are not presented in any effort to prioritize, nor are they intended to be exhaustive. They serve to illustrate the fact that our understanding of the range of human response to traumatic stress is in its infancy and only beginning to evolve.

- **Early interventions/posttrauma treatment.** In early intervention (in the hours or days after a traumatic event), the aim is to reduce immediate distress, but ideally it might also be to prevent the development of ASD or PTSD. However, relatively little is known about prevention. Small, controlled studies of psychotherapy suggest efficacy (135, 136, 448),

as do the studies of early case management interventions (131–134). In addition, a few small controlled studies suggest that early pharmacological interventions may reduce development of posttraumatic symptoms (137, 172, 433). However, larger controlled trials and long-term follow-up studies are needed to fully address the efficacy and effectiveness of psychotherapeutic, psychopharmacological, psychoeducational, and supportive interventions in reducing initial distress and later development of ASD or PTSD, as well as in improving social and occupational functioning.

- **Identification of risk factors for development of ASD or PTSD.** Given the wide variability of human response to traumatic events, future intervention strategies would be aided by a greater understanding of the extent to which ASD or other diagnoses or factors are associated with subsequent development of PTSD. Elucidation of markers or risk factors (e.g., biological or genetic markers, psychological traits, other life experiences, or ethnocultural variables) that specifically relate to the development or severity of ASD or PTSD after initial or subsequent exposures to potentially traumatic events would be valuable (179, 449, 450). Neurobiological markers are being identified, for example, that are associated with reduced susceptibility to developing disorders after exposure (or exposures) to potentially traumatic events (451). Further study of markers for both vulnerability and resilience may help explain variability in the development of ASD or PTSD within populations exposed to similar traumatic events and may contribute to a better understanding of the natural history of these conditions. Better identification of at-risk populations within groups similarly exposed may also guide future preventive and acute intervention strategies. In addition to the independent effects of specific markers or risk factors, interactions among identified biological, psychological, and social factors may further alter the likelihood of developing ASD or PTSD and also merit additional study.
- **Subthreshold and complex PTSD.** Persons may develop significant symptoms in one or more of the three ASD or PTSD symptom clusters but not meet the full diagnostic criteria for ASD or PTSD (452–454). These individuals may be significantly impaired (452, 455), raising questions about the appropriateness of current threshold criteria for PTSD. Similar questions may be raised about the current DSM-IV-TR criterion that to be considered traumatic, a person's response to an event must include "intense fear, helplessness, or horror," since this criterion excludes many persons who report feeling numb or who demonstrate dissociative responses (19). Further study is needed to determine whether such individuals, who might otherwise qualify for these diagnoses, would benefit from treatment.

  Randomized, controlled trials of therapy and medications have focused on reducing readily identifiable core symptoms that are outlined in the current diagnostic criteria for PTSD; these symptoms lend themselves to quantification with available severity scales. Clinicians recognize that PTSD and ASD are associated with changes in belief systems, view of self, and ability to trust others, as well as related changes in social, occupational, and interpersonal functioning that may affect patients' lives to a far greater extent than more readily quantifiable core clinical features. The extent to which these issues rather than the more easily recognized or reliably reported reexperiencing phenomena or hyperarousal represent the more disabling aspects of the illnesses also bears further investigation. Another question for further study is whether these often-observed changes represent symptoms that should be included in refined diagnostic criteria for PTSD or should signify a separate diagnostic entity (e.g., occurring perhaps as a consequence of earlier or repeated exposure to trauma). More difficult to assess is the extent to which deterioration in spheres of functioning is mitigated by currently available treatments and which approaches may be most effective for addressing the illnesses' effects on functioning.

  Whether or not traumatic grief and complicated bereavement should be recognized as separate diagnostic entities, response to loss is often a focus for persons seeking treatment (303, 456). Since traumatic loss is common, further study of potential treatments for prolonged or disabling grief is warranted.

- **Medication treatments and psychotherapies.** For the most part, studies of psychotherapy and medication treatment for ASD and PTSD have been small and of relatively brief duration. While larger, well-controlled studies of SSRIs have been conducted, similar studies are lacking and are needed for virtually all other available medication treatments. Newer medications such as tiagabine (457) have been pilot tested but will also require larger-scale controlled studies to establish efficacy.

  Benzodiazepines are a widely used and effective treatment for other psychiatric disorders, including anxiety disorders. Although they may improve sleep in ASD or PTSD, some evidence suggests that benzodiazepines also may increase the likelihood of developing PTSD (157, 438). Given the widespread use and prescription of these medications in emergency settings, well-controlled studies are needed in patients with ASD and PTSD.

  Studies of pharmacological treatments are also needed to provide evidence on stepwise or algorithmic approaches to treatment choice and to define the role of adjunctive medications in patients with partial responses to first-line agents. Pharmacokinetic or pharmacodynamic properties of medications within subclasses have yet to be studied with regard to their effect on efficacy in treatment of PTSD, nor have the effects of ethnic or cultural considerations on treatment response been clearly delineated.

  At the neurobiological level, the mechanisms by which specific medications alter putative disease processes remain unclear. Studies of the neurobiological effects of specific interventions may provide clues to the pathophysiology of these disorders and suggest other avenues of treatment.

  Cognitive and behavioral therapies—particularly as early interventions—have demonstrated efficacy largely in victims of sexual assault, interpersonal violence, and industrial or vehicular accidents. Replication of these studies in combat veterans or other victims of mass violence is also important. Preliminary findings with innovative psychotherapies (368, 413, 415–417) require further study in larger controlled trials. Manualizing both emerging and traditional psychotherapies is one approach that may promote more rigorous study. Given the widespread use of psychodynamic psychotherapy, it is particularly important to encourage controlled studies to examine the techniques used and their efficacy.

  In the clinical setting, psychotherapeutic approaches are most often used in combination with one another. Regardless of theoretical orientation, clinicians use elements of psychodynamic therapy, supportive therapy, cognitive behavior therapy, or other approaches incorporating various degrees of imaginal or in vivo exposure. Identification of the effective subcomponents of various cognitive and behavior therapies and EMDR in the research setting has not been accomplished, and even less is known about effective subcomponents of these therapies in typical clinical populations. Investigations of combinations of various psychotherapies are few (177, 397, 458). Effectiveness trials that assess whether efficacious psychotherapeutic and psychopharmacological interventions can be adapted beneficially to typical clinical settings are similarly necessary (25).
- **Treatment of specific symptoms or clinical concerns.** Given mixed results with benzodiazepines and the prominence of sleep disturbance in traumatized individuals (459–461), it is critical to identify medications or therapies that can target nightmares and insomnia without increasing the patient's likelihood of developing other symptoms (426, 462). Further study may also help to identify particular interventions that reduce other specific symptoms in patients with ASD or PTSD, such as self-injurious, deliberately self-harmful, or suicidal behaviors (277). The role of active involvement of family members and community supports in enhancing adherence—as has been applied to other severe mental disorders—requires further exploration (84). There are few studies of the potential of family or couples therapy for reducing symptoms or dysfunction in PTSD (372). The effect of other treatments on reducing functional impairment is another broad area that requires further investigation.

- **Generalization of research trials to clinical populations.** As for most disorders, the generalizability of medication trials and therapy studies for the treatment of ASD and PTSD is frequently limited by high levels of subject exclusion because of comorbidity, high subject dropout rates, and relatively short durations of follow-up periods (277). Consequently, the robust treatment responses observed in research settings may not always be seen in typical patients treated in clinical practice. Longer-term follow-up studies must also be conducted to determine whether initial gains made in therapy or with medication are long-lasting and whether maintenance treatment is necessary. More studies are needed to clarify potential adverse effects of treatment and patient factors that reduce adherence to specific regimens (463). Effectiveness trials are also necessary to assess whether efficacious therapeutic and/or psychopharmacological interventions for ASD or PTSD can produce meaningful and lasting changes in patients who typically present in community settings. The importance of PTSD as a comorbid disorder in serious and persistent mental disorders such as schizophrenia or bipolar disorder highlights a particular need for study of PTSD treatment in these patient groups.

The fact that stressful life events may cause emotional and behavioral effects has long been recognized. Psychiatrists concerned themselves with the consequences of traumatic experience decades before the diagnoses of ASD and PTSD were specifically identified. Clinical experience, descriptive literature, and case study guided treatment of persons suffering from the effects of traumatic exposure long before randomized, controlled trials were conceptualized or became a standard for evaluating new evidence. Disregarding clinical experience accumulated before these advances in research design would be as imprudent as believing that research conducted under current standards has adequately demonstrated the full range of effective treatment. Standards for gathering and evaluating new evidence are evolving and should inform the development of future guidelines for assessing and treating mental disorders that arise in the aftermath of exposure to traumatic events.

INDIVIDUALS AND ORGANIZATIONS THAT SUBMITTED COMMENTS

Jon G. Allen, Ph.D.
William Arroyo, M.D.
J. Wesson Ashford, M.D., Ph.D.
Donald Banzhaf, M.D.
Romano Biancoli, Ph.D.
Evelyn Bromet, Ph.D.
David W. Brook, M.D.
Bonnie J. Buchele, Ph.D.
Fredric Busch, M.D.
Peter Roy Byrne, M.D.
Judy Cohen, M.D.
Mary Ann Cohen, M.D.
Mirean Coleman, M.S.W., L.I.C.S.W., C.T.
Joan Cook, M.D.
Jonathan Davidson, M.D.
Cleto DiGiovanni, Jr., M.D.
Lois T. Flaherty, M.D.
Jane Meschan Foy, M.D.
Terry Fullerton, Ph.D.
Leslie Hartley Gise, M.D.
Robert M. Goisman, M.D.
Michael Good, M.D.
Tina Haynes, M.T.-B.C.
Al Herzog, M.D.
Mardi Horowitz, M.D.
Craig L. Katz, M.D.
Harold Kudler, M.D.
Barry Landau, M.D.
Melvin Lansky, M.D.
Dori Laub, M.D.

Fred M. Levin, M.D., S.C.
Brett Litz, Ph.D.
John Markowitz, M.D.
Julia Matthews, Ph.D., M.D.
Miles McFall, Ph.D.
Thomas A. Mellman, M.D.
Thomas Neylan, M.D.
Carol S. North, M.D.
Andrei Novac, M.D.
John D. O'Brien, M.D.
Herbert S. Peyser, M.D.
Roger Pitman, M.D.
Charles W. Portney, M.D.
Murray Raskind, M.D.
Barbara R. Rosenfeld, M.D.
Barbara O. Rothbaum, M.D.
Patricia Rowell, R.N., Ph.D., C.N.P.
Diane H. Schetky, M.D.
David Servan-Schreiber, M.D., Ph.D.
Jonathan Shay, M.D., Ph.D.
Bradley D. Stein, M.D., Ph.D.
Robert Stern, M.D., Ph.D.
Nicholas E. Stratas, M.D.
Elisa G. Triffleman, M.D.
Bessel A. van der Kolk, M.D.
Sidney Zisook, M.D.

American Academy of Child and Adolescent Psychiatry
American Academy of Clinical Psychiatrists
American Academy of Pediatrics
American Academy of Psychoanalysis and Dynamic Psychiatry
American Association of Community Psychiatrists
American Group Psychotherapy Association
American Music Therapy Association
American Nurses Association
International Federation of Psychoanalytic Societies
National Association of Social Workers
National Center for Post-Traumatic Stress Disorder

REFERENCES

The following coding system is used to indicate the nature of the supporting evidence in the references:

[A] *Randomized double-blind clinical trial.* A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.

[A–] *Randomized clinical trial.* Same as above but not double-blind.

[B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.

[C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.

[D] *Control study.* A study in which a group of patients and a group of control subjects are identified in the present and information about them is pursued retrospectively or backward in time.

[E] *Review with secondary data analysis.* A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.

[F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.

[G] *Other.* Textbooks, expert opinion, case reports, and other reports not included above.

1. Veterans Health Administration: Management of Post-Traumatic Stress. Office of Quality and Performance publication 10Q-CPG/PTSD-04. Washington, DC, VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, 2003. http://www.oqp.med.va.gov/cpg/PTSD/PTSD_Base.htm [G]
2. Foa EB, Keane TM, Friedman MJ (eds): Effective Treatments for PTSD: Practice Guidelines From the International Society for Traumatic Stress Studies. New York, Guilford, 2000 [G]
3. American Academy of Child and Adolescent Psychiatry: Summary of the Practice Parameters for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder. J Am Acad Child Adolesc Psychiatry 1998; 37:997–1001 [G]
4. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB: Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1995; 52:1048–1060 [G]
5. Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P: Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. Arch Gen Psychiatry 1998; 55:626–632 [G]
6. Harvey AG, Bryant RA: The relationship between acute stress disorder and posttraumatic stress disorder: a 2-year prospective evaluation. J Consult Clin Psychol 1999; 67:985–988 [C]
7. Marshall RD, Spitzer R, Liebowitz MR: Review and critique of the new DSM-IV diagnosis of acute stress disorder. Am J Psychiatry 1999; 156:1677–1685 [F]
8. Staab JP, Grieger TA, Fullerton CS, Ursano RJ: Acute stress disorder, subsequent posttraumatic stress disorder and depression after a series of typhoons. Anxiety 1996; 2:219–225 [G]
9. Bryant RA, Harvey AG, Guthrie RM, Moulds ML: A prospective study of psychophysiological arousal, acute stress disorder, and posttraumatic stress disorder. J Abnorm Psychol 2000; 109:341–344 [C]
10. Stein MB, McQuaid JR, Pedrelli P, Lenox R, McCahill ME: Posttraumatic stress disorder in the primary care medical setting. Gen Hosp Psychiatry 2000; 22:261–269 [G]
11. Silver RC, Holman EA, McIntosh DN, Poulin M, Gil-Rivas V: Nationwide longitudinal study of psychological responses to September 11. JAMA 2002; 288:1235–1244 [G]
12. North CS, Nixon SJ, Shariat S, Mallonee S, McMillen JC, Spitznagel EL, Smith EM: Psychiatric disorders among survivors of the Oklahoma City bombing. JAMA 1999; 282:755–762 [G]
13. Weine SM, Becker DF, McGlashan TH, Laub D, Lazrove S, Vojvoda D, Hyman L: Psychiatric consequences of "ethnic cleansing": clinical assessments and trauma testimonies of newly resettled Bosnian refugees. Am J Psychiatry 1995; 152:536–542 [G]
14. Bromet E, Sonnega A, Kessler RC: Risk factors for DSM-III-R posttraumatic stress disorder: findings from the National Comorbidity Survey. Am J Epidemiol 1998; 147:353–361 [G]
15. Breslau N, Davis GC, Andreski P, Peterson EL, Schultz LR: Sex differences in posttraumatic stress disorder. Arch Gen Psychiatry 1997; 54:1044–1048 [G]
16. Meltzer-Brody S, Churchill E, Davidson JR: Derivation of the SPAN, a brief diagnostic screening test for post-traumatic stress disorder. Psychiatry Res 1999; 88:63–70 [G]
17. Breslau N, Peterson EL, Kessler RC, Schultz LR: Short screening scale for DSM-IV posttraumatic stress disorder. Am J Psychiatry 1999; 156:908–911 [G]
18. Brewin CR, Rose S, Andrews B, Green J, Tata P, McEvedy C, Turner S, Foa EB: Brief screening instrument for post-traumatic stress disorder. Br J Psychiatry 2002; 181:158–162 [G]
19. Shalev AY: Acute stress reactions in adults. Biol Psychiatry 2002; 51:532–543 [F]
20. Shalev AY, Peri T, Rogel-Fuchs Y, Ursano RJ, Marlowe D: Historical group debriefing after combat exposure. Mil Med 1998; 163:494–498 [B]
21. Marmar CR, Weiss DS, Pynoos RS: Dynamic psychotherapy of post-traumatic stress disorder, in Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder. Edited by Friedman MJ, Charney DS, Deutch AY. Philadelphia, Lippincott-Raven, 1995, pp 495–506 [F]

22. Marmar CR, Weiss DS, Schlenger WE, Fairbank JA, Jordan BK, Kulka RA, Hough RL: Peritraumatic dissociation and posttraumatic stress in male Vietnam theater veterans. Am J Psychiatry 1994; 151:902–907 [G]
23. Weathers FW, Litz BT, Huska J, Keane TM: PTSD Checklist (PCL) for DSM-IV. Boston, National Center for PTSD, Behavioral Science Division, 1994 [G]
24. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. Psychosom Med 1979; 41:209–218 [G]
25. Horowitz MJ: Treatment of Stress Response Syndromes. Arlington, VA, American Psychiatric Publishing, 2003 [G]
26. Davidson JR, Book SW, Colket JT, Tupler LA, Roth S, David D, Hertzberg M, Mellman T, Beckham JC, Smith RD, Davison RM, Katz R, Feldman ME: Assessment of a new self-rating scale for post-traumatic stress disorder. Psychol Med 1997; 27:153–160 [G]
27. Weathers FW, Keane TM, Davidson JR: Clinician-Administered PTSD Scale: a review of the first ten years of research. Depress Anxiety 2001; 13:132–156 [E]
28. Davidson JR, Malik MA, Travers J: Structured Interview for PTSD (SIP): psychometric validation for DSM-IV criteria. Depress Anxiety 1997; 5:127–129 [G]
29. American Psychiatric Association: Practice Guideline for Psychiatric Evaluation of Adults, 2nd ed. Am J Psychiatry (in press) [G]
30. Connor KM, Butterfield MI: Posttraumatic stress disorder. Focus 2003; 1:247–262 [F]
31. Scurfield RM, Blank AS: A guide to obtaining a military history from Viet Nam veterans, in The Trauma of War: Stress and Recovery in Viet Nam Veterans. Edited by Sonnenberg SM, Blank AS Jr, Talbott JA. Washington, DC, American Psychiatric Press, 1985, pp 263–291 [G]
32. Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Foa EB, Kessler RC, McFarlane AC, Shalev AY: Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry 2000; 61(suppl 5):60–66 [G]
33. Breslau N, Chilcoat HD, Kessler RC, Davis GC: Previous exposure to trauma and PTSD effects of subsequent trauma: results from the Detroit Area Survey of Trauma. Am J Psychiatry 1999; 156:902–907 [G]
34. Ursano RJ, Fullerton CS, Epstein RS, Crowley B, Kao TC, Vance K, Craig KJ, Dougall AL, Baum A: Acute and chronic posttraumatic stress disorder in motor vehicle accident victims. Am J Psychiatry 1999; 156:589–595 [C]
35. Devilly GJ, Spence SH: The relative efficacy and treatment distress of EMDR and a cognitive-behavior trauma treatment protocol in the amelioration of posttraumatic stress disorder. J Anxiety Disord 1999; 13:131–157 [A–]
36. Strasburger LH, Gutheil TG, Brodsky A: On wearing two hats: role conflict in serving as both psychotherapist and expert witness. Am J Psychiatry 1997; 154:448–456 [G]
37. Gutheil TG, Hilliard JT: The treating psychiatrist thrust into the role of expert witness. Psychiatr Serv 2001; 52:1526–1527 [G]
38. Vallabhajosula B, van Gorp WG: Post-Daubert admissibility of scientific evidence on malingering of cognitive deficits. J Am Acad Psychiatry Law 2001; 29:207–215 [F]
39. Beckham JC, Lytle BL, Vrana SR, Hertzberg MA, Feldman ME, Shipley RH: Smoking withdrawal symptoms in response to a trauma-related stressor among Vietnam combat veterans with posttraumatic stress disorder. Addict Behav 1996; 21:93–101 [B]
40. Beckham JC: Smoking and anxiety in combat veterans with chronic posttraumatic stress disorder: a review. J Psychoactive Drugs 1999; 31:103–110 [F]
41. Silverman JJ, Peed SF, Goldberg S, Hamer RM, Stockman SJ: Surgical staff recognition of psychopathology in trauma patients. J Trauma 1985; 25:544–546 [C]
42. Whetsell LA, Patterson CM, Young DH, Schiller WR: Preinjury psychopathology in trauma patients. J Trauma 1989; 29:1158–1161 [C]
43. Cerda G, Zatzick D, Wise M, Greenhalgh D: Computerized registry recording of psychiatric disorders of pediatric patients with burns. J Burn Care Rehabil 2000; 21:368–370 [C]

44. Zatzick DF, Kang SM, Kim SY, Leigh P, Kravitz R, Drake C, Sue S, Wisner D: Patients with recognized psychiatric disorders in trauma surgery: incidence, inpatient length of stay, and cost. J Trauma 2000; 49:487–495 [C]
45. Coverdale JH, Turbott SH: Sexual and physical abuse of chronically ill psychiatric outpatients compared with a matched sample of medical outpatients. J Nerv Ment Dis 2000; 188:440–445 [D]
46. Goodman LA, Rosenberg SD, Mueser KT, Drake RE: Physical and sexual assault history in women with serious mental illness: prevalence, correlates, treatment, and future research directions. Schizophr Bull 1997; 23:685–696 [F]
47. Mueser KT, Goodman LB, Trumbetta SL, Rosenberg SD, Osher C, Vidaver R, Auciello P, Foy DW: Trauma and posttraumatic stress disorder in severe mental illness. J Consult Clin Psychol 1998; 66:493–499 [G]
48. Neria Y, Bromet EJ, Sievers S, Lavelle J, Fochtmann LJ: Trauma exposure and posttraumatic stress disorder in psychosis: findings from a first-admission cohort. J Consult Clin Psychol 2002; 70:246–251 [G]
49. Switzer GE, Dew MA, Thompson K, Goycoolea JM, Derricott T, Mullins SD: Posttraumatic stress disorder and service utilization among urban mental health center clients. J Trauma Stress 1999; 12:25–39 [G]
50. Rose SM, Peabody CG, Stratigeas B: Undetected abuse among intensive case management clients. Hosp Community Psychiatry 1991; 42:499–503 [D]
51. Mueser KT, Salyers MP, Rosenberg SD, Goodman LA, Essock SM, Osher FC, Swartz MS, Butterfield MI, 5 Site Health and Risk Study Research Committee: Interpersonal trauma and posttraumatic stress disorder in patients with severe mental illness: demographic, clinical, and health correlates. Schizophr Bull 2004; 30:45–57 [D]
52. Famularo R, Kinscherff R, Fenton T: Posttraumatic stress disorder among children clinically diagnosed as borderline personality disorder. J Nerv Ment Dis 1991; 179:428–431 [G]
53. Goldman SJ, D'Angelo EJ, DeMaso DR, Mezzacappa E: Physical and sexual abuse histories among children with borderline personality disorder. Am J Psychiatry 1992; 149:1723–1726 [D]
54. Yen S, Shea MT, Battle CL, Johnson DM, Zlotnick C, Dolan-Sewell R, Skodol AE, Grilo CM, Gunderson JG, Sanislow CA, Zanarini MC, Bender DS, Rettew JB, McGlashan TH: Traumatic exposure and posttraumatic stress disorder in borderline, schizotypal, avoidant, and obsessive-compulsive personality disorders: findings from the collaborative longitudinal personality disorders study. J Nerv Ment Dis 2002; 190:510–518 [G]
55. Bonin MF, Norton GR, Asmundson GJ, Dicurzio S, Pidlubney S: Drinking away the hurt: the nature and prevalence of PTSD in substance abuse patients attending a community-based treatment program. J Behav Ther Exp Psychiatry 2000; 31:55–66 [G]
56. Epstein JN, Saunders BE, Kilpatrick DG, Resnick HS: PTSD as a mediator between childhood rape and alcohol use in adult women. Child Abuse Negl 1998; 22:223–234 [G]
57. Duncan RD, Saunders BE, Kilpatrick DG, Hanson RF, Resnick HS: Childhood physical assault as a risk factor for PTSD, depression, and substance abuse: findings from a national survey. Am J Orthopsychiatry 1996; 66:437–448 [D]
58. Brady KT, Wohlreich M: Victimization, PTSD, and substance abuse. Women's Psychiatric Health 1994; 3:12–14 [D]
59. deGroot JM, Kennedy S, Rodin G, McVey G: Correlates of sexual abuse in women with anorexia nervosa and bulimia nervosa. Can J Psychiatry 1992; 37:516–518 [G]
60. McFarlane AC, McFarlane CM, Gilchrist PN: Posttraumatic bulimia and anorexia nervosa. Int J Eat Disord 1988; 7:705–708 [G]
61. Herzog DB, Staley JE, Carmody S, Robbins WM, van der Kolk BA: Childhood sexual abuse in anorexia nervosa and bulimia nervosa: a pilot study. J Am Acad Child Adolesc Psychiatry 1993; 32:962–966 [G]

62. Zisook S, Chentsova-Dutton Y, Shuchter SR: PTSD following bereavement. Ann Clin Psychiatry 1998; 10:157–163 [B]
63. Dobie DJ, Kivlahan DR, Maynard C, Bush KR, Davis TM, Bradley KA: Posttraumatic stress disorder in female veterans: association with self-reported health problems and functional impairment. Arch Intern Med 2004; 164:394–400 [G]
64. American Psychiatric Association: Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors. Am J Psychiatry 2003; 160(Nov suppl) [G]
65. Morgan HG, Burns-Cox CJ, Pocock H, Pottle S: Deliberate self-harm: clinical and socio-economic characteristics of 368 patients. Br J Psychiatry 1975; 127:564–574 [G]
66. Pattison EM, Kahan J: The deliberate self-harm syndrome. Am J Psychiatry 1983; 140:867–872 [G]
67. Anderson PL, Tiro JA, Price AW, Bender MA, Kaslow NJ: Additive impact of childhood emotional, physical, and sexual abuse on suicide attempts among low-income African American women. Suicide Life Threat Behav 2002; 32:131–138 [G]
68. Windle M, Windle RC, Scheidt DM, Miller GB: Physical and sexual abuse and associated mental disorders among alcoholic inpatients. Am J Psychiatry 1995; 152:1322–1328 [D]
69. Friedman MJ: Post Traumatic Stress Disorder: The Latest Assessment and Treatment Strategies. Kansas City, Mo, Compact Clinicals, 2000 [G]
70. Wilson JP, Friedman MJ, Lindy JD (eds): Treating Psychological Trauma and PTSD. New York, Guilford, 2001 [G]
71. Williams MB, Sommer JF Jr: Handbook of Post-Traumatic Therapy. Westport, Conn, Greenwood Press, 1994 [G]
72. Rosenheck R, Fontana A: Impact of efforts to reduce inpatient costs on clinical effectiveness: treatment of posttraumatic stress disorder in the Department of Veterans Affairs. Med Care 2001; 39:168–180 [D]
73. Roy-Byrne P, Berliner L, Russo J, Zatzick D, Pitman RK: Treatment preferences and determinants in victims of sexual and physical assault. J Nerv Ment Dis 2003; 191:161–165 [G]
74. Weisaeth L: The stressors and the post-traumatic stress syndrome after an industrial disaster. Acta Psychiatr Scand Suppl 1989; 355:25–37 [D]
75. Wilson JP, Lindy JD (eds): Countertransference in the Treatment of PTSD. New York, Guilford, 1994 [G]
76. Kimerling R, Calhoun KS: Somatic symptoms, social support, and treatment seeking among sexual assault victims. J Consult Clin Psychol 1994; 62:333–340 [C]
77. McFarlane AC, Atchison M, Rafalowicz E, Papay P: Physical symptoms in post-traumatic stress disorder. J Psychosom Res 1994; 38:715–726 [C]
78. Andreski P, Chilcoat H, Breslau N: Post-traumatic stress disorder and somatization symptoms: a prospective study. Psychiatry Res 1998; 79:131–138 [C]
79. Engel CC Jr, Liu X, McCarthy BD, Miller RF, Ursano R: Relationship of physical symptoms to posttraumatic stress disorder among veterans seeking care for Gulf War-related health concerns. Psychosom Med 2000; 62:739–745 [D]
80. Ghahramanlou M, Boradbeck C: Predictors of secondary trauma in sexual assault counselors. Int J Emerg Ment Health 2000; 4:229–240 [D]
81. Figley C (ed): Compassion Fatigue: Coping With Secondary Traumatic Stress Disorders in Those Who Treat the Traumatized. New York, Brunner-Routledge, 1995 [G]
82. Lin EH, Von Korff M, Katon W, Bush T, Simon GE, Walker E, Robinson P: The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 1995; 33:67–74 [B]
83. Zygmunt A, Olfson M, Boyer CA, Mechanic D: Interventions to improve medication adherence in schizophrenia. Am J Psychiatry 2002; 159:1653–1664 [E]

84. Phillips SD, Burns BJ, Edgar ER, Mueser KT, Linkins KW, Rosenheck RA, Drake RE, McDonel Herr EC: Moving assertive community treatment into standard practice. Psychiatr Serv 2001; 52:771–779 [F]
85. Marshall M, Lockwood A: Assertive community treatment for people with severe mental disorders. Cochrane Database Syst Rev 2000; (2):CD001089 [E]
86. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Schizophrenia, Second Edition. Am J Psychiatry 2004; 161(Feb suppl) [G]
87. Galea S, Resnick H, Ahern J, Gold J, Bucuvalas M, Kilpatrick D, Stuber J, Vlahov D: Posttraumatic stress disorder in Manhattan, New York City, after the September 11th terrorist attacks. J Urban Health 2002; 79:340–353 [D]
88. Glantz MD, Sloboda Z: Analysis and reconceptualization of resilience, in Resilience and Development: Positive Life Adaptations. Edited by Glantz MD, Johnson JL. New York, Kluwer Academic/Plenum, 1999, pp 109–126 [G]
89. Kaplan HB: Toward an understanding of resilience: a critical review of definitions and models, in Resilience and Development: Positive Life Adaptations. Edited by Glantz MD, Johnson JL. New York, Kluwer Academic/Plenum, 1999, pp 17–84 [F]
90. Barnes DH, Bell CC: Paradoxes of black suicide. Preventing Suicide: The National Journal 2003; 2:2–4 [F]
91. Beck AT, Weissman A, Kovacs M: Alcoholism, hopelessness and suicidal behavior. J Stud Alcohol 1976; 37:66–77 [D]
92. Linehan MM, Goodstein JL, Nielsen SL, Chiles JA: Reasons for staying alive when you are thinking of killing yourself: the reasons for living inventory. J Consult Clin Psychol 1983; 51:276–286 [F]
93. Range LM, Penton SR: Hope, hopelessness, and suicidality in college students. Psychol Rep 1994; 75:456–458 [G]
94. Scheier M, Carver C: Effects of optimism on psychological and physical well-being: theoretical overview and empirical update. Cognitive Therapy and Research 1992; 16:201–228 [F]
95. Taylor SE, Kemeny ME, Reed GM, Bower JE, Gruenewald TL: Psychological resources, positive illusions, and health. Am Psychol 2000; 55:99–109 [G]
96. Werner EE: Vulnerable but invincible: high risk children from birth to adulthood. Eur Child Adolesc Psychiatry 1996; 5(suppl 1):47–51 [G]
97. Wyman PA, Cowen EL, Work WC, Kerley JH: The role of children's future expectations in self-esteem functioning and adjustment to life stress: a prospective study of urban at-risk children. Dev Psychopathol 1993; 5:649–661 [C]
98. Antoni MH, Lehman JM, Kilbourn KM, Boyers AE, Culver JL, Alferi SM, Yount SE, McGregor BA, Arena PL, Harris SD, Price AA, Carver CS: Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. Health Psychol 2001; 20:20–32 [D]
99. Brissette I, Scheier MF, Carver CS: The role of optimism in social network development, coping, and psychological adjustment during a life transition. J Pers Soc Psychol 2002; 82:102–111 [C]
100. Jaycox LH, Reivich KJ, Gillham J, Seligman ME: Prevention of depressive symptoms in school children. Behav Res Ther 1994; 32:801–816 [B]
101. Gillham JE, Reivich KJ, Jaycox LH, Seligman MEP: Prevention of depressive symptoms in school children: two-year follow-up. Psychol Sci 1995; 6:343–351 [A–]
102. Chemtob CM, Nakashima JP, Hamada RS: Psychosocial intervention for postdisaster trauma symptoms in elementary school children: a controlled community field study. Arch Pediatr Adolesc Med 2002; 156:211–216 [A]

103. Friedman M, Schnurr PP: The relationship between trauma, post-traumatic stress disorder and physical health, in Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder. Edited by Friedman M, Charney DS, Deutch AY. Philadelphia, Lippincott-Raven, 1995, pp 507–524 [G]
104. Breslau N, Davis GC, Peterson EL, Schultz L: Psychiatric sequelae of posttraumatic stress disorder in women. Arch Gen Psychiatry 1997; 54:81–87 [D]
105. McCarroll JE, Ursano RJ, Fullerton CS, Liu X, Lundy A: Somatic symptoms in Gulf War mortuary workers. Psychosom Med 2002; 64:29–33 [G]
106. Schnurr PP, Friedman MJ, Sengupta A, Jankowski MK, Holmes T: PTSD and utilization of medical treatment services among male Vietnam veterans. J Nerv Ment Dis 2000; 188:496–504 [D]
107. Benedikt RA, Kolb LC: Preliminary findings on chronic pain and posttraumatic stress disorder. Am J Psychiatry 1986; 143:908–910 [G]
108. Geisser ME, Roth RS, Bachman JE, Eckert TA: The relationship between symptoms of post-traumatic stress disorder and pain, affective disturbance and disability among patients with accident and non-accident related pain. Pain 1996; 66:207–214 [D]
109. Pecukonis EV: Childhood sex abuse in women with chronic intractable back pain. Soc Work Health Care 1996; 23:1–16 [C]
110. Badura AS, Reiter RC, Altmaier EM, Rhomberg A, Elas D: Dissociation, somatization, substance abuse, and coping in women with chronic pelvic pain. Obstet Gynecol 1997; 90:405–410 [G]
111. Drossman DA: Sexual and physical abuse and gastrointestinal illness. Scand J Gastroenterol Suppl 1995; 208:90–96 [G]
112. Plichta SB, Abraham C: Violence and gynecologic health in women <50 years old. Am J Obstet Gynecol 1996; 174:903–907 [G]
113. Walling MK, O'Hara MW, Reiter RC, Milburn AK, Lilly G, Vincent SD: Abuse history and chronic pain in women, II: a multivariate analysis of abuse and psychological morbidity. Obstet Gynecol 1994; 84:200–206 [D]
114. Walker EA, Gelfand AN, Gelfand MD, Green C, Katon WJ: Chronic pelvic pain and gynecological symptoms in women with irritable bowel syndrome. J Psychosom Obstet Gynaecol 1996; 17:39–46 [G]
115. Amaya-Jackson L, Davidson JR, Hughes DC, Swartz M, Reynolds V, George LK, Blazer DG: Functional impairment and utilization of services associated with posttraumatic stress in the community. J Trauma Stress 1999; 12:709–724 [C]
116. Booth BM, Blow FC, Cook CA: Functional impairment and co-occurring psychiatric disorders in medically hospitalized men. Arch Intern Med 1998; 158:1551–1559 [D]
117. Holbrook TL, Anderson JP, Sieber WJ, Browner D, Hoyt DB: Outcome after major trauma: 12-month and 18-month follow-up results from the Trauma Recovery Project. J Trauma 1999; 46:765–771 [C]
118. Holbrook TL, Hoyt DB, Stein MB, Sieber WJ: Perceived threat to life predicts posttraumatic stress disorder after major trauma: risk factors and functional outcome. J Trauma 2001; 51:287–292 [G]
119. Mollica RF, Donelan K, Tor S, Lavelle J, Elias C, Frankel M, Blendon RJ: The effect of trauma and confinement on functional health and mental health status of Cambodians living in Thailand-Cambodia border camps. JAMA 1993; 270:581–586 [G]
120. Momartin S, Silove D, Manicavasagar V, Steel Z: Dimensions of trauma associated with posttraumatic stress disorder (PTSD) caseness, severity and functional impairment: a study of Bosnian refugees resettled in Australia. Soc Sci Med 2003; 57:775–781 [G]
121. Schnurr PP, Ford JD, Friedman MJ, Green BL, Dain BJ, Sengupta A: Predictors and outcomes of posttraumatic stress disorder in World War II veterans exposed to mustard gas. J Consult Clin Psychol 2000; 68:258–268 [G]

122. Zatzick DF, Marmar CR, Weiss DS, Browner WS, Metzler TJ, Golding JM, Stewart A, Schlenger WE, Wells KB: Posttraumatic stress disorder and functioning and quality of life outcomes in a nationally representative sample of male Vietnam veterans. Am J Psychiatry 1997; 154:1690–1695 [C]
123. Davidson J, Pearlstein T, Londborg P, Brady KT, Rothbaum B, Bell J, Maddock R, Hegel MT, Farfel G: Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. Am J Psychiatry 2001; 158:1974–1981 [A]
124. Kudler HS, Blank AS, Krupnick JL: The psychodynamic treatment of PTSD, in Effective Treatments for PTSD: Practice Guidelines From the International Society for Traumatic Stress Studies. Edited by Foa EB, Keane TM, Friedman MJ. New York, Guilford, 2000, pp 176–198 [F]
125. Harvey AG, Bryant RA, Tarrier N: Cognitive behaviour therapy for posttraumatic stress disorder. Clin Psychol Rev 2003; 23:501–522 [F]
126. Plichta S: Violence and abuse, in Women's Health: The Commonwealth Fund Survey. Edited by Falik M, Collins KS. Baltimore, Johns Hopkins University Press, 1996, pp 237–270 [D]
127. Holloway HC, Ursano RJ: The Vietnam veteran: memory, social context, and metaphor. Psychiatry 1984; 47:103–108 [G]
128. Wessely S, Bisson J, Rose S: A systematic review of brief psychological interventions ("debriefing") for the treatment of immediate trauma related symptoms and the prevention of posttraumatic stress disorder, in The Cochrane Library 1998, issue 3. Oxford, UK, Update Software (http://www.update-software.com/cochrane) [E]
129. van Emmerik AA, Kamphuis JH, Hulsbosch AM, Emmelkamp PM: Single session debriefing after psychological trauma: a meta-analysis. Lancet 2002; 360:766–771 [E]
130. Litz BT, Gray M: Early intervention for trauma in adults, in Early Intervention for Trauma and Traumatic Loss. Edited by Litz BT. New York, Guilford, 2004, pp 87–111 [G]
131. Zatzick D, Roy-Byrne P, Russo J, Rivara F, Droesh R, Wagner A, Dunn C, Jurkovich G, Uehara E, Katon W: A randomized effectiveness trial of stepped collaborative care for acutely injured trauma survivors. Arch Gen Psychiatry 2004; 61:498–506 [A–]
132. Bordow S, Porritt D: An experimental evaluation of crisis intervention. Soc Sci Med 1979; 13A:251–256 [B]
133. Gidron Y, Gal R, Freedman S, Twiser I, Lauden A, Snir Y, Benjamin J: Translating research findings to PTSD prevention: results of a randomized-controlled pilot study. J Trauma Stress 2001; 14:773–780 [A–]
134. Zatzick DF, Roy-Byrne P, Russo JE, Rivara FP, Koike A, Jurkovich GJ, Katon W: Collaborative interventions for physically injured trauma survivors: a pilot randomized effectiveness trial. Gen Hosp Psychiatry 2001; 23:114–123 [A–]
135. Bryant RA, Sackville T, Dang ST, Moulds M, Guthrie R: Treating acute stress disorder: an evaluation of cognitive behavior therapy and supportive counseling techniques. Am J Psychiatry 1999; 156:1780–1786 [A]
136. Bryant RA, Harvey AG, Dang ST, Sackville T, Basten C: Treatment of acute stress disorder: a comparison of cognitive-behavioral therapy and supportive counseling. J Consult Clin Psychol 1998; 66:862–866 [B]
137. Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, Cahill L, Orr SP: Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry 2002; 51:189–192 [A]
138. Rehm LP: How can we better disentangle placebo and drug effects? Commentary on The emperor's new drugs: an analysis of antidepressant medication data submitted to the US Food and Drug Administration. Prevention & Treatment 2002, volume 5. Washington, DC, American Psychological Association (http://journals.apa.org/prevention/volume5/pre0050031c.html) [G]

139. Rothbaum B, Foa E: Subtypes of posttraumatic stress disorder and duration of symptoms, in Posttraumatic Stress Disorder: DSM-IV and Beyond. Edited by Davidson J, Foa E. Washington, DC, American Psychiatric Press, 1994, pp 23–35 [F]
140. Blanchard EB, Hickling EJ: Acute stress disorder among MVA survivors, in After the Crash: Assessment and Treatment of Motor Vehicle Accident Survivors. Washington, DC, American Psychological Association, 1997, pp 187–196 [G]
141. Marshall RD, Beebe KL, Oldham M, Zaninelli R: Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry 2001; 158:1982–1988 [A]
142. Connor KM, Sutherland SM, Tupler LA, Malik ML, Davidson JR: Fluoxetine in post-traumatic stress disorder: randomised, double-blind study. Br J Psychiatry 1999; 175:17–22 [A]
143. van der Kolk BA, Dreyfuss D, Michaels M, Shera D, Berkowitz R, Fisler R, Saxe G: Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry 1994; 55:517–522 [A]
144. Brady K, Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR, Farfel GM: Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA 2000; 283:1837–1844 [A]
145. Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts CD: Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001; 62:860–868 [A]
146. Martenyi F, Brown EB, Zhang H, Prakash A, Koke SC: Fluoxetine versus placebo in posttraumatic stress disorder. J Clin Psychiatry 2002; 63:199–206 [A]
147. Neylan TC, Metzler TJ, Schoenfeld FB, Weiss DS, Lenoci M, Best SR, Lipsey TL, Marmar CR: Fluvoxamine and sleep disturbances in posttraumatic stress disorder. J Trauma Stress 2001; 14:461–467 [B]
148. Rapaport MH, Endicott J, Clary CM: Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. J Clin Psychiatry 2002; 63:59–65 [A]
149. Davidson JR, Landerman LR, Farfel GM, Clary CM: Characterizing the effects of sertraline in post-traumatic stress disorder. Psychol Med 2002; 32:661–670 [A]
150. Marmar CR, Schoenfeld F, Weiss DS, Metzler T, Zatzick D, Wu R, Smiga S, Tecott L, Neylan T: Open trial of fluvoxamine treatment for combat-related posttraumatic stress disorder. J Clin Psychiatry 1996; 57(suppl 8):66–70 [B]
151. Kosten TR, Frank JB, Dan E, McDougle CJ, Giller EL Jr: Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. J Nerv Ment Dis 1991; 179:366–370 [G]
152. Davidson J, Kudler H, Smith R, Mahorney SL, Lipper S, Hammett E, Saunders WB, Cavenar JO Jr: Treatment of posttraumatic stress disorder with amitriptyline and placebo. Arch Gen Psychiatry 1990; 47:259–266 [A]
153. Reist C, Kauffmann CD, Haier RJ, Sangdahl C, DeMet EM, Chicz-DeMet A, Nelson JN: A controlled trial of desipramine in 18 men with posttraumatic stress disorder. Am J Psychiatry 1989; 146:513–516 [A]
154. Katz RJ, Lott MH, Arbus P, Crocq L, Herlobsen P, Lingjaerde O, Lopez G, Loughrey GC, MacFarlane DJ, McIvor R, Mehlum L, Nugent D, Turner SW, Waisaeth L, Yule W: Pharmacotherapy of post-traumatic stress disorder with a novel psychotropic. Anxiety 1994–1995; 1:169–174 [G]
155. Baker DG, Diamond BI, Gillette GM, Hamner MB, Katzelnick D, Keller TW, Mellman TA, Pontius EB, Rosenthal M, Tucker P, van der Kolk BA, Katz RJ: A double-blind, randomized, placebo-controlled, multi-center study of brofaromine in the treatment of post-traumatic stress disorder. Psychopharmacology (Berl) 1995; 122:386–389 [A]
156. Mellman TA, Bustamante V, David D, Fins AI: Hypnotic medication in the aftermath of trauma. J Clin Psychiatry 2002; 63:1183–1184 [G]
157. Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY: Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiatry 1996; 57:390–394 [B]

158. Risse SC, Whitters A, Burke J, Chen S, Scurfield RM, Raskind MA: Severe withdrawal symptoms after discontinuation of alprazolam in eight patients with combat-induced posttraumatic stress disorder. J Clin Psychiatry 1990; 51:206–209 [B]
159. Kosten TR, Fontana A, Sernyak MJ, Rosenheck R: Benzodiazepine use in posttraumatic stress disorder among veterans with substance abuse. J Nerv Ment Dis 2000; 188:454–459 [C]
160. Lipper S, Davidson JR, Grady TA, Edinger JD, Hammett EB, Mahorney SL, Cavenar JO Jr: Preliminary study of carbamazepine in post-traumatic stress disorder. Psychosomatics 1986; 27:849–854 [B]
161. Clark RD, Canive JM, Calais LA, Qualls CR, Tuason VB: Divalproex in posttraumatic stress disorder: an open-label clinical trial. J Trauma Stress 1999; 12:395–401 [B]
162. Fesler FA: Valproate in combat-related posttraumatic stress disorder. J Clin Psychiatry 1991; 52:361–364 [B]
163. Hertzberg MA, Butterfield MI, Feldman ME, Beckham JC, Sutherland SM, Connor KM, Davidson JR: A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. Biol Psychiatry 1999; 45:1226–1229 [A]
164. Butterfield MI, Becker ME, Connor KM, Sutherland S, Churchill LE, Davidson JR: Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. Int Clin Psychopharmacol 2001; 16:197–203 [A]
165. Petty F, Brannan S, Casada J, Davis LL, Gajewski V, Kramer GL, Stone RC, Teten AL, Worchel J, Young KA: Olanzapine treatment for post-traumatic stress disorder: an open-label study. Int Clin Psychopharmacol 2001; 16:331–337 [B]
166. Stein MB, Kline NA, Matloff JL: Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry 2002; 159:1777–1779 [A]
167. Hamner MB, Deitsch SE, Brodrick PS, Ulmer HG, Lorberbaum JP: Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. J Clin Psychopharmacol 2003; 23:15–20 [B]
168. Hamner MB, Faldowski RA, Ulmer HG, Frueh BC, Huber MG, Arana GW: Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. Int Clin Psychopharmacol 2003; 18:1–8 [A]
169. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas RG, McFall MM: Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003; 160:371–373 [A]
170. Kinzie JD, Leung P: Clonidine in Cambodian patients with posttraumatic stress disorder. J Nerv Ment Dis 1989; 177:546–550 [B]
171. Faustman WO, White PA: Diagnostic and psychopharmacological treatment characteristics of 536 inpatients with posttraumatic stress disorder. J Nerv Ment Dis 1989; 177:154–159 [D]
172. Vaiva G, Ducrocq F, Jezequel K, Averland B, Lestavel P, Brunet A, Marmar CR: Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol Psychiatry 2003; 54:947–949 [B]
173. Foa EB, Rothbaum BO: Treating the Trauma of Rape: Cognitive-Behavioral Therapy for PTSD. New York, Guilford, 1997 [G]
174. Keane TM, Gerarali RJ, Quinn SJ, Litz BT: Behavioral treatment of posttraumatic stress disorder, in Handbook of Clinical Behavior Therapy, 2nd ed. Edited by Turner SM, Calhoun KS, Adams HE. New York, Wiley, 1992, pp 87–97 [G]
175. Bryant RA, Moulds ML, Nixon RV: Cognitive behaviour therapy of acute stress disorder: a four-year follow-up. Behav Res Ther 2003; 41:489–494 [A]
176. Solomon SD, Johnson DM: Psychosocial treatment of posttraumatic stress disorder: a practice-friendly review of outcome research. J Clin Psychol 2002; 58:947–959 [F]

177. Marks I, Lovell K, Noshirvani H, Livanou M, Thrasher S: Treatment of posttraumatic stress disorder by exposure and/or cognitive restructuring: a controlled study. Arch Gen Psychiatry 1998; 55:317–325 [A]
178. Tarrier N, Pilgrim H, Sommerfield C, Faragher B, Reynolds M, Graham E, Barrowclough C: A randomized trial of cognitive therapy and imaginal exposure in the treatment of chronic posttraumatic stress disorder. J Consult Clin Psychol 1999; 67:13–18 [A]
179. Hembree EA, Foa EB: Posttraumatic stress disorder: psychological factors and psychosocial interventions. J Clin Psychiatry 2000; 61(suppl 7):33–39 [F]
180. Resick PA, Jordan CG, Girelli SA, Hutter CK, Marhoefer-Dvorak S: A comparative victim study of behavioral group therapy for sexual assault victims. Behav Ther 1988; 19:385–401 [B]
181. Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA: A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. J Consult Clin Psychol 2002; 70:867–879 [A–]
182. Foa EB: Trauma and women: course, predictors, and treatment. J Clin Psychiatry 1997; 58(suppl 9):25–28 [E]
183. Foy DW, Ruzek JI, Glynn SM, Riney SA, Gusman FD: Trauma focus group therapy for combat-related PTSD. Psychotherapy in Practice 1996; 3(4):59–73 [G]
184. Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, Tandberg D, Lauriello J, McBride L, Cutchen L, Cheng D, Emmons S, Germain A, Melendrez D, Sandoval D, Prince H: Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. JAMA 2001; 286:537–545 [A–]
185. Forbes D, Phelps A, McHugh T: Treatment of combat-related nightmares using imagery rehearsal: a pilot study. J Trauma Stress 2001; 14:433–442 [B]
186. Tarrier N, Sommerfield C, Pilgrim H, Faragher B: Factors associated with outcome of cognitive-behavioural treatment of chronic post-traumatic stress disorder. Behav Res Ther 2000; 38:191–202 [A]
187. Tarrier N, Sommerfield C, Pilgrim H, Humphreys L: Cognitive therapy or imaginal exposure in the treatment of post-traumatic stress disorder: twelve-month follow-up. Br J Psychiatry 1999; 175:571–575 [A]
188. Resick PA, Schnicke MK: Cognitive processing therapy for sexual assault victims. J Consult Clin Psychol 1992; 60:748–756 [A–]
189. PTSD Treatment Guidelines Task Force: Guidelines for treatment of PTSD: eye movement desensitization and reprocessing. J Trauma Stress 2000; 13:539–588 [E]
190. Foa EB, Meadows EA: Psychosocial treatments for posttraumatic stress disorder: a critical review. Annu Rev Psychol 1997; 48:449–480 [F]
191. Shepherd J, Stein K, Milne R: Eye movement desensitization and reprocessing in the treatment of post-traumatic stress disorder: a review of an emerging therapy. Psychol Med 2000; 30:863–871 [F]
192. Van Etten M, Taylor S: Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. Clinical Psychology and Psychotherapy 1998; 5:126–144 [E]
193. Maxfield L, Hyer L: The relationship between efficacy and methodology in studies investigating EMDR treatment of PTSD. J Clin Psychol 2002; 58:23–41 [E]
194. Davidson PR, Parker KC: Eye movement desensitization and reprocessing (EMDR): a meta-analysis. J Consult Clin Psychol 2001; 69:305–316 [E]
195. Hembree EA, Foa EB, Dorfan NM, Street GP, Kowalski J, Tu X: Do patients drop out prematurely from exposure therapy for PTSD? J Trauma Stress 2003; 16:555–562 [F]
196. Herbert JD, Lilienfeld SO, Lohr JM, Montgomery RW, O'Donohue WT, Rosen GM, Tolin DF: Science and pseudoscience in the development of eye movement desensitization and reprocessing: implications for clinical psychology. Clin Psychol Rev 2000; 20:945–971 [F]

197. Lipke H: Comment on Hembree and Foa (2003) and EMDR. J Trauma Stress 2003; 16:573–574 [G]
198. Kardiner A: The Traumatic Neurosis of War. New York, Hoeber, 1941 [G]
199. Grinker RR Sr, Spiegel JP: Men Under Stress. Philadelphia, Blakiston, 1945 [G]
200. Grinker RR Sr, Spiegel JP: A psychodynamic view of character pathology in Vietnam combat veterans. Bull Menninger Clin 1983; 47:472–474 [G]
201. Brom D, Kleber RJ, Defares PB: Brief psychotherapy for posttraumatic stress disorders. J Consult Clin Psychol 1989; 57:607–612 [B]
202. Regarding Hypnosis: Position Statement [APA Document Reference No. 610001]. Washington, DC, American Psychiatric Association, Feb 1961. http://www.psych.org/edu/other_res/lib_archives/archives/610001.pdf [G]
203. Sherman JJ: Effects of psychotherapeutic treatments for PTSD: a meta-analysis of controlled clinical trials. J Trauma Stress 1998; 11:413–435 [E]
204. Freud A: Comments on trauma, in Psychic Trauma. Edited by Furst SS. New York, Basic Books, 1967, pp 235–245 [G]
205. Weiss J, Sampson H, Mount Zion Psychotherapy Research Group: The Psychoanalytic Process: Theory, Clinical Observations, and Empirical Research. New York, Guilford, 1986 [E]
206. Modlin HC: The trauma in "traumatic neurosis." Bull Menninger Clin 1960; 24:49–56 [F]
207. Shaw JA: Unmasking the illusion of safety: psychic trauma in war. Bull Menninger Clin 1987; 51:49–63 [F]
208. Lindy JD, Green BL, Grace M, Titchener J: Psychotherapy with survivors of the Beverly Hills Supper Club fire. Am J Psychother 1983; 37:593–610 [D]
209. Marmar CR: Brief dynamic psychotherapy of post-traumatic stress disorder. Psychiatr Ann 1991; 21:405–414 [F]
210. Gabbard GO: Psychodynamic Psychiatry in Clinical Practice, 3rd ed. Washington, DC, American Psychiatric Press, 2000 [G]
211. Ursano RJ, Silberman EK: Psychoanalysis, psychoanalytic psychotherapy, and supportive psychotherapy, in The American Psychiatric Publishing Textbook of Clinical Psychiatry, 4th ed. Edited by Hales RE, Yudofsky SC. Arlington, VA, American Psychiatric Publishing, 2003, pp 1177–1203 [F]
212. Chertoff J: Psychodynamic assessment and treatment of traumatized patients. J Psychother Pract Res 1997; 7:35–46 [F]
213. Conlon L, Fahy TJ, Conroy R: PTSD in ambulant RTA victims: a randomized controlled trial of debriefing. J Psychosom Res 1999; 46:37–44 [A]
214. Lee C, Slade P, Lygo V: The influence of psychological debriefing on emotional adaptation in women following early miscarriage: a preliminary study. Br J Med Psychol 1996; 69(pt 1): 47–58 [B]
215. Rose S, Brewin CR, Andrews B, Kirk M: A randomized controlled trial of individual psychological debriefing for victims of violent crime. Psychol Med 1999; 29:793–799 [A–]
216. Raphael B: Early interventions and the debriefing debate, in Terrorism and Disaster: Individual and Community Mental Health Interventions. Edited by Ursano RJ, Fullerton CS, Norwood AE. Cambridge, UK, Cambridge University Press, 2003, pp 146–161 [F]
217. Bisson JI, Jenkins PL, Alexander J, Bannister C: Randomised controlled trial of psychological debriefing for victims of acute burn trauma. Br J Psychiatry 1997; 171:78–81 [A–]
218. Hobbs M, Mayou R, Harrison B, Worlock P: A randomised controlled trial of psychological debriefing for victims of road traffic accidents. BMJ 1996; 313:1438–1439 [A–]
219. Mayou RA, Ehlers A, Hobbs M: Psychological debriefing for road traffic accident victims: three-year follow-up of a randomised controlled trial. Br J Psychiatry 2000; 176:589–593 [C]
220. Litz BT, Gray MJ, Bryant R, Adler AB: Early intervention for trauma: current status and future directions. Clinical Psychology: Science and Practice 2002; 9:112–134 [F]

221. Suzanna R, Jonathan B, Simon W: Psychological debriefing for preventing post traumatic stress disorder (PTSD). Cochrane Database Syst Rev 2001; (3):CD000560 [E]
222. Brewin CR, Andrews B, Valentine JD: Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J Consult Clin Psychol 2000; 68:748–766 [E]
223. Breslau N: The epidemiology of posttraumatic stress disorder: what is the extent of the problem? J Clin Psychiatry 2001; 62(suppl 17):16–22 [F]
224. Russell DE: The incidence and prevalence of intrafamilial and extrafamilial sexual abuse of female children. Child Abuse Negl 1983; 7:133–146 [G]
225. Finkelhor D, Hotaling G, Lewis IA, Smith C: Sexual abuse in a national survey of adult men and women: prevalence, characteristics, and risk factors. Child Abuse Negl 1990; 14:19–28 [D]
226. Breslau N: Gender differences in trauma and posttraumatic stress disorder. J Gend Specif Med 2002; 5:34–40 [G]
227. de Vries MW: Trauma in cultural perspective, in Traumatic Stress: The Effects of Overwhelming Experience on Mind, Body, and Society. Edited by van der Kolk BA, McFarlane AC, Weisaeth L. New York, Guilford, 1996, pp 398–413 [F]
228. Lazarus RS, Folkman S: Stress, Appraisal, and Coping. New York, Springer, 1984 [G]
229. Kluft RP, Bloom SL, Kinzie JD: Treating traumatized patients and victims of violence. New Dir Ment Health Serv 2000; 86:79–102 [F]
230. Rosenheck R, Fontana A: Utilization of mental health services by minority veterans of the Vietnam era. J Nerv Ment Dis 1994; 182:685–691 [E]
231. Lin KM, Smith MW, Ortiz V: Culture and psychopharmacology. Psychiatr Clin North Am 2001; 24:523–538 [F]
232. Cascorbi I: Pharmacogenetics of cytochrome p4502D6: genetic background and clinical implication. Eur J Clin Invest 2003; 33(suppl 2):17–22 [G]
233. Poolsup N, Li Wan Po A, Knight TL: Pharmacogenetics and psychopharmacotherapy. J Clin Pharm Ther 2000; 25:197–220 [F]
234. Bertilsson L, Dahl ML, Tybring G: Pharmacogenetics of antidepressants: clinical aspects. Acta Psychiatr Scand Suppl 1997; 391:14–21 [F]
235. Gelernter J, Kranzler H, Cubells JF: Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. Hum Genet 1997; 101:243–246 [G]
236. Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, Kuhn CM, Lewis JG, Schanberg SM, Stafford-Smith M, Suarez EC, Clary GL, Svenson IK, Siegler IC: Serotonin-related gene polymorphisms and central nervous system serotonin function. Neuropsychopharmacology 2003; 28:533–541 [G]
237. Salmon P, Calderbank S: The relationship of childhood physical and sexual abuse to adult illness behavior. J Psychosom Res 1996; 40:329–336 [G]
238. Fukudo S, Nomura T, Muranaka M, Taguchi F: Brain-gut response to stress and cholinergic stimulation in irritable bowel syndrome: a preliminary study. J Clin Gastroenterol 1993; 17:133–141 [A–]
239. Irwin C, Falsetti SA, Lydiard RB, Ballenger JC, Brock CD, Brener W: Comorbidity of posttraumatic stress disorder and irritable bowel syndrome. J Clin Psychiatry 1996; 57:576–578 [G]
240. Leserman J, Drossman DA, Li Z, Toomey TC, Nachman G, Glogau L: Sexual and physical abuse history in gastroenterology practice: how types of abuse impact health status. Psychosom Med 1996; 58:4–15 [F]
241. Walker EA, Katon WJ, Hansom J, Harrop-Griffiths J, Holm L, Jones ML, Hickok L, Jemelka RP: Medical and psychiatric symptoms in women with childhood sexual abuse. Psychosom Med 1992; 54:658–664 [E]

242. Davidson JR, Hughes D, Blazer DG, George LK: Post-traumatic stress disorder in the community: an epidemiological study. Psychol Med 1991; 21:713–721 [G]
243. Amir M, Kaplan Z, Neumann L, Sharabani R, Shani N, Buskila D: Posttraumatic stress disorder, tenderness and fibromyalgia. J Psychosom Res 1997; 42:607–613 [D]
244. Walker EA, Gelfand A, Katon WJ, Koss MP, Von Korff M, Bernstein D, Russo J: Adult health status of women with histories of childhood abuse and neglect. Am J Med 1999; 107:332–339 [D]
245. Fierman EJ, Hunt MF, Pratt LA, Warshaw MG, Yonkers KA, Peterson LG, Epstein-Kaye TM, Norton HS: Trauma and posttraumatic stress disorder in subjects with anxiety disorders. Am J Psychiatry 1993; 150:1872–1874 [D]
246. Green BL, Lindy JD, Grace MC, Leonard AC: Chronic posttraumatic stress disorder and diagnostic comorbidity in a disaster sample. J Nerv Ment Dis 1992; 180:760–766 [C]
247. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS: Trauma and the Vietnam War Generation: Report of Findings From the National Vietnam Veterans Readjustment Study. New York, Brunner/Mazel, 1990 [G]
248. Boudewyns PA, Albrecht JW, Talbert FS, Hyer LA: Comorbidity and treatment outcome of inpatients with chronic combat-related PTSD. Hosp Community Psychiatry 1991; 42:847–849 [C]
249. Davidson JET, Fairbank JA: The epidemiology of posttraumatic stress disorder, in Posttraumatic Stress Disorder: DSM-IV and Beyond. Edited by Davidson JET, Foa EB. Washington, DC, American Psychiatric Press, 1993, pp 147–169 [F]
250. Keane TM, Wolfe J: Comorbidity in post-traumatic stress disorder: an analysis of community and clinical studies. J Appl Soc Psychol 1990; 20:1776–1788 [F]
251. Jordan BK, Schlenger WE, Hough R, Kulka RA, Weiss D, Fairbank JA, Marmar CR: Lifetime and current prevalence of specific psychiatric disorders among Vietnam veterans and controls. Arch Gen Psychiatry 1991; 48:207–215 [D]
252. Southwick SM, Yehuda R, Giller EL Jr: Personality disorders in treatment-seeking combat veterans with posttraumatic stress disorder. Am J Psychiatry 1993; 150:1020–1023 [G]
253. Solomon SD, Davidson JR: Trauma: prevalence, impairment, service use, and cost. J Clin Psychiatry 1997; 58(suppl 9):5–11 [F]
254. Breslau N, Davis GC, Andreski P, Peterson E: Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen Psychiatry 1991; 48:216–222 [G]
255. Smith DW, Christiansen EH, Vincent R, Hann NE: Population effects of the bombing of Oklahoma City. J Okla State Med Assoc 1999; 92:193–198 [G]
256. Vlahov D, Galea S, Resnick H, Ahern J, Boscarino JA, Bucuvalas M, Gold J, Kilpatrick D: Increased use of cigarettes, alcohol, and marijuana among Manhattan, New York, residents after the September 11th terrorist attacks. Am J Epidemiol 2002; 155:988–996 [C]
257. Galea S, Ahern J, Resnick H, Kilpatrick D, Bucuvalas M, Gold J, Vlahov D: Psychological sequelae of the September 11 terrorist attacks in New York City. N Engl J Med 2002; 346:982–987 [C]
258. Goenjian A: A mental health relief programme in Armenia after the 1988 earthquake: implementation and clinical observations. Br J Psychiatry 1993; 163:230–239 [C]
259. Curtis T, Miller BC, Berry EH: Changes in reports and incidence of child abuse following natural disasters. Child Abuse Negl 2000; 24:1151–1162 [C]
260. Reijneveld SA, Crone MR, Verhulst FC, Verloove-Vanhorick SP: The effect of a severe disaster on the mental health of adolescents: a controlled study. Lancet 2003; 362:691–696 [D]
261. Kagan J: A conceptual analysis of the affects. J Am Psychoanal Assoc 1991; 39(suppl):109–130 [G]
262. Ornitz EM, Pynoos RS: Startle modulation in children with posttraumatic stress disorder. Am J Psychiatry 1989; 146:866–870 [C]

263. van der Kolk BA, Fisler RE: Childhood abuse and neglect and loss of self-regulation. Bull Menninger Clin 1994; 58:145–168 [G]
264. Briere J, Runtz M: Symptomatology associated with childhood sexual victimization in a nonclinical adult sample. Child Abuse Negl 1988; 12:51–59 [G]
265. Hall RC, Tice L, Beresford TP, Wooley B, Hall AK: Sexual abuse in patients with anorexia nervosa and bulimia. Psychosomatics 1989; 30:73–79 [D]
266. Palmer RL, Oppenheimer R, Dignon A, Chaloner DA, Howells K: Childhood sexual experiences with adults reported by women with eating disorders: an extended series. Br J Psychiatry 1990; 156:699–703 [G]
267. van der Kolk BA, Perry JC, Herman JL: Childhood origins of self-destructive behavior. Am J Psychiatry 1991; 148:1665–1671 [C]
268. Browne A, Finkelhor D: Impact of child sexual abuse: a review of the research. Psychol Bull 1986; 99:66–77 [F]
269. Amir M, Kaplan Z, Efroni R, Kotler M: Suicide risk and coping styles in posttraumatic stress disorder patients. Psychother Psychosom 1999; 68:76–81 [B]
270. Grieger TA, Fullerton CS, Ursano RJ: Posttraumatic stress disorder, alcohol use, and perceived safety after the terrorist attack on the Pentagon. Psychiatr Serv 2003; 54:1380–1382 [G]
271. Lewis DO: Neuropsychiatric and experiential correlates of violent juvenile delinquency. Neuropsychol Rev 1990; 1:125–136 [F]
272. Lewis DO: From abuse to violence: psychophysiological consequences of maltreatment. J Am Acad Child Adolesc Psychiatry 1992; 31:383–391 [F]
273. Kessler RC: Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry 2000; 61(suppl 5):4–12 [E]
274. Molnar BE, Berkman LF, Buka SL: Psychopathology, childhood sexual abuse and other childhood adversities: relative links to subsequent suicidal behaviour in the US. Psychol Med 2001; 31:965–977 [F]
275. Kessler RC, Borges G, Walters EE: Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. Arch Gen Psychiatry 1999; 56:617–626 [C]
276. Allgulander C: Psychiatric aspects of suicidal behavior: anxiety disorders, in The International Handbook of Suicide and Attempted Suicide. Edited by Hawton K, van Herringen K. Chichester, UK, John Wiley & Sons, 2000, pp 179–192 [F]
277. Institute of Medicine: Reducing Suicide: A National Imperative. Washington, DC, National Academies Press, 2002 [E]
278. Seedat S, Lockhat R, Kaminer D, Zungu-Dirwayi N, Stein DJ: An open trial of citalopram in adolescents with post-traumatic stress disorder. Int Clin Psychopharmacol 2001; 16:21–25 [B]
279. Londborg PD, Hegel MT, Goldstein S, Goldstein D, Himmelhoch JM, Maddock R, Patterson WM, Rausch J, Farfel GM: Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. J Clin Psychiatry 2001; 62:325–331 [B]
280. Malik ML, Connor KM, Sutherland SM, Smith RD, Davison RM, Davidson JR: Quality of life and posttraumatic stress disorder: a pilot study assessing changes in SF-36 scores before and after treatment in a placebo-controlled trial of fluoxetine. J Trauma Stress 1999; 12:387–393 [A]
281. Cowdry RW, Gardner DL: Pharmacotherapy of borderline personality disorder: alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. Arch Gen Psychiatry 1988; 45:111–119 [A]
282. Wickham EA, Reed JV: Lithium for the control of aggressive and self-mutilating behavior. Int Clin Psychopharmacol 1987; 2:181–190 [F]
283. Herman BH, Hammock MK, Arthur-Smith A, Egan J, Chatoor I, Werner A, Zelnik N: Naltrexone decreases self-injurious behavior. Ann Neurol 1987; 22:550–552 [B]

284. Linehan MM: Behavioral treatments of suicidal behaviors: definitional obfuscation and treatment outcomes. Ann N Y Acad Sci 1997; 836:302–328 [G]
285. Mellman L: Consequences of violence against women, in Women's Health: A Lifelong Guide. New York, Scientific American Digital, 1998 [G]
286. Ursano RJ, Fullerton CS, Epstein RS, Crowley B, Vance K, Kao TC, Baum A: Peritraumatic dissociation and posttraumatic stress disorder following motor vehicle accidents. Am J Psychiatry 1999; 156:1808–1810 [C]
287. Epstein RS, Fullerton CS, Ursano RJ: Posttraumatic stress disorder following an air disaster: a prospective study. Am J Psychiatry 1998; 155:934–938 [C]
288. Zatzick D: Posttraumatic stress, functional impairment, and service utilization after injury: a public health approach. Semin Clin Neuropsychiatry 2003; 8:149–157 [F]
289. Rynearson EK, Favell J: Manual for Criminal Death Support Groups. Seattle, Virginia Mason Medical Center, 2000 [F]
290. Prigerson HG, Shear MK, Jacobs SC, Reynolds CF 3rd, Maciejewski PK, Davidson JR, Rosenheck R, Pilkonis PA, Wortman CB, Williams JB, Widiger TA, Frank E, Kupfer DJ, Zisook S: Consensus criteria for traumatic grief: a preliminary empirical test. Br J Psychiatry 1999; 174:67–73 [G]
291. Shear MK, Smith-Caroff K: Traumatic loss and the syndrome of complicated grief. PTSD Research Quarterly 2002; 13:1–8 [G]
292. Mollica RF, Sarajlic N, Chernoff M, Lavelle J, Vukovic IS, Massagli MP: Longitudinal study of psychiatric symptoms, disability, mortality, and emigration among Bosnian refugees. JAMA 2001; 286:546–554 [C]
293. Zatzick DF, Jurkovich GJ, Gentilello L, Wisner D, Rivara FP: Posttraumatic stress, problem drinking, and functional outcomes after injury. Arch Surg 2002; 137:200–205 [C]
294. Soderstrom CA, Smith GS, Dischinger PC, McDuff DR, Hebel JR, Gorelick DA, Kerns TJ, Ho SM, Read KM: Psychoactive substance use disorders among seriously injured trauma center patients. JAMA 1997; 277:1769–1774 [F]
295. Dunn C, Zatzick D, Russo J, Rivara F, Roy-Byrne P, Ries R, Wisner D, Gentilello L: Hazardous drinking by trauma patients during the year after injury. J Trauma 2003; 54:707–712 [C]
296. Rivara FP, Jurkovich GJ, Gurney JG, Seguin D, Fligner CL, Ries R, Raisys VA, Copass M: The magnitude of acute and chronic alcohol abuse in trauma patients. Arch Surg 1993; 128:907–912 [C]
297. Brown PJ, Wolfe J: Substance abuse and post-traumatic stress disorder comorbidity. Drug Alcohol Depend 1994; 35:51–59 [F]
298. McFarlane AC: Epidemiological evidence about the relationship between PTSD and alcohol abuse: the nature of the association. Addict Behav 1998; 23:813–825 [E]
299. Jacobsen LK, Southwick SM, Kosten TR: Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. Am J Psychiatry 2001; 158:1184–1190 [F]
300. Engel CC Jr, Ursano R, Magruder C, Tartaglione R, Jing Z, Labbate LA, Debakey S: Psychological conditions diagnosed among veterans seeking Department of Defense care for Gulf War-related health concerns. J Occup Environ Med 1999; 41:384–392 [G]
301. Zatzick DF, Russo JE, Katon W: Somatic, posttraumatic stress, and depressive symptoms among injured patients treated in trauma surgery. Psychosomatics 2003; 44:479–484 [C]
302. Schnurr PP, Green BL: Trauma and Health: Physical Health Consequences of Exposure to Extreme Stress. Washington, DC, American Psychological Association, 2004 [G]
303. Horowitz MJ, Siegel B, Holen A, Bonanno GA, Milbrath C, Stinson CH: Diagnostic criteria for complicated grief disorder. Am J Psychiatry 1997; 154:904–910 [C]
304. Layne CM, Pynoos RS, Saltzman WR, Arslanagic B, Black M, Savjak N, Popovic T, Durakovic E, Music M, Campara N, Djapo N, Houston R: Trauma/grief-focused group

psychotherapy: school-based postwar intervention with traumatized Bosnian adolescents. Group Dynamics 2001; 5:277–290 [B]

305. Giaconia RM, Reinherz HZ, Silverman AB, Pakiz B, Frost AK, Cohen E: Traumas and posttraumatic stress disorder in a community population of older adolescents. J Am Acad Child Adolesc Psychiatry 1995; 34:1369–1380 [G]
306. Resnick HS, Kilpatrick DG, Dansky BS, Saunders BE, Best CL: Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. J Consult Clin Psychol 1993; 61:984–991 [G]
307. Norris FH: Epidemiology of trauma: frequency and impact of different potentially traumatic events on different demographic groups. J Consult Clin Psychol 1992; 60:409–418 [G]
308. Helzer JE, Robins LN, McEvoy L: Post-traumatic stress disorder in the general population: findings of the Epidemiologic Catchment Area survey. N Engl J Med 1987; 317:1630–1634 [G]
309. Freedman SA, Gluck N, Tuval-Mashiach R, Brandes D, Peri T, Shalev AY: Gender differences in responses to traumatic events: a prospective study. J Trauma Stress 2002; 15:407–413 [C]
310. Jenkins EJ, Bell CC: Exposure and response to community violence among children and adolescents, in Children in a Violent Society. Edited by Osofsky J. New York, Guilford, 1997, pp 9–31 [G]
311. US Department of Health and Human Services: Mental Health: Culture, Race, Ethnicity—A Supplement to Mental Health: Report of the Surgeon General. Rockville, Md, US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, 2001 [G]
312. Greenfeld LA, Smith SK: American Indians and Crime. Washington, DC, US Department of Justice, Office of Justice Programs, Bureau of Justice Statistics, 1999 [G]
313. Jones MC, Dauphinais P, Sack WH, Somervell PD: Trauma-related symptomatology among American Indian adolescents. J Trauma Stress 1997; 10:163–173 [G]
314. Robin RW, Chester B, Rasmussen JK, Jaranson JM, Goldman D: Prevalence and characteristics of trauma and posttraumatic stress disorder in a southwestern American Indian community. Am J Psychiatry 1997; 154:1582–1588 [G]
315. Fairbank JA, Friedman MJ, Southwick SM: Veterans of armed conflicts, in The Mental Health Consequences of Torture. Edited by Gerrity ET, Keane TM, Tuma F. New York, Kluwer Academic/Plenum, 2001, pp 121–131 [G]
316. McLeod JD, Kessler RC: Socioeconomic status differences in vulnerability to undesirable life events. J Health Soc Behav 1990; 31:162–172 [C]
317. Bremner JD, Southwick SM, Johnson DR, Yehuda R, Charney DS: Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. Am J Psychiatry 1993; 150:235–239 [D]
318. Matsunaga Vietnam Veterans Project. White River Junction, Vt, National Center for Post-Traumatic Stress Disorder and the National Center for American Indian and Alaska Native Mental Health Research, 1996 [C]
319. Beals J, Manson SM, Shore JH, Friedman M, Ashcraft M, Fairbank JA, Schlenger WE: The prevalence of posttraumatic stress disorder among American Indian Vietnam veterans: disparities and context. J Trauma Stress 2002; 15:89–97 [F]
320. Ruef AM, Litz BT, Schlenger WE: Hispanic ethnicity and risk for combat-related posttraumatic stress disorder. Cultur Divers Ethnic Minor Psychol 2000; 6:235–251 [F]
321. Ortega AN, Rosenheck R: Posttraumatic stress disorder among Hispanic Vietnam veterans. Am J Psychiatry 2000; 157:615–619 [E]
322. Schnyder U, Moergeli H, Klaghofer R, Buddeberg C: Incidence and prediction of posttraumatic stress disorder symptoms in severely injured accident victims. Am J Psychiatry 2001; 158:594–599 [C]

323. Malt U: The long-term psychiatric consequences of accidental injury: a longitudinal study of 107 adults. Br J Psychiatry 1988; 153:810–818 [C]
324. Harvey AG, Bryant RA: The relationship between acute stress disorder and posttraumatic stress disorder: a prospective evaluation of motor vehicle accident survivors. J Consult Clin Psychol 1998; 66:507–512 [C]
325. Shalev AY, Peri T, Canetti L, Schreiber S: Predictors of PTSD in injured trauma survivors: a prospective study. Am J Psychiatry 1996; 153:219–225 [C]
326. Mayou R, Bryant B, Duthie R: Psychiatric consequences of road traffic accidents. BMJ 1993; 307:647–651 [C]
327. Michaels AJ, Michaels CE, Moon CH, Smith JS, Zimmerman MA, Taheri PA, Peterson C: Posttraumatic stress disorder after injury: impact on general health outcome and early risk assessment. J Trauma 1999; 47:460–466 [C]
328. Mellman TA, David D, Bustamante V, Fins AI, Esposito K: Predictors of post-traumatic stress disorder following severe injury. Depress Anxiety 2001; 14:226–231 [C]
329. O'Donnell ML, Creamer M, Bryant RA, Schnyder U, Shalev A: Posttraumatic disorders following injury: empirical and methodological review. Clin Psychol Rev 2003; 23:587–603 [E]
330. Bleich A, Gelkopf M, Solomon Z: Exposure to terrorism, stress-related mental health symptoms, and coping behaviors among a nationally representative sample in Israel. JAMA 2003; 290:612–620 [G]
331. Sabin M, Lopes Cardozo B, Nackerud L, Kaiser R, Varese L: Factors associated with poor mental health among Guatemalan refugees living in Mexico 20 years after civil conflict. JAMA 2003; 290:635–642 [G]
332. de Jong JT, Komproe IH, Van Ommeren M, El Masri M, Araya M, Khaled N, van De Put W, Somasundaram D: Lifetime events and posttraumatic stress disorder in 4 postconflict settings. JAMA 2001; 286:555–562 [C]
333. Kinzie JD, Boehnlein JK, Leung PK, Moore LJ, Riley C, Smith D: The prevalence of posttraumatic stress disorder and its clinical significance among Southeast Asian refugees. Am J Psychiatry 1990; 147:913–917 [G]
334. US Department of Health and Human Services: Mental Health: A Report of the Surgeon General. Rockville, Md, US Department of Health and Human Services, 1999 [C]
335. Kroll J, Habenicht M, Mackenzie T, Yang M, Chan S, Vang T, Nguyen T, Ly M, Phommasouvanh B, Nguyen H, Vang Y, Souvannasoth L, Cabugao R: Depression and posttraumatic stress disorder in Southeast Asian refugees. Am J Psychiatry 1989; 146:1592–1597 [C]
336. Blair RG: Risk factors associated with PTSD and major depression among Cambodian refugees in Utah. Health Soc Work 2000; 25:23–30 [C]
337. Caspi Y, Poole C, Mollica RF, Frankel M: Relationship of child loss to psychiatric and functional impairment in resettled Cambodian refugees. J Nerv Ment Dis 1998; 186:484–491 [G]
338. Kinzie JD, Sack W, Angell R, Clarke G, Ben R: A three-year follow-up of Cambodian young people traumatized as children. J Am Acad Child Adolesc Psychiatry 1989; 28:501–504 [C]
339. Chung RC, Kagawa-Singer M: Predictors of psychological distress among Southeast Asian refugees. Soc Sci Med 1993; 36:631–639 [G]
340. Farias P: Central and South American refugees: some mental health challenges, in Amidst Peril and Pain: The Mental Health and Well Being of the World's Refugees. Edited by Marsella AJ, Bornemann T, Ekblad S, Orley J. Washington, DC, American Psychological Association, 1994, pp 101–113 [G]
341. Cervantes RC, Salgado de Snyder VN, Padilla AM: Posttraumatic stress in immigrants from Central America and Mexico. Hosp Community Psychiatry 1989; 40:615–619 [D]
342. Michultka D, Blanchard EB, Kalous T: Responses to civilian war experiences: predictors of psychological functioning and coping. J Trauma Stress 1998; 11:571–577 [G]

343. Arroyo W, Eth S: Children traumatized by Central American warfare, in Posttraumatic Stress Disorder in Children. Edited by Eth S, Pynoos RS. Washington, DC, American Psychiatric Press, 1984, pp 103–117 [G]
344. Eisenman DP, Gelberg L, Liu H, Shapiro MF: Mental health and health-related quality of life among adult Latino primary care patients living in the United States with previous exposure to political violence. JAMA 2003; 290:627–634 [G]
345. Blanchard EB, Hickling EJ, Barton KA, Taylor AE, Loos WR, Jones-Alexander J: One-year prospective follow-up of motor vehicle accident victims. Behav Res Ther 1996; 34:775–786 [C]
346. Tedeschi RG, Calhoun LG: The Posttraumatic Growth Inventory: measuring the positive legacy of trauma. J Trauma Stress 1996; 9:455–471 [G]
347. Herman JL, Perry JC, van der Kolk BA: Childhood trauma in borderline personality disorder. Am J Psychiatry 1989; 146:490–495 [D]
348. Perry JC, Herman HL, van der Kolk BA, Holk LA: Psychotherapy and psychological trauma in borderline personality disorder. Psychiatr Ann 1990; 20:33–43 [G]
349. Pollack MH, Otto MW, Rosenbaum JF, Sachs GS: Personality disorders in patients with panic disorder: association with childhood anxiety disorders, early trauma, comorbidity, and chronicity. Compr Psychiatry 1992; 33:78–83 [C]
350. Zatzick DF, Weiss DS, Marmar CR, Metzler TJ, Wells K, Golding JM, Stewart A, Schlenger WE, Browner WS: Post-traumatic stress disorder and functioning and quality of life outcomes in female Vietnam veterans. Mil Med 1997; 162:661–665 [C]
351. Mendlowicz MV, Stein MB: Quality of life in individuals with anxiety disorders. Am J Psychiatry 2000; 157:669–682 [F]
352. Bryant RA, Marosszeky JE, Crooks J, Baguley IJ, Gurka JA: Posttraumatic stress disorder and psychosocial functioning after severe traumatic brain injury. J Nerv Ment Dis 2001; 189:109–113 [C]
353. Zayfert C, Dums AR, Ferguson RJ, Hegel MT: Health functioning impairments associated with posttraumatic stress disorder, anxiety disorders, and depression. J Nerv Ment Dis 2002; 190:233–240 [C]
354. Beckham JC, Moore SD, Feldman ME, Hertzberg MA, Kirby AC, Fairbank JA: Health status, somatization, and severity of posttraumatic stress disorder in Vietnam combat veterans with posttraumatic stress disorder. Am J Psychiatry 1998; 155:1565–1569 [C]
355. Boscarino JA: Diseases among men 20 years after exposure to severe stress: implications for clinical research and medical care. Psychosom Med 1997; 59:605–614 [C]
356. Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, Ballenger JC, Fyer AJ: The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry 1999; 60:427–435 [E]
357. Livanou M, Basoglu M, Marks IM, De SP, Noshirvani H, Lovell K, Thrasher S: Beliefs, sense of control and treatment outcome in post-traumatic stress disorder. Psychol Med 2002; 32:157–165 [A]
358. Krupnick JL: Brief psychodynamic treatment of PTSD. J Clin Psychol 2002; 58:919–932 [G]
359. Plakun EM, Shapiro ER: Psychodynamic psychotherapy for PTSD. J Clin Psychiatry 2000; 61:787–788 [F]
360. Lansky MR: The transformation of affect in posttraumatic nightmares. Bull Menninger Clin 1991; 55:470–490 [G]
361. Peniston EG: EMG biofeedback-assisted desensitization treatment for Vietnam combat veterans' post-traumatic stress disorder. Clinical Biofeedback and Health 1986; 9:35–41 [A–]
362. Keane TM, Fairbank JA, Caddell JM, Zimering RT: Implosive (flooding) therapy reduces symptoms of PTSD in Vietnam combat veterans. Behav Ther 1989; 20:245–260 [A–]
363. Cooper NA, Clum GA: Imaginal flooding as a supplementary treatment for PTSD in combat veterans: a controlled study. Behav Ther 1989; 20:381–391 [B]

364. Boudewyns PA, Hyer L: Physiological response to combat memories and preliminary treatment outcome in Vietnam veteran PTSD patients treated with direct therapeutic exposure. Behav Ther 1990; 21:63–87 [A–]
365. Boudewyns PA, Hyer L, Woods MG, Harrison WR, McCranie E: PTSD among Vietnam veterans: an early look at treatment outcome using direct therapeutic exposure. J Trauma Stress 1990; 3:359–368 [B]
366. Richards DA, Lovell K, Marks IM: Post-traumatic stress disorder: evaluation of a behavioral treatment program. J Trauma Stress 1994; 7:669–680 [A–]
367. Rothbaum BO, Hodges LF: The use of virtual reality exposure in the treatment of anxiety disorders. Behav Modif 1999; 23:507–525 [G]
368. Rothbaum BO, Hodges LF, Ready D, Graap K, Alarcon RD: Virtual reality exposure therapy for Vietnam veterans with posttraumatic stress disorder. J Clin Psychiatry 2001; 62:617–622 [B]
369. Krakow B, Hollifield M, Schrader R, Koss M, Tandberg D, Lauriello J, McBride L, Warner TD, Cheng D, Edmond T, Kellner R: A controlled study of imagery rehearsal for chronic nightmares in sexual assault survivors with PTSD: a preliminary report. J Trauma Stress 2000; 13:589–609 [A–]
370. Forbes D, Phelps AJ, McHugh AF, Debenham P, Hopwood M, Creamer M: Imagery rehearsal in the treatment of posttraumatic nightmares in Australian veterans with chronic combat-related PTSD: 12-month follow-up data. J Trauma Stress 2003; 16:509–513 [B]
371. Falsetti SA, Resnick HS, Davis HJ, Gallagher NG: Treatment of posttraumatic stress disorder with comorbid panic attacks: combining cognitive processing therapy with panic control treatment techniques. Group Dynamics 2001; 5:252–260 [A]
372. Glynn SM, Eth S, Randolph ET, Foy DW, Urbaitis M, Boxer L, Paz GG, Leong GB, Firman G, Salk JD, Katzman JW, Crothers J: A test of behavioral family therapy to augment exposure for combat-related posttraumatic stress disorder. J Consult Clin Psychol 1999; 67:243–251 [A–]
373. Fecteau G, Nicki R: Cognitive behavioural treatment of posttraumatic stress disorder after motor vehicle accident. Behavioural and Cognitive Psychotherapy 1999; 27:201–214 [E]
374. Foa EB, Rothbaum BO, Riggs DS, Murdock TB: Treatment of posttraumatic stress disorder in rape victims: a comparison between cognitive-behavioral procedures and counseling. J Consult Clin Psychol 1991; 59:715–723 [A]
375. Echeburua E, de Corral P, Zubizarreta I, Sarasua B: Psychological treatment of chronic posttraumatic stress disorder in victims of sexual aggression. Behav Modif 1997; 21:433–456 [A–]
376. Silver SM, Brooks A, Obenchain J: Treatment of Vietnam War veterans with PTSD: a comparison of eye movement desensitization and reprocessing, biofeedback, and relaxation training. J Trauma Stress 1995; 8:337–342 [B]
377. Paunovic N, Ost LG: Cognitive-behavior therapy vs exposure therapy in the treatment of PTSD in refugees. Behav Res Ther 2001; 39:1183–1197 [A–]
378. Chemtob CM, Novaco RW, Hamada RS, Gross DM: Cognitive-behavioral treatment for severe anger in posttraumatic stress disorder. J Consult Clin Psychol 1997; 65:184–189 [A–]
379. Foa EB, Hearst-Ikeda D, Perry KJ: Evaluation of a brief cognitive-behavioral program for the prevention of chronic PTSD in recent assault victims. J Consult Clin Psychol 1995; 63:948–955 [B]
380. Gillespie K, Duffy M, Hackmann A, Clark DM: Community based cognitive therapy in the treatment of posttraumatic stress disorder following the Omagh bomb. Behav Res Ther 2002; 40:345–357 [B]
381. Ehlers A, Clark D: Early psychological interventions for adult survivors of trauma: a review. Biol Psychiatry 2003; 53:817–826 [F]

382. Marcus SV: Controlled study of treatment of PTSD using EMDR in an HMO setting. Psychotherapy 1997; 34:307–315 [A–]
383. Rothbaum BO: A controlled study of eye movement desensitization and reprocessing in the treatment of posttraumatic stress disordered sexual assault victims. Bull Menninger Clin 1997; 61:317–334 [A–]
384. Scheck MM, Schaeffer JA, Gillette C: Brief psychological intervention with traumatized young women: the efficacy of eye movement desensitization and reprocessing. J Trauma Stress 1998; 11:25–44 [A–]
385. Wilson SA, Becker LA, Tinker RH: Eye movement desensitization and reprocessing (EMDR) treatment for psychologically traumatized individuals. J Consult Clin Psychol 1995; 63:928–937 [A–]
386. Wilson SA, Becker LA, Tinker RH: Fifteen-month follow-up of eye movement desensitization and reprocessing (EMDR) treatment for posttraumatic stress disorder and psychological trauma. J Consult Clin Psychol 1997; 65:1047–1056 [C]
387. Ironson G, Freund B, Strauss JL, Williams J: Comparison of two treatments for traumatic stress: a community-based study of EMDR and prolonged exposure. J Clin Psychol 2002; 58:113–128 [A–]
388. Devilly GJ, Spence SH, Rapee RM: Statistical and reliable change with eye movement desensitization and reprocessing: treating trauma within a veteran population. Behav Ther 1998; 29:435–455 [A]
389. Macklin ML, Metzger LJ, Lasko NB, Berry NJ, Orr SP, Pitman RK: Five-year follow-up study of eye movement desensitization and reprocessing therapy for combat-related posttraumatic stress disorder. Compr Psychiatry 2000; 41:24–27 [B]
390. Cusack K, Spates CR: The cognitive dismantling of eye movement desensitization and reprocessing (EMDR) treatment of posttraumatic stress disorder (PTSD). J Anxiety Disord 1999; 13:87–99 [A–]
391. Classen C, Butler LD, Koopman C, Miller E, DiMiceli S, Giese-Davis J, Fobair P, Carlson RW, Kraemer HC, Spiegel D: Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trial. Arch Gen Psychiatry 2001; 58:494–501 [F]
392. Zlotnick C, Shea TM, Rosen K, Simpson E, Mulrenin K, Begin A, Pearlstein T: An affect-management group for women with posttraumatic stress disorder and histories of childhood sexual abuse. J Trauma Stress 1997; 10:425–436 [A]
393. Schnurr PP, Friedman MJ, Foy DW, Shea MT, Hsieh FY, Lavori PW, Glynn SM, Wattenberg M, Bernardy NC: Randomized trial of trauma-focused group therapy for posttraumatic stress disorder: results from a Department of Veterans Affairs cooperative study. Arch Gen Psychiatry 2003; 60:481–489 [A–]
394. Zoellner LA, Feeny NC, Cochran B, Pruitt L: Treatment choice for PTSD. Behav Res Ther 2003; 41:879–886 [C]
395. Foa EB, Zoellner LA, Feeny NC, Hembree EA, Alvarez-Conrad J: Does imaginal exposure exacerbate PTSD symptoms? J Consult Clin Psychol 2002; 70:1022–1028 [D]
396. Bradley RG, Follingstad DR: Group therapy for incarcerated women who experienced interpersonal violence: a pilot study. J Trauma Stress 2003; 16:337–340 [A–]
397. Drozdek B: Follow-up study of concentration camp survivors from Bosnia-Herzegovina: three years later. J Nerv Ment Dis 1997; 185:690–694 [G]
398. Cloitre M, Koenen KC: The impact of borderline personality disorder on process group outcome among women with posttraumatic stress disorder related to childhood abuse. Int J Group Psychother 2001; 51:379–398 [A–]
399. Vaa G, Egner R, Sexton H: Sexually abused women after multimodal group therapy: a long-term follow-up study. Nord J Psychiatry 2002; 56:215–221 [B]

400. Vandeusen KM, Carr JL: Recovery from sexual assault: an innovative two-stage group therapy model. Int J Group Psychother 2003; 53:201–223 [G]
401. Busuttil W, Turnbull GJ, Neal LA, Rollins J, West AG, Blanch N, Herepath R: Incorporating psychological debriefing techniques within a brief group psychotherapy programme for the treatment of post-traumatic stress disorder. Br J Psychiatry 1995; 167:495–502 [B]
402. Murphy SA: A bereavement intervention for parents following the sudden, violent deaths of their 12–28-year-old children: description and applications to clinical practice. Can J Nurs Res 1997; 29:51–72 [B]
403. Foy DW, Glynn SM, Schnurr PP, Jankowski MK, Wattenberg MS, Weiss DS, Marmar CR, Gusman GD: Group psychotherapy, in Effective Treatments for PTSD: Practical Guidelines From the International Society for Traumatic Stress Studies. Edited by Foa EB, Keane TM, Friedman MJ. New York, Guilford, 2000, pp 155–175 [F]
404. Cohen JA, Mannarino AP: A treatment outcome study for sexually abused preschool children: initial findings. J Am Acad Child Adolesc Psychiatry 1996; 35:42–50 [A]
405. Cohen JA, Mannarino AP: Factors that mediate treatment outcome of sexually abused preschool children: six- and 12-month follow-up. J Am Acad Child Adolesc Psychiatry 1998; 37:44–51 [B]
406. March JS, Amaya-Jackson L, Murray MC, Schulte A: Cognitive-behavioral psychotherapy for children and adolescents with posttraumatic stress disorder after a single-incident stressor. J Am Acad Child Adolesc Psychiatry 1998; 37:585–593 [B]
407. Saltzman WR, Pynoos RS, Layne CM, Steinberg A, Aisenberg E: School-based trauma/grief group psychotherapy program for youth exposed to community violence. Group Dynamics 2001; 5:291–303 [B]
408. Davies DR, Burlingame GM, Layne CM: Integrating small group process principles into trauma-focused group psychotherapy: what should a group trauma therapist know? in Group Approaches for Psychological Effects of Terrorist Disasters. Edited by Schein LA, Burlingame GM, Spitz HI, Muskin PR. New York, Haworth (in press) [G]
409. Rose S, Brewin CR, Andrews B, Kirk M: A randomized controlled trial of individual psychological debriefing for victims of violent crime. Psychol Med 1999; 29:793–799 [A–]
410. Carlier IV, Voerman AE, Gersons BP: The influence of occupational debriefing on post-traumatic stress symptomatology in traumatized police officers. Br J Med Psychol 2000; 73(pt 1):87–98 [A]
411. Deahl M, Srinivasan M, Jones N, Thomas J, Neblett C, Jolly A: Preventing psychological trauma in soldiers: the role of operational stress training and psychological debriefing. Br J Med Psychol 2000; 73(pt 1):77–85 [A]
412. Campfield KM, Hills AM: Effect of timing of critical incident stress debriefing (CISD) on posttraumatic symptoms. J Trauma Stress 2001; 14:327–340 [B]
413. Lange A, van de Ven JP, Schrieken B, Emmelkamp PM: Interapy, treatment of posttraumatic stress through the Internet: a controlled trial. J Behav Ther Exp Psychiatry 2001; 32:73–90 [A]
414. Lange A, Rietdijk D, Hudcovicova M, van de Ven JP, Schrieken B, Emmelkamp PM: Interapy: a controlled randomized trial of the standardized treatment of posttraumatic stress through the Internet. J Consult Clin Psychol 2003; 71:901–909 [A]
415. Ragsdale KG, Cox RD, Finn P, Eisler RM: Effectiveness of short-term specialized inpatient treatment for war-related posttraumatic stress disorder: a role for adventure-based counseling and psychodrama. J Trauma Stress 1996; 9:269–283 [B]
416. Hyer L, Boyd S, Scurfield R, Smith D, Burke J: Effects of Outward Bound experience as an adjunct to inpatient PTSD treatment of war veterans. J Clin Psychol 1996; 52:263–278 [B]
417. Gidron Y, Peri T, Connolly JF, Shalev AY: Written disclosure in posttraumatic stress disorder: is it beneficial for the patient? J Nerv Ment Dis 1996; 184:505–507 [A]
418. Reynolds M, Tarrier N: Monitoring of intrusions in post-traumatic stress order: a report of single case studies. Br J Med Psychol 1996; 69(pt 4):371–379 [G]

419. Silver SM, Wilson JP: Native American healing and purification rituals for war stress, in Human Adaptation to Extreme Stress: From the Holocaust to Vietnam. Edited by Wilson JP, Kahana B. New York, Plenum, 1989, pp 337–355 [G]
420. Zatzick DF, Johnson FA: Alternative psychotherapeutic practice among middle class Americans, I: case studies and follow-up. Cult Med Psychiatry 1997; 21:53–88 [G]
421. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM: Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. Arch Gen Psychiatry 2001; 58:485–492 [A]
422. Davis LL, Nugent AL, Murray J, Kramer GL, Petty F: Nefazodone treatment for chronic posttraumatic stress disorder: an open trial. J Clin Psychopharmacol 2000; 20:159–164 [B]
423. Hidalgo R, Hertzberg MA, Mellman T, Petty F, Tucker P, Weisler R, Zisook S, Chen S, Churchill E, Davidson J: Nefazodone in post-traumatic stress disorder: results from six open-label trials. Int Clin Psychopharmacol 1999; 14:61–68 [E]
424. Zisook S, Chentsova-Dutton YE, Smith-Vaniz A, Kline NA, Ellenor GL, Kodsi AB, Gillin JC: Nefazodone in patients with treatment-refractory posttraumatic stress disorder. J Clin Psychiatry 2000; 61:203–208 [B]
425. Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Leykin Y, Metzler TJ, Schoenfeld FB, Marmar CR: The effect of nefazodone on subjective and objective sleep quality in posttraumatic stress disorder. J Clin Psychiatry 2003; 64:445–450 [B]
426. Mellman TA, David D, Barza L: Nefazodone treatment and dream reports in chronic PTSD. Depress Anxiety 1999; 9:146–148 [B]
427. Hertzberg MA, Feldman ME, Beckham JC, Davidson JR: Trial of trazodone for posttraumatic stress disorder using a multiple baseline group design. J Clin Psychopharmacol 1996; 16:294–298 [B]
428. Canive JM, Clark RD, Calais LA, Qualls C, Tuason VB: Bupropion treatment in veterans with posttraumatic stress disorder: an open study. J Clin Psychopharmacol 1998; 18:379–383 [B]
429. Smajkic A, Weine S, Djuric-Bijedic Z, Boskailo E, Lewis J, Pavkovic I: Sertraline, paroxetine, and venlafaxine in refugee posttraumatic stress disorder with depression symptoms. J Trauma Stress 2001; 14:445–452 [B]
430. Connor KM, Davidson JR, Weisler RH, Ahearn E: A pilot study of mirtazapine in posttraumatic stress disorder. Int Clin Psychopharmacol 1999; 14:29–31 [B]
431. Davidson JR, Weisler RH, Butterfield MI, Casat CD, Connor KM, Barnett S, van Meter S: Mirtazapine vs placebo in posttraumatic stress disorder: a pilot trial. Biol Psychiatry 2003; 53:188–191 [A]
432. Southwick SM, Yehuda R, Giller EL Jr, Charney DS: Use of tricyclics and monoamine oxidase inhibitors in the treatment of PTSD: a quantitative review, in Catecholamine Function in Post-Traumatic Stress Disorder: Emerging Concepts. Edited by Murburg MM. Washington, DC, American Psychiatric Press, 1994, pp 293–305 [E]
433. Robert R, Blakeney PE, Villarreal C, Rosenberg L, Meyer WJ 3rd: Imipramine treatment in pediatric burn patients with symptoms of acute stress disorder: a pilot study. J Am Acad Child Adolesc Psychiatry 1999; 38:873–882 [A]
434. Neal LA, Shapland W, Fox C: An open trial of moclobemide in the treatment of posttraumatic stress disorder. Int Clin Psychopharmacol 1997; 12:231–237 [B]
435. Katz RJ, Lott MH, Arbus P, Crocq L, Herlobsen P, Lingjaerde O, Lopez G, Loughrey GC, MacFarlane DJ, McIvor R, Mehlum L, Nugent D, Turner SW, Weisaeth L, Yule W: Pharmacotherapy of post-traumatic stress disorder with a novel psychotropic. Anxiety 1994–1995; 1:169–174 [A]
436. Connor KM, Hidalgo RB, Crockett B, Malik M, Katz RJ, Davidson JR: Predictors of treatment response in patients with posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 2001; 25:337–345 [E]

437. Braun P, Greenberg D, Dasberg H, Lerer B: Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. J Clin Psychiatry 1990; 51:236–238 [A]
438. Mellman TA, Byers PM, Augenstein JS: Pilot evaluation of hypnotic medication during acute traumatic stress response. J Trauma Stress 1998; 11:563–569 [B]
439. Duffy JD, Malloy PF: Efficacy of buspirone in the treatment of posttraumatic stress disorder: an open trial. Ann Clin Psychiatry 1994; 6:33–37 [B]
440. Wells BG, Chu CC, Johnson R, Nasdahl C, Ayubi MA, Sewell E, Statham P: Buspirone in the treatment of posttraumatic stress disorder. Pharmacotherapy 1991; 11:340–343 [B]
441. Raskind MA, Thompson C, Petrie EC, Dobie DJ, Rein RJ, Hoff DJ, McFall ME, Peskind ER: Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. J Clin Psychiatry 2002; 63:565–568 [B]
442. Jacobs-Rebhun S, Schnurr PP, Friedman MJ, Peck R, Brophy M, Fuller D: Posttraumatic stress disorder and sleep difficulty. Am J Psychiatry 2000; 157:1525–1526 [A]
443. Clark RD, Canive JM, Calais LA, Qualls C, Brugger RD, Vosburgh TB: Cyproheptadine treatment of nightmares associated with posttraumatic stress disorder. J Clin Psychopharmacol 1999; 19:486–487 [B]
444. Kaplan Z, Amir M, Swartz M, Levine J: Inositol treatment of post-traumatic stress disorder. Anxiety 1996; 2:51–52 [A]
445. Schelling G: Effects of stress hormones on traumatic memory formation and the development of posttraumatic stress disorder in critically ill patients. Neurobiol Learn Mem 2002; 78:596–609 [E]
446. Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhausler HB, Kapfhammer HP: The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry 2001; 50:978–985 [B]
447. Saxe G, Stoddard F, Courtney D, Cunningham K, Chawla N, Sheridan R, King D, King L: Relationship between acute morphine and the course of PTSD in children with burns. J Am Acad Child Adolesc Psychiatry 2001; 40:915–921 [D]
448. Ehlers A, Clark DM, Hackmann A, McManus F, Fennell M, Herbert C, Mayou R: A randomized controlled trial of cognitive therapy, a self-help booklet, and repeated assessments as early interventions for posttraumatic stress disorder. Arch Gen Psychiatry 2003; 60:1024–1032 [A–]
449. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB: Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 2000; 284:592–597 [G]
450. Heim C, Nemeroff CB: The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry 2001; 49:1023–1039 [F]
451. Charney DS: Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiatry 2004; 161:195–216 [G]
452. Zlotnick C, Franklin CL, Zimmerman M: Does "subthreshold" posttraumatic stress disorder have any clinical relevance? Compr Psychiatry 2002; 43:413–419 [D]
453. Weiss DS, Marmar CR, Schlenger WE, Fairbank JA, Jordan BK, Hough RL, Kulka RA: The prevalence of lifetime and partial post-traumatic stress disorder in Vietnam theater veterans. J Trauma Stress 1992; 5:365–376 [D]
454. Schutzwohl M, Maercker A: Effects of varying diagnostic criteria for posttraumatic stress disorder are endorsing the concept of partial PTSD. J Trauma Stress 1999; 12:155–165 [G]
455. Stein MB, Walker JR, Hazen AL, Forde DR: Full and partial posttraumatic stress disorder: findings from a community survey. Am J Psychiatry 1997; 154:1114–1119 [G]
456. Shear MK, Zuckoff A, Frank E: The syndrome of traumatic grief. CNS Spectrums 2001; 6:339–346 [G]
457. Taylor FB: Tiagabine for posttraumatic stress disorder: a case series of 7 women. J Clin Psychiatry 2003; 64:1421–1425 [G]

458. Foa EB, Rothbaum BO, Furr JM: Augmenting exposure therapy with other CBT procedures. Psychiatr Ann 2003; 33:47–53 [F]
459. Ross RJ, Ball WA, Dinges DF, Kribbs NB, Morrison AR, Silver SM, Mulvaney FD: Rapid eye movement sleep disturbance in posttraumatic stress disorder. Biol Psychiatry 1994; 35:195–202 [D]
460. Ross RJ, Ball WA, Sullivan KA, Caroff SN: Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry 1989; 146:697–707 [G]
461. Pitman RK, Orr SP, Shalev AY, Metzger LJ, Mellman TA: Psychophysiological alterations in post-traumatic stress disorder. Semin Clin Neuropsychiatry 1999; 4:234–241 [G]
462. Rothbaum BO, Mellman TA: Dreams and exposure therapy in PTSD. J Trauma Stress 2001; 14:481–490 [F]
463. Foa EB, Riggs DS, Massie ED, Yarczower M: The impact of fear activation and anger on the efficacy of exposure treatment for posttraumatic stress disorder. Behav Ther 1995; 26:487–499 [C]

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

Wylie C. Hembree,[1] Peggy T. Cohen-Kettenis,[2] Louis Gooren,[3] Sabine E. Hannema,[4] Walter J. Meyer,[5] M. Hassan Murad,[6] Stephen M. Rosenthal,[7] Joshua D. Safer,[8] Vin Tangpricha,[9] and Guy G. T'Sjoen[10]

[1]New York Presbyterian Hospital, Columbia University Medical Center, New York, New York 10032 (Retired); [2]VU University Medical Center, 1007 MB Amsterdam, Netherlands (Retired); [3]VU University Medical Center, 1007 MB Amsterdam, Netherlands (Retired); [4]Leiden University Medical Center, 2300 RC Leiden, Netherlands; [5]University of Texas Medical Branch, Galveston, Texas 77555; [6]Mayo Clinic Evidence-Based Practice Center, Rochester, Minnesota 55905; [7]University of California San Francisco, Benioff Children's Hospital, San Francisco, California 94143; [8]Boston University School of Medicine, Boston, Massachusetts 02118; [9]Emory University School of Medicine and the Atlanta VA Medical Center, Atlanta, Georgia 30322; and [10]Ghent University Hospital, 9000 Ghent, Belgium

*Cosponsoring Associations: American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society–appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 24 July 2017. Accepted 24 August 2017.
First Published Online 13 September 2017

Abbreviations: BMD, bone mineral density; DSD, disorder/difference of sex development; DSM, Diagnostic and Statistical Manual of Mental Disorders; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; MHP, mental health professional; VTE, venous thromboembolism.

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (***J Clin Endocrinol Metab*** **102: 3869–3903, 2017)**

Summary of Recommendations

1.0 Evaluation of youth and adults

1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

doi: 10.1210/jc.2017-01658

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

2.0 Treatment of adolescents

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 |⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 |⊕⊕◯◯)

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 |⊕⊕◯◯)

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 |⊕⊕◯◯).

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 |⊕⊕◯◯)

3.0 Hormonal therapy for transgender adults

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕◯◯◯)

4.0 Adverse outcome prevention and long-term care

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 |⊕⊕◯◯)

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 |⊕⊕◯◯)

4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 |⊕⊕◯◯)

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 |⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕◯◯◯)

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 |⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 |⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 |⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 |⊕◯◯◯)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of "gender dysphoria/gender incongruence." It also reviews the development of "gender identity" and summarizes its natural development. The section on clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low–quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

doi: 10.1210/jc.2017-01658

values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society's Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are "trapped" in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote "The Transsexual Phenomenon" (4), it was Hirschfeld who coined the term "transsexual" in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through "something in between" to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (*e.g.*, Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (*e.g.*, the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

doi: 10.1210/jc.2017-01658

Table 1. Definitions of Terms Used in This Guideline

Biological sex, biological male or female: These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (*e.g.*, a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.
Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "non-transgender people."
Gender-affirming (hormone) treatment: See "gender reassignment"
Gender dysphoria: This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced "gender identity disorder" with "gender dysphoria" and changed the criteria for diagnosis.
Gender expression: This refers to external manifestations of gender, expressed through one's name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.
Gender identity/experienced gender: This refers to one's internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.
Gender identity disorder: This is the term used for GD/gender incongruence in previous versions of DSM (see "gender dysphoria"). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using "gender incongruence of childhood."
Gender incongruence: This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.
Gender variance: See "gender incongruence"
Gender reassignment: This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.
Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.
Gender role: This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.
Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy.
Sex: This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.
Sexual orientation: This term describes an individual's enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.
Transgender: This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.
Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.
Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.
Transition: This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.
Transsexual: This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called "desisters"). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people's lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender
   4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:
   1. The condition exists with a disorder of sex development.
   2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

Reference: American Psychiatric Association (14).

doi: 10.1210/jc.2017-01658

of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:
1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
- the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
- gender dysphoria worsened with the onset of puberty,
- any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
- the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,

2. And the adolescent:
- has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
- agrees with the indication for GnRH agonist treatment,
- has confirmed that puberty has started in the adolescent (Tanner stage ≥G2/B2),
- has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
- the persistence of gender dysphoria,
- any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
- the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,

2. And the adolescent:
- has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
- agrees with the indication for sex hormone treatment,
- has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

doi: 10.1210/jc.2017-01658

reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermarche was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the "normal range" (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 |⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 |⊕⊕◯◯)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

doi: 10.1210/jc.2017-01658

barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam's apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 l⊕⊕○○)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:
1. Prepubertal
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:
1. Prepubertal, testicular volume <4 mL
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
3. Penis longer, testes larger (8–12 mL)
4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
5. Penis adult size; testicular volume > 15 ml

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after "gender-reassignment surgery" (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD *z* scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD *z* scores and of bone mineral apparent density *z* scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (±1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (±1.4) years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (±2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD *z* scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog–treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D–deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog–treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

doi: 10.1210/jc.2017-01658

want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 |⊕⊕◯◯)

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 |⊕⊕◯◯)

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OH vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β-estradiol, increasing the dose every 6 mo:
- 5 μg/kg/d
- 10 μg/kg/d
- 15 μg/kg/d
- 20 μg/kg/d
- Adult dose = 2–6 mg/d
- *In postpubertal transgender female adolescents, the dose of 17β-estradiol can be increased more rapidly:*
  - 1 mg/d for 6 mo
  - 2 mg/d

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):
- 6.25–12.5 μg/24 h (cut 25-μg patch into quarters, then halves)
- 25 μg/24 h
- 37.5 μg/24 h
- Adult dose = 50–200 μg/24 h
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).*

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):
- 25 mg/m^2/2 wk (or alternatively, half this dose weekly, or double the dose every 4 wk)
- 50 mg/m^2/2 wk
- 75 mg/m^2/2 wk
- 100 mg/m^2/2 wk
- Adult dose = 100–200 mg every 2 wk
- *In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:*
  - 75 mg/2 wk for 6 mo
  - 125 mg/2 wk
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).*

Adapted from Hembree *et al.* (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo
- •Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo
- •In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D
- •In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y
- •BMD using DXA
- •Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).
For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree *et al.* (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

doi: 10.1210/jc.2017-01658

for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17β-estradiol may be an alternative for oral 17β-estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 "Adverse Outcome Prevention and Long-Term Care") and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen
Very high risk of adverse outcomes:
•Thromboembolic disease
Moderate risk of adverse outcomes:
•Macroprolactinoma
•Breast cancer
•Coronary artery disease
•Cerebrovascular disease
•Cholelithiasis
•Hypertriglyceridemia
Transgender male: testosterone
Very high risk of adverse outcomes:
•Erythrocytosis (hematocrit > 50%)
Moderate risk of adverse outcomes:
•Severe liver dysfunction (transaminases > threefold upper limit of normal)
•Coronary artery disease
•Cerebrovascular disease
•Hypertension
•Breast or uterine cancer

doi: 10.1210/jc.2017-01658

Table 11. Hormone Regimens in Transgender Persons

Transgender females[a]	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate[b]	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate[c]	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6%[d]	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

[a]Estrogens used with or without antiandrogens or GnRH agonist.

[b]Not available in the United States.

[c]One thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

[d]Avoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5α-Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17β-estradiol, or transdermal 17β-estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the "first pass effect" than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (*e.g.*, male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕○○○)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and antiandrogen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

[a] Prevention and treatment as recommended for biological men.

[b] Menorrhagia requires diagnosis and treatment by a gynecologist.

doi: 10.1210/jc.2017-01658

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

[a]Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b]Familial scalp hair loss may occur if estrogens are stopped.

[c]Treatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone–induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

[a] Adapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 l⊕⊕◯◯)

Evidence

Estrogen therapy can increase the growth of pituitary lactrotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
   a. Serum testosterone levels should be <50 ng/dL.
   b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

doi: 10.1210/jc.2017-01658

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕◯◯)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low–quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕◯◯)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pretreatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than −2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (*e.g.*, when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 |⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕◯◯◯)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1 30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

doi: 10.1210/jc.2017-01658

provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the "threshold of 18 should not be seen as an indication in itself for active intervention." If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologuous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (*e.g.*, cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕◯◯◯)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

doi: 10.1210/jc.2017-01658

causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

Financial Disclosures of the Task Force*

Wylie C. Hembree (chair)—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Peggy T. Cohen-Kettenis**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Louis Gooren**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Sabine E. Hannema**—financial or business/organizational interests: none declared, significant financial interest or leadership position: Ferring Pharmaceuticals Inc. (lecture/conference), Pfizer (lecture). **Walter J. Meyer**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **M. Hassan Murad****—financial or business/organizational interests: Mayo Clinic, Evidence-based Practice Center, significant financial interest or leadership position: none declared. **Stephen M. Rosenthal**—financial or business/organizational interests: AbbVie (consultant), National Institutes of Health (grantee), significant financial interest or leadership position: Pediatric Endocrine Society (immediate past president). **Joshua D. Safer, FACP**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Vin Tangpricha**—financial or business/organizational interests: Cystic Fibrosis Foundation (grantee), National Institutes of Health (grantee), significant financial interest or leadership position, Elsevier *Journal of Clinical and Translational Endocrinology* (editor). **Guy G. T'Sjoen**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared.* Financial, business, and organizational disclosures of the task force cover the year prior to publication. Disclosures prior to this time period are archived.**Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.

Acknowledgments

Correspondence and Reprint Requests: The Endocrine Society, 2055 L Street NW, Suite 600, Washington, DC 20036. E-mail: publications@endocrine.org; Phone: 202971-3636.

Disclosure Summary: See Financial Disclosures.

Disclaimer: The Endocrine Society's clinical practice guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgement of healthcare providers and each patient's individual circumstances.

The Endocrine Society makes no warranty, express or implied, regarding the guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect,

special, incidental, or consequential damages related to the use of the information contained herein.

References

1. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW, Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;**328**(7454):1490.
2. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab*. 2008;**93**(3):666–673.
3. Bullough VL. Transsexualism in history. *Arch Sex Behav*. 1975; **4**(5):561–571.
4. Benjamin H. The transsexual phenomenon. *Trans N Y Acad Sci*. 1967;**29**(4):428–430.
5. Meyerowitz J. *How Sex Changed: A History of Transsexuality in the United States*. Cambridge, MA: Harvard University Press; 2002.
6. Hirschfeld M. *Was muss das Volk vom Dritten Geschlecht wissen*. Verlag Max Spohr, Leipzig; 1901.
7. Fisk NM. Editorial: Gender dysphoria syndrome—the conceptualization that liberalizes indications for total gender reorientation and implies a broadly based multi-dimensional rehabilitative regimen. *West J Med*. 1974;**120**(5):386–391.
8. Diamond L. Transgender experience and identity. In: Schwartz SJ, Luyckx K, Vignoles VL, eds. *Handbook of Identity Theory and Research*. New York, NY: Springer; 2011:629–647.
9. Queen C, Schimel L, eds. *PoMoSexuals: Challenging Assumptions About Gender and Sexuality*. San Francisco, CA: Cleis Press; 1997.
10. Case LK, Ramachandran VS. Alternating gender incongruity: a new neuropsychiatric syndrome providing insight into the dynamic plasticity of brain-sex. *Med Hypotheses*. 2012;**78**(5): 626–631.
11. Johnson TW, Wassersug RJ. Gender identity disorder outside the binary: when gender identity disorder-not otherwise specified is not good enough. *Arch Sex Behav*. 2010;**39**(3):597–598.
12. Wibowo E, Wassersug R, Warkentin K, Walker L, Robinson J, Brotto L, Johnson T. Impact of androgen deprivation therapy on sexual function: a response. *Asian J Androl*. 2012;**14**(5):793–794.
13. Pasquesoone V. 7 countries giving transgender people fundamental rights the U.S. still won't. 2014. Available at: https://mic.com/articles/87149/7-countries-giving-transgender-people-fundamental-rights-the-u-s-still-won-t. Accessed 26 August 2016.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association Publishing.
15. Drescher J, Cohen-Kettenis P, Winter S. Minding the body: situating gender identity diagnoses in the ICD-11. *Int Rev Psychiatry*. 2012;**24**(6):568–577.
16. World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. Available at: http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926. Accessed 1 September 2017.
17. Kreukels BP, Haraldsen IR, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis PT. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012;**27**(6):445–450.
18. Dekker MJ, Wierckx K, Van Caenegem E, Klaver M, Kreukels BP, Elaut E, Fisher AD, van Trotsenburg MA, Schreiner T, den Heijer M, T'Sjoen G. A European network for the investigation of gender incongruence: endocrine part. *J Sex Med*. 2016;**13**(6):994–999.
19. Ruble DN, Martin CL, Berenbaum SA. Gender development. In: Damon WL, Lerner RM, Eisenberg N, eds. *Handbook of Child Psychology: Social, Emotional, and Personality Development*. **Vol. 3**. 6th ed. New York, NY: Wiley; 2006;858–931.
20. Steensma TD, Kreukels BP, de Vries AL, Cohen-Kettenis PT. Gender identity development in adolescence. *Horm Behav*. 2013; **64**(2):288–297.
21. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrinol Metab*. 2014;**99**(12): 4379–4389.
22. Saraswat A, Weinand JD, Safer JD. Evidence supporting the biologic nature of gender identity. *Endocr Pract*. 2015;**21**(2): 199–204.
23. Gooren L. The biology of human psychosexual differentiation. *Horm Behav*. 2006;**50**(4):589–601.
24. Berenbaum SA, Meyer-Bahlburg HF. Gender development and sexuality in disorders of sex development. *Horm Metab Res*. 2015; **47**(5):361–366.
25. Dessens AB, Slijper FME, Drop SLS. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Arch Sex Behav*. 2005;**34**(4):389–397.
26. Meyer-Bahlburg HFL, Dolezal C, Baker SW, Ehrhardt AA, New MI. Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. *Arch Sex Behav*. 2006; **35**(6):667–684.
27. Frisén L, Nordenström A, Falhammar H, Filipsson H, Holmdahl G, Janson PO, Thorén M, Hagenfeldt K, Möller A, Nordenskjöld A. Gender role behavior, sexuality, and psychosocial adaptation in women with congenital adrenal hyperplasia due to CYP21A2 deficiency. *J Clin Endocrinol Metab*. 2009;**94**(9):3432–3439.
28. Meyer-Bahlburg HFL, Dolezal C, Baker SW, Carlson AD, Obeid JS, New MI. Prenatal androgenization affects gender-related behavior but not gender identity in 5–12-year-old girls with congenital adrenal hyperplasia. *Arch Sex Behav*. 2004;**33**(2):97–104.
29. Cohen-Kettenis PT. Gender change in 46,XY persons with 5α-reductase-2 deficiency and 17β-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005;**34**(4):399–410.
30. Reiner WG, Gearhart JP. Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. *N Engl J Med*. 2004;**350**(4):333–341.
31. Meyer-Bahlburg HFL. Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. *Arch Sex Behav*. 2005;**34**(4):423–438.
32. Coolidge FL, Thede LL, Young SE. The heritability of gender identity disorder in a child and adolescent twin sample. *Behav Genet*. 2002;**32**(4):251–257.
33. Heylens G, De Cuypere G, Zucker KJ, Schelfaut C, Elaut E, Vanden Bossche H, De Baere E, T'Sjoen G. Gender identity disorder in twins: a review of the case report literature. *J Sex Med*. 2012;**9**(3):751–757.
34. Fernández R, Esteva I, Gómez-Gil E, Rumbo T, Almaraz MC, Roda E, Haro-Mora J-J, Guillamón A, Pásaro E. Association study of ERβ, AR, and CYP19A1 genes and MtF transsexualism. *J Sex Med*. 2014;**11**(12):2986–2994.
35. Henningsson S, Westberg L, Nilsson S, Lundström B, Ekselius L, Bodlund O, Lindström E, Hellstrand M, Rosmond R, Eriksson E, Landén M. Sex steroid-related genes and male-to-female transsexualism. *Psychoneuroendocrinology*. 2005;**30**(7):657–664.
36. Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009;**65**(1):93–96.
37. Lombardo F, Toselli L, Grassetti D, Paoli D, Masciandaro P, Valentini F, Lenzi A, Gandini L. Hormone and genetic study in

doi: 10.1210/jc.2017-01658

male to female transsexual patients. *J Endocrinol Invest*. 2013; **36**(8):550–557.
38. Ujike H, Otani K, Nakatsuka M, Ishii K, Sasaki A, Oishi T, Sato T, Okahisa Y, Matsumoto Y, Namba Y, Kimata Y, Kuroda S. Association study of gender identity disorder and sex hormone-related genes. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;**33**(7):1241–1244.
39. Kreukels BP, Guillamon A. Neuroimaging studies in people with gender incongruence. *Int Rev Psychiatry*. 2016;**28**(1): 120–128.
40. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;**16**(4):499–516.
41. Wallien MSC, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. *J Am Acad Child Adolesc Psychiatry*. 2008;**47**(12):1413–1423.
42. Steensma TD, McGuire JK, Kreukels BPC, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013;**52**(6):582–590.
43. Cohen-Kettenis PT, Owen A, Kaijser VG, Bradley SJ, Zucker KJ. Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: a cross-national, cross-clinic comparative analysis. *J Abnorm Child Psychol*. 2003;**31**(1):41–53.
44. Dhejne C, Van Vlerken R, Heylens G, Arcelus J. Mental health and gender dysphoria: a review of the literature. *Int Rev Psychiatry*. 2016;**28**(1):44–57.
45. Pasterski V, Gilligan L, Curtis R. Traits of autism spectrum disorders in adults with gender dysphoria. *Arch Sex Behav*. 2014; **43**(2):387–393.
46. Spack NP, Edwards-Leeper L, Feldman HA, Leibowitz S, Mandel F, Diamond DA, Vance SR. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;**129**(3):418–425.
47. Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res*. 2012;**200**(2-3):469–474.
48. VanderLaan DP, Leef JH, Wood H, Hughes SK, Zucker KJ. Autism spectrum disorder risk factors and autistic traits in gender dysphoric children. *J Autism Dev Disord*. 2015;**45**(6):1742–1750.
49. de Vries ALC, Doreleijers TAH, Steensma TD, Cohen-Kettenis PT. Psychiatric comorbidity in gender dysphoric adolescents. *J Child Psychol Psychiatry*. 2011;**52**(11):1195–1202.
50. de Vries ALC, Noens ILJ, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord*. 2010; **40**(8):930–936.
51. Wallien MSC, Swaab H, Cohen-Kettenis PT. Psychiatric comorbidity among children with gender identity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;**46**(10):1307–1314.
52. Kuiper AJ, Cohen-Kettenis PT. Gender role reversal among postoperative transsexuals. Available at: https://www.atria.nl/ezines/web/IJT/97-03/numbers/symposion/ijtc0502.htm. Accessed 26 August 2016.
53. Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand*. 1998; **97**(4):284–289.
54. Olsson S-E, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long-term follow-up. *Arch Sex Behav*. 2006;**35**(4):501–506.
55. Pfäfflin F, Junge A, eds. *Geschlechtsumwandlung: Abhandlungen zur Transsexualität*. Stuttgart, Germany: Schattauer; 1992.
56. Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav*. 2003;**32**(4):299–315.
57. Cohen-Kettenis PT, Pfäfflin F. *Transgenderism and Intersexuality in Childhood and Adolescence: Making Choices*. Thousand Oaks, CA: SAGE Publications; 2003.
58. Di Ceglie D, Freedman D, McPherson S, Richardson P. Children and adolescents referred to a specialist gender identity development service: clinical features and demographic characteristics. Available at: https://www.researchgate.net/publication/276061306_Children_and_Adolescents_Referred_to_a_Specialist_Gender_Identity_Development_Service_Clinical_Features_and_Demographic_Characteristics. Accessed 20 July 2017.
59. Gijs L, Brewaeys A. Surgical treatment of gender dysphoria in adults and adolescents: recent developments, effectiveness, and challenges. *Annu Rev Sex Res*. 2007;**18**:178–224.
60. Cohen-Kettenis PT, van Goozen SHM. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997;**36**(2):263–271.
61. Smith YLS, van Goozen SHM, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2001;**40**(4):472–481.
62. Smith YLS, Van Goozen SHM, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med*. 2005;**35**(1):89–99.
63. de Vries ALC, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TAH, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014;**134**(4):696–704.
64. Cole CM, O'Boyle M, Emory LE, Meyer WJ III. Comorbidity of gender dysphoria and other major psychiatric diagnoses. *Arch Sex Behav*. 1997;**26**(1):13–26.
65. Cohen-Kettenis PT, Schagen SEE, Steensma TD, de Vries ALC, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. *Arch Sex Behav*. 2011; **40**(4):843–847.
66. First MB. Desire for amputation of a limb: paraphilia, psychosis, or a new type of identity disorder. *Psychol Med*. 2005;**35**(6): 919–928.
67. Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedecker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod*. 2012;**27**(2):483–487.
68. Wierckx K, Stuyver I, Weyers S, Hamada A, Agarwal A, De Sutter P, T'Sjoen G. Sperm freezing in transsexual women. *Arch Sex Behav*. 2012;**41**(5):1069–1071.
69. Bertelloni S, Baroncelli GI, Ferdeghini M, Menchini-Fabris F, Saggese G. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. *Eur J Pediatr*. 2000;**159**(5):369–374.
70. Büchter D, Behre HM, Kliesch S, Nieschlag E. Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases. *Eur J Endocrinol*. 1998; **139**(3):298–303.
71. Liu PY, Turner L, Rushford D, McDonald J, Baker HW, Conway AJ, Handelsman DJ. Efficacy and safety of recombinant human follicle stimulating hormone (Gonal-F) with urinary human chorionic gonadotrophin for induction of spermatogenesis and fertility in gonadotrophin-deficient men. *Hum Reprod*. 1999; **14**(6):1540–1545.
72. Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. *J Clin Endocrinol Metab*. 2008;**93**(1):190–195.
73. Magiakou MA, Manousaki D, Papadaki M, Hadjidakis D, Levidou G, Vakaki M, Papaefstathiou A, Lalioti N, Kanaka-Gantenbein C, Piaditis G, Chrousos GP, Dacou-Voutetakis C. The

efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *J Clin Endocrinol Metab*. 2010;**95**(1):109–117.
74. Baba T, Endo T, Honnma H, Kitajima Y, Hayashi T, Ikeda H, Masumori N, Kamiya H, Moriwaka O, Saito T. Association between polycystic ovary syndrome and female-to-male transsexuality. *Hum Reprod*. 2007;**22**(4):1011–1016.
75. Spinder T, Spijkstra JJ, van den Tweel JG, Burger CW, van Kessel H, Hompes PGA, Gooren LJG. The effects of long term testosterone administration on pulsatile luteinizing hormone secretion and on ovarian histology in eugonadal female to male transsexual subjects. *J Clin Endocrinol Metab*. 1989;**69**(1):151–157.
76. Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med*. 2011;**8**(6):1686–1693.
77. Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med*. 2009;**6**(4):1018–1023.
78. Ikeda K, Baba T, Noguchi H, Nagasawa K, Endo T, Kiya T, Saito T. Excessive androgen exposure in female-to-male transsexual persons of reproductive age induces hyperplasia of the ovarian cortex and stroma but not polycystic ovary morphology. *Hum Reprod*. 2013;**28**(2):453–461.
79. Trebay G. He's pregnant. You're speechles. New York Times. 22 June 2008.
80. Light AD, Obedin-Maliver J, Sevelius JM, Kerns JL. Transgender men who experienced pregnancy after female-to-male gender transitioning. *Obstet Gynecol*. 2014;**124**(6):1120–1127.
81. De Sutter P. Donor inseminations in partners of female-to-male transsexuals: should the question be asked? *Reprod Biomed Online*. 2003;**6**(3):382, author reply 282–283.
82. De Roo C, Tilleman K, T'Sjoen G, De Sutter P. Fertility options in transgender people. *Int Rev Psychiatry*. 2016;**28**(1):112–119.
83. Wennink JMB, Delemarre-van de Waal HA, Schoemaker R, Schoemaker H, Schoemaker J. Luteinizing hormone and follicle stimulating hormone secretion patterns in boys throughout puberty measured using highly sensitive immunoradiometric assays. *Clin Endocrinol (Oxf)*. 1989;**31**(5):551–564.
84. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJG. The treatment of adolescent transsexuals: changing insights. *J Sex Med*. 2008;**5**(8):1892–1897.
85. Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol*. 2006;**155**:S131–S137.
86. de Vries ALC, Steensma TD, Doreleijers TAH, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med*. 2011;**8**(8):2276–2283.
87. Bouman MB, van Zeijl MCT, Buncamper ME, Meijerink WJHJ, van Bodegraven AA, Mullender MG. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med*. 2014;**11**(7):1835–1847.
88. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Antoniazzi F, Berenbaum S, Bourguignon JP, Chrousos GP, Coste J, Deal S, de Vries L, Foster C, Heger S, Holland J, Jahnukainen K, Juul A, Kaplowitz P, Lahlou N, Lee MM, Lee P, Merke DP, Neely EK, Oostdijk W, Phillip M, Rosenfield RL, Shulman D, Styne D, Tauber M, Wit JM; ESPE-LWPES GnRH Analogs Consensus Conference Group. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;**123**(4):e752–e762.
89. Roth CL, Brendel L, Rückert C, Hartmann K. Antagonistic and agonistic GnRH analogue treatment of precocious puberty: tracking gonadotropin concentrations in urine. *Horm Res*. 2005;**63**(5):257–262.
90. Roth C. Therapeutic potential of GnRH antagonists in the treatment of precocious puberty. *Expert Opin Investig Drugs*. 2002;**11**(9):1253–1259.
91. Tuvemo T. Treatment of central precocious puberty. *Expert Opin Investig Drugs*. 2006;**15**(5):495–505.
92. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. *J Sex Med*. 2016;**13**(7):1125–1132.
93. Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, Hill SC, Loriaux DL, Cutler GB, Jr. Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. *J Clin Endocrinol Metab*. 1988;**67**(2):368–372.
94. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab*. 2015;**100**(2):E270–E275.
95. Finkelstein JS, Klibanski A, Neer RM. A longitudinal evaluation of bone mineral density in adult men with histories of delayed puberty. *J Clin Endocrinol Metab*. 1996;**81**(3):1152–1155.
96. Bertelloni S, Baroncelli GI, Ferdeghini M, Perri G, Saggese G. Normal volumetric bone mineral density and bone turnover in young men with histories of constitutional delay of puberty. *J Clin Endocrinol Metab*. 1998;**83**(12):4280–4283.
97. Darelid A, Ohlsson C, Nilsson M, Kindblom JM, Mellström D, Lorentzon M. Catch up in bone acquisition in young adult men with late normal puberty. *J Bone Miner Res*. 2012;**27**(10):2198–2207.
98. Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. *J Clin Endocrinol Metab*. 2002;**87**(8):3656–3661.
99. Saggese G, Bertelloni S, Baroncelli GI, Battini R, Franchi G. Reduction of bone density: an effect of gonadotropin releasing hormone analogue treatment in central precocious puberty. *Eur J Pediatr*. 1993;**152**(9):717–720.
100. Neely EK, Bachrach LK, Hintz RL, Habiby RL, Slemenda CW, Feezle L, Pescovitz OH. Bone mineral density during treatment of central precocious puberty. *J Pediatr*. 1995;**127**(5):819–822.
101. Bertelloni S, Baroncelli GI, Sorrentino MC, Perri G, Saggese G. Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr*. 1998;**157**(5):363–367.
102. Thornton P, Silverman LA, Geffner ME, Neely EK, Gould E, Danoff TM. Review of outcomes after cessation of gonadotropin-releasing hormone agonist treatment of girls with precocious puberty. *Pediatr Endocrinol Rev*. 2014;**11**(3):306–317.
103. Lem AJ, van der Kaay DC, Hokken-Koelega AC. Bone mineral density and body composition in short children born SGA during growth hormone and gonadotropin releasing hormone analog treatment. *J Clin Endocrinol Metab*. 2013;**98**(1):77–86.
104. Antoniazzi F, Zamboni G, Bertoldo F, Lauriola S, Mengarda F, Pietrobelli A, Tatò L. Bone mass at final height in precocious puberty after gonadotropin-releasing hormone agonist with and without calcium supplementation. *J Clin Endocrinol Metab*. 2003;**88**(3):1096–1101.
105. Calcaterra V, Mannarino S, Corana G, Codazzi AC, Mazzola A, Brambilla P, Larizza D. Hypertension during therapy with triptorelin in a girl with precocious puberty. *Indian J Pediatr*. 2013;**80**(10):884–885.
106. Siomou E, Kosmeri C, Pavlou M, Vlahos AP, Argyropoulou MI, Siamopoulou A. Arterial hypertension during treatment with triptorelin in a child with Williams-Beuren syndrome. *Pediatr Nephrol*. 2014;**29**(9):1633–1636.
107. Staphorsius AS, Kreukels BPC, Cohen-Kettenis PT, Veltman DJ, Burke SM, Schagen SEE, Wouters FM, Delemarre-van de Waal

HA, Bakker J. Puberty suppression and executive functioning: an fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology*. 2015;**56**:190–199.
108. Hough D, Bellingham M, Haraldsen IR, McLaughlin M, Rennie M, Robinson JE, Solbakk AK, Evans NP. Spatial memory is impaired by peripubertal GnRH agonist treatment and testosterone replacement in sheep. *Psychoneuroendocrinology*. 2017; **75**:173–182.
109. Collipp PJ, Kaplan SA, Boyle DC, Plachte F, Kogut MD. Constitutional Isosexual Precocious Puberty. *Am J Dis Child*. 1964; **108**:399–405.
110. Hahn HB, Jr, Hayles AB, Albert A. Medroxyprogesterone and constitutional precocious puberty. *Mayo Clin Proc*. 1964;**39**: 182–190.
111. Kaplan SA, Ling SM, Irani NG. Idiopathic isosexual precocity. *Am J Dis Child*. 1968;**116**(6):591–598.
112. Schoen EJ. Treatment of idiopathic precocious puberty in boys. *J Clin Endocrinol Metab*. 1966;**26**(4):363–370.
113. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res*. 2005;**64**(Suppl 2):31–36.
114. Moore E, Wisniewski A, Dobs A. Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab*. 2003;**88**(8):3467–3473.
115. Krueger RB, Hembree W, Hill M. Prescription of medroxyprogesterone acetate to a patient with pedophilia, resulting in Cushing's syndrome and adrenal insufficiency. *Sex Abuse*. 2006; **18**(2):227–228.
116. Lynch MM, Khandheria MM, Meyer WJ. Retrospective study of the management of childhood and adolescent gender identity disorder using medroxyprogesterone acetate. *Int J Transgenderism*. 2015;**16**:201–208.
117. Tack LJW, Craen M, Dhondt K, Vanden Bossche H, Laridaen J, Cools M. Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. *Biol Sex Differ*. 2016;**7**:14.
118. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;**94**(9):3132–3154.
119. Mann L, Harmoni R, Power C. Adolescent decision-making: the development of competence. *J Adolesc*. 1989;**12**(3):265–278.
120. Stultiëns L, Goffin T, Borry P, Dierickx K, Nys H. Minors and informed consent: a comparative approach. *Eur J Health Law*. 2007;**14**(1):21–46.
121. Arshagouni P. "But I'm an adult now … sort of". Adolescent consent in health care decision-making and the adolescent brain. Available at: http://digitalcommons.law.umaryland.edu/cgi/viewcontent.cgi?article=1124&context=jhclp. Accessed 25 June 2017.
122. NHS. Prescribing of cross-sex hormones as part of the gender identity development service for children and adolescents. Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/08/clinical-com-pol-16046p.pdf. Accessed 14 June 2017.
123. Ankarberg-Lindgren C, Kriström B, Norjavaara E. Physiological estrogen replacement therapy for puberty induction in girls: a clinical observational study. *Horm Res Paediatr*. 2014;**81**(4): 239–244.
124. Olson J, Schrager SM, Clark LF, Dunlap SL, Belzer M. Subcutaneous testosterone: an effective delivery mechanism for masculinizing young transgender men. *LGBT Health*. 2014;**1**(3): 165–167.
125. Spratt DI, Stewart I, Savage C, Craig W, Spack NP, Chandler DW, Spratt LV, Eimicke T, Olshan JS. Subcutaneous injection of testosterone is an effective and preferred alternative to intramuscular injection: demonstration in female-to-male transgender patients. *J Clin Endocrinol Metab*. 2017. doi:10.1210/jc.2017-00359
126. Eisenegger C, von Eckardstein A, Fehr E, von Eckardstein S. Pharmacokinetics of testosterone and estradiol gel preparations in healthy young men. *Psychoneuroendocrinology*. 2013;**38**(2): 171–178.
127. de Ronde W, ten Kulve J, Woerdeman J, Kaufman J-M, de Jong FH. Effects of oestradiol on gonadotrophin levels in normal and castrated men. *Clin Endocrinol (Oxf)*. 2009;**71**(6):874–879.
128. Money J, Ehrhardt A. Man & woman, boy & girl: differentiation and dimorphism of gender identity from conception to maturity. Baltimore, MD: Johns Hopkins University Press; 1972:202–206.
129. Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med*. 2014;**11**(1):119–126.
130. Costa R, Colizzi M. The effect of cross-sex hormonal treatment on gender dysphoria individuals' mental health: a systematic review. *Neuropsychiatr Dis Treat*. 2016;**12**:1953–1966.
131. Gooren LJG, Giltay EJ. Review of studies of androgen treatment of female-to-male transsexuals: effects and risks of administration of androgens to females. *J Sex Med*. 2008;**5**(4):765–776.
132. Levy A, Crown A, Reid R. Endocrine intervention for transsexuals. *Clin Endocrinol (Oxf)*. 2003;**59**(4):409–418.
133. Tangpricha V, Ducharme SH, Barber TW, Chipkin SR. Endocrinologic treatment of gender identity disorders. *Endocr Pract*. 2003;**9**(1):12–21.
134. Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf)*. 2015;**83**(5):597–606.
135. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2006;**91**(6): 1995–2010.
136. Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola MC. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014;**11**(12):3002–3011.
137. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;**291**(14):1701–1712.
138. Dickersin K, Munro MG, Clark M, Langenberg P, Scherer R, Frick K, Zhu Q, Hallock L, Nichols J, Yalcinkaya TM; Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding (STOP-DUB) Research Group. Hysterectomy compared with endometrial ablation for dysfunctional uterine bleeding: a randomized controlled trial. *Obstet Gynecol*. 2007;**110**(6): 1279–1289.
139. Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab*. 2008;**93**(1):19–25.
140. Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. *Arch Sex Behav*. 1989;**18**(1):49–57.
141. Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes*. 2005;**113**(10):586–592.

142. Stripp B, Taylor AA, Bartter FC, Gillette JR, Loriaux DL, Easley R, Menard RH. Effect of spironolactone on sex hormones in man. *J Clin Endocrinol Metab*. 1975;**41**(4):777–781.
143. Levy J, Burshell A, Marbach M, Afllalo L, Glick SM. Interaction of spironolactone with oestradiol receptors in cytosol. *J Endocrinol*. 1980;**84**(3):371–379.
144. Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med*. 2014;**11**(1):107–118.
145. Chiriacò G, Cauci S, Mazzon G, Trombetta C. An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia. *Andrology*. 2016;**4**(2):245–250.
146. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol (Oxf)*. 2016; **85**(2):239–246.
147. Casper RF, Yen SS. Rapid absorption of micronized estradiol-17 beta following sublingual administration. *Obstet Gynecol*. 1981; **57**(1):62–64.
148. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17β-estradiol. *Obstet Gynecol*. 1997;**89**(3): 340–345.
149. Toorians AWFT, Thomassen MCLGD, Zweegman S, Magdeleyns EJP, Tans G, Gooren LJG, Rosing J. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. *J Clin Endocrinol Metab*. 2003;**88**(12): 5723–5729.
150. Mepham N, Bouman WP, Arcelus J, Hayter M, Wylie KR. People with gender dysphoria who self-prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med*. 2014; **11**(12):2995–3001.
151. Richards C, Bouman WP, Seal L, Barker MJ, Nieder TO, T'Sjoen G. Non-binary or genderqueer genders. *Int Rev Psychiatry*. 2016; **28**(1):95–102.
152. Cosyns M, Van Borsel J, Wierckx K, Dedecker D, Van de Peer F, Daelman T, Laenen S, T'Sjoen G. Voice in female-to-male transsexual persons after long-term androgen therapy. *Laryngoscope*. 2014;**124**(6):1409–1414.
153. Deuster D, Matulat P, Knief A, Zitzmann M, Rosslau K, Szukaj M, am Zehnhoff-Dinnesen A, Schmidt CM. Voice deepening under testosterone treatment in female-to-male gender dysphoric individuals. *Eur Arch Otorhinolaryngol*. 2016;**273**(4):959–965.
154. Lapauw B, Taes Y, Simoens S, Van Caenegem E, Weyers S, Goemaere S, Toye K, Kaufman J-M, T'Sjoen GG. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. *Bone*. 2008;**43**(6):1016–1021.
155. Meyer III WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav*. 1986;**15**(2): 121–138.
156. Asscheman H, Gooren LJ, Assies J, Smits JP, de Slegte R. Prolactin levels and pituitary enlargement in hormone-treated male-to-female transsexuals. *Clin Endocrinol (Oxf)*. 1988;**28**(6):583–588.
157. Gooren LJ, Harmsen-Louman W, van Kessel H. Follow-up of prolactin levels in long-term oestrogen-treated male-to-female transsexuals with regard to prolactinoma induction. *Clin Endocrinol (Oxf)*. 1985;**22**(2):201–207.
158. Wierckx K, Van Caenegem E, Schreiner T, Haraldsen I, Fisher AD, Toye K, Kaufman JM, T'Sjoen G. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med*. 2014;**11**(8):1999–2011.
159. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril*. 2010;**93**(4):1267–1272.
160. Giltay EJ, Hoogeveen EK, Elbers JMH, Gooren LJG, Asscheman H, Stehouwer CDA. Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. *J Clin Endocrinol Metab*. 1998;**83**(2):550–553.
161. van Kesteren PJM, Asscheman H, Megens JAJ, Gooren LJG. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997;**47**(3): 337–343.
162. Wierckx K, Gooren L, T'Sjoen G. Clinical review: breast development in trans women receiving cross-sex hormones. *J Sex Med*. 2014;**11**(5):1240–1247.
163. Bird D, Vowles K, Anthony PP. Spontaneous rupture of a liver cell adenoma after long term methyltestosterone: report of a case successfully treated by emergency right hepatic lobectomy. *Br J Surg*. 1979;**66**(3):212–213.
164. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. *Lancet*. 1977; **2**(8032):262–263.
165. Weinand JD, Safer JD. Hormone therapy in transgender adults is safe with provider supervision; a review of hormone therapy sequelae for transgender individuals. *J Clin Transl Endocrinol*. 2015;**2**(2):55–60.
166. Roberts TK, Kraft CS, French D, Ji W, Wu AH, Tangpricha V, Fantz CR. Interpreting laboratory results in transgender patients on hormone therapy. *Am J Med*. 2014;**127**(2):159–162.
167. Vesper HW, Botelho JC, Wang Y. Challenges and improvements in testosterone and estradiol testing. *Asian J Androl*. 2014;**16**(2): 178–184.
168. Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola MC, Mueller A, Kuhn A, Dhejne C, Morel-Journel N, Gooren LJ. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014;**46**(7):791–795.
169. Righini M, Perrier A, De Moerloose P, Bounameaux H. D-dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost*. 2008;**6**(7):1059–1071.
170. Gooren LJ, Assies J, Asscheman H, de Slegte R, van Kessel H. Estrogen-induced prolactinoma in a man. *J Clin Endocrinol Metab*. 1988;**66**(2):444–446.
171. Kovacs K, Stefaneanu L, Ezzat S, Smyth HS. Prolactin-producing pituitary adenoma in a male-to-female transsexual patient with protracted estrogen administration. A morphologic study. *Arch Pathol Lab Med*. 1994;**118**(5):562–565.
172. Serri O, Noiseux D, Robert F, Hardy J. Lactotroph hyperplasia in an estrogen treated male-to-female transsexual patient. *J Clin Endocrinol Metab*. 1996;**81**(9):3177–3179.
173. Cunha FS, Domenice S, Câmara VL, Sircili MH, Gooren LJ, Mendonça BB, Costa EM. Diagnosis of prolactinoma in two male-to-female transsexual subjects following high-dose cross-sex hormone therapy. *Andrologia*. 2015;**47**(6):680–684.
174. Nota NM, Dekker MJHJ, Klaver M, Wiepjes CM, van Trotsenburg MA, Heijboer AC, den Heijer M. Prolactin levels during short- and long-term cross-sex hormone treatment: an observational study in transgender persons. *Andrologia*. 2017;**49**(6).
175. Bunck MC, Debono M, Giltay EJ, Verheijen AT, Diamant M, Gooren LJ. Autonomous prolactin secretion in two male-to-female transgender patients using conventional oestrogen dosages. *BMJ Case Rep*. 2009;**2009**:bcr0220091589.
176. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010;**72**(1):1–10.
177. Berra M, Armillotta F, D'Emidio L, Costantino A, Martorana G, Pelusi G, Meriggiola MC. Testosterone decreases adiponectin

levels in female to male transsexuals. *Asian J Androl*. 2006;**8**(6):725–729.
178. Elbers JMH, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, Gooren LJG. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. *Clin Endocrinol (Oxf)*. 2003;**58**(5):562–571.
179. Giltay EJ, Lambert J, Gooren LJG, Elbers JMH, Steyn M, Stehouwer CDA. Sex steroids, insulin, and arterial stiffness in women and men. *Hypertension*. 1999;**34**(4 Pt 1):590–597.
180. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ. Induction of insulin resistance by androgens and estrogens. *J Clin Endocrinol Metab*. 1994;**79**(1):265–271.
181. Maraka S. Effect of sex steroids on lipids, venous thromboembolism, cardiovascular disease and mortality in transgender individuals: a systematic review and meta-analysis. Available at: http://press.endocrine.org/doi/abs/10.1210/endo-meetings.2016.RE.15.FRI-136. Accessed 3 July 2017.
182. Meriggiola MC, Armillotta F, Costantino A, Altieri P, Saad F, Kalhorn T, Perrone AM, Ghi T, Pelusi C, Pelusi G. Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. *J Sex Med*. 2008;**5**(10):2442–2453.
183. Giltay EJ, Toorians AW, Sarabdjitsingh AR, de Vries NA, Gooren LJ. Established risk factors for coronary heart disease are unrelated to androgen-induced baldness in female-to-male transsexuals. *J Endocrinol*. 2004;**180**(1):107–112.
184. Giltay EJ, Verhoef P, Gooren LJG, Geleijnse JM, Schouten EG, Stehouwer CDA. Oral and transdermal estrogens both lower plasma total homocysteine in male-to-female transsexuals. *Atherosclerosis*. 2003;**168**(1):139–146.
185. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci*. 2005;**60**(11):1451–1457.
186. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;**285**(19):2486–2497.
187. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010;**72**(2):214–231.
188. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman JM, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015;**172**(2):163–171.
189. Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V. Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. *Clin Endocrinol (Oxf)*. 2004;**61**(5):560–566.
190. van Kesteren P, Lips P, Gooren LJG, Asscheman H, Megens J. Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1998;**48**(3):347–354.
191. Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman JM, Schreiner T, Haraldsen I, T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013;**54**(1):92–97.
192. Amin S, Zhang Y, Sawin CT, Evans SR, Hannan MT, Kiel DP, Wilson PW, Felson DT. Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham study. *Ann Intern Med*. 2000;**133**(12):951–963.
193. Gennari L, Khosla S, Bilezikian JP. Estrogen and fracture risk in men. *J Bone Miner Res*. 2008;**23**(10):1548–1551.
194. Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J Clin Endocrinol Metab*. 1998;**83**(7):2266–2274.
195. Mueller A, Dittrich R, Binder H, Kuehnel W, Maltaris T, Hoffmann I, Beckmann MW. High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. *Eur J Endocrinol*. 2005;**153**(1):107–113.
196. Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K. Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. *Osteoporos Int*. 2005;**16**(7):791–798.
197. Ganly I, Taylor EW. Breast cancer in a trans-sexual man receiving hormone replacement therapy. *Br J Surg*. 1995;**82**(3):341.
198. Pritchard TJ, Pankowsky DA, Crowe JP, Abdul-Karim FW. Breast cancer in a male-to-female transsexual. A case report. *JAMA*. 1988;**259**(15):2278–2280.
199. Symmers WS. Carcinoma of breast in trans-sexual individuals after surgical and hormonal interference with the primary and secondary sex characteristics. *BMJ*. 1968;**2**(5597):83–85.
200. Brown GR. Breast cancer in transgender veterans: a ten-case series. *LGBT Health*. 2015;**2**(1):77–80.
201. Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer*. 2011;**11**(6):417–419.
202. Nikolic DV, Djordjevic ML, Granic M, Nikolic AT, Stanimirovic VV, Zdravkovic D, Jelic S. Importance of revealing a rare case of breast cancer in a female to male transsexual after bilateral mastectomy. *World J Surg Oncol*. 2012;**10**:280.
203. Bösze P, Tóth A, Török M. Hormone replacement and the risk of breast cancer in Turner's syndrome. *N Engl J Med*. 2006;**355**(24):2599–2600.
204. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA; UK Clinical Cytogenetics Group. Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. *Lancet Oncol*. 2008;**9**(3):239–246.
205. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2006. *CA Cancer J Clin*. 2006;**56**(1):11–25, quiz 49–50.
206. Wilson JD, Roehrborn C. Long-term consequences of castration in men: lessons from the Skoptzy and the eunuchs of the Chinese and Ottoman courts. *J Clin Endocrinol Metab*. 1999;**84**(12):4324–4331.
207. van Kesteren P, Meinhardt W, van der Valk P, Geldof A, Megens J, Gooren L. Effects of estrogens only on the prostates of aging men. *J Urol*. 1996;**156**(4):1349–1353.
208. Brown JA, Wilson TM. Benign prostatic hyperplasia requiring transurethral resection of the prostate in a 60-year-old male-to-female transsexual. *Br J Urol*. 1997;**80**(6):956–957.
209. Casella R, Bubendorf L, Schaefer DJ, Bachmann A, Gasser TC, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;**75**(3):288–290.
210. Dorff TB, Shazer RL, Nepomuceno EM, Tucker SJ. Successful treatment of metastatic androgen-independent prostate carcinoma in a transsexual patient. *Clin Genitourin Cancer*. 2007;**5**(5):344–346.
211. Thurston AV. Carcinoma of the prostate in a transsexual. *Br J Urol*. 1994;**73**(2):217.

212. van Harst EP, Newling DW, Gooren LJ, Asscheman H, Prenger DM. Metastatic prostatic carcinoma in a male-to-female transsexual. *BJU Int*. 1998;**81**:776.
213. Turo R, Jallad S, Prescott S, Cross WR. Metastatic prostate cancer in transsexual diagnosed after three decades of estrogen therapy. *Can Urol Assoc J*. 2013;**7**(7–8):E544–E546.
214. Miksad RA, Bubley G, Church P, Sanda M, Rofsky N, Kaplan I, Cooper A. Prostate cancer in a transgender woman 41 years after initiation of feminization. *JAMA*. 2006;**296**(19):2316–2317.
215. Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;**157**(2):120–134.
216. Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav*. 1998; **27**(2):209–226.
217. Miller N, Bédard YC, Cooter NB, Shaul DL. Histological changes in the genital tract in transsexual women following androgen therapy. *Histopathology*. 1986;**10**(7):661–669.
218. O'Hanlan KA, Dibble SL, Young-Spint M. Total laparoscopic hysterectomy for female-to-male transsexuals. *Obstet Gynecol*. 2007;**110**(5):1096–1101.
219. Dizon DS, Tejada-Berges T, Koelliker S, Steinhoff M, Granai CO. Ovarian cancer associated with testosterone supplementation in a female-to-male transsexual patient. *Gynecol Obstet Invest*. 2006; **62**(4):226–228.
220. Hage JJ, Dekker JJML, Karim RB, Verheijen RHM, Bloemena E. Ovarian cancer in female-to-male transsexuals: report of two cases. *Gynecol Oncol*. 2000;**76**(3):413–415.
221. Mueller A, Gooren L. Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2008;**159**(3):197–202.
222. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfaefflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism*. 2012;**13**:165–232.
223. Colebunders B, D'Arpa S, Weijers S, Lumen N, Hoebeke P, Monstrey S. Female-to-male gender reassignment surgery. In: Ettner R, Monstrey S, Coleman E, eds. *Principles of Transgender Medicine and Surgery*. 2nd ed. New York, NY: Routledge Taylor & Francis Group; 2016:279–317.
224. Monstrey S, Hoebeke P, Dhont M, De Cuypere G, Rubens R, Moerman M, Hamdi M, Van Landuyt K, Blondeel P. Surgical therapy in transsexual patients: a multi-disciplinary approach. *Acta Chir Belg*. 2001;**101**(5):200–209.
225. Selvaggi G, Ceulemans P, De Cuypere G, VanLanduyt K, Blondeel P, Hamdi M, Bowman C, Monstrey S. Gender identity disorder: general overview and surgical treatment for vaginoplasty in male-to-female transsexuals. *Plast Reconstr Surg*. 2005;**116**(6): 135e–145e.
226. Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR. Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J*. 2007;**83**(984):638–642.
227. Horbach SER, Bouman M-B, Smit JM, Özer M, Buncamper ME, Mullender MG. Outcome of vaginoplasty in male-to-female transgenders: a systematic review of surgical techniques. *J Sex Med*. 2015;**12**(6):1499–1512.
228. Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes*. 2013; **20**(6):570–574.
229. Morrison SD, Satterwhite T, Grant DW, Kirby J, Laub DR, Sr, VanMaasdam J. Long-term outcomes of rectosigmoid neocolporrhaphy in male-to-female gender reassignment surgery. *Plast Reconstr Surg*. 2015;**136**(2):386–394.
230. Dessy LA, Mazzocchi M, Corrias F, Ceccarelli S, Marchese C, Scuderi N. The use of cultured autologous oral epithelial cells for vaginoplasty in male-to-female transsexuals: a feasibility, safety, and advantageousness clinical pilot study. *Plast Reconstr Surg*. 2014;**133**(1):158–161.
231. Li FY, Xu YS, Zhou CD, Zhou Y, Li SK, Li Q. Long-term outcomes of vaginoplasty with autologous buccal micromucosa. *Obstet Gynecol*. 2014;**123**(5):951–956.
232. Kanhai RC. Sensate vagina pedicled-spot for male-to-female transsexuals: the experience in the first 50 patients. *Aesthetic Plast Surg*. 2016;**40**(2):284–287.
233. Straayer C. Transplants for transsexuals? Ambitions, concerns, ideology. Paper presented at: Trans*Studies: An International Transdisciplinary Conference on Gender, Embodiment, and Sexuality; 7–10 September 2016; University of Arizona, Tucson, AZ.
234. Bucci S, Mazzon G, Liguori G, Napoli R, Pavan N, Bormioli S, Ollandini G, De Concilio B, Trombetta C. Neovaginal prolapse in male-to-female transsexuals: an 18-year-long experience. *Biomed Res Int*. 2014;**2014**:240761.
235. Raigosa M, Avvedimento S, Yoon TS, Cruz-Gimeno J, Rodriguez G, Fontdevila J. Male-to-female genital reassignment surgery: a retrospective review of surgical technique and complications in 60 patients. *J Sex Med*. 2015;**12**(8):1837–1845.
236. Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res*. 1998;**10**(Suppl 1): S22–S24.
237. Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014;**111**(47):795–801.
238. Nygren U, Nordenskjold A, Arver S, Sodersten M. Effects on voice fundamental frequency and satisfaction with voice in trans men during testosterone treatment—a longitudinal study. *J Voice*. 2016;**30**(6):766.e23-766.e34.
239. Becking AG, Tuinzing DB, Hage JJ, Gooren LJG. Transgender feminization of the facial skeleton. *Clin Plast Surg*. 2007;**34**(3): 557–564.
240. Giraldo F, Esteva I, Bergero T, Cano G, González C, Salinas P, Rivada E, Lara JS, Soriguer F; Andalusia Gender Team. Corona glans clitoroplasty and urethropreputial vestibuloplasty in male-to-female transsexuals: the vulval aesthetic refinement by the Andalusia Gender Team. *Plast Reconstr Surg*. 2004;**114**(6): 1543–1550.
241. Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med*. 2007;**4**(4 Pt 1): 981–989.
242. Hage JJ, de Graaf FH, Bouman FG, Bloem JJAM. Sculpturing the glans in phalloplasty. *Plast Reconstr Surg*. 1993;**92**(1):157–161, discussion 162.
243. Thiagaraj D, Gunasegaram R, Loganath A, Peh KL, Kottegoda SR, Ratnam SS. Histopathology of the testes from male transsexuals on oestrogen therapy. *Ann Acad Med Singapore*. 1987; **16**(2):347–348.
244. Monstrey SJ, Ceulemans P, Hoebeke P. Sex reassignment surgery in the female-to-male transsexual. *Semin Plast Surg*. 2011;**25**(3): 229–244.
245. Perovic SV, Djinovic R, Bumbasirevic M, Djordjevic M, Vukovic P. Total phalloplasty using a musculocutaneous latissimus dorsi flap. *BJU Int*. 2007;**100**(4):899–905, discussion 905.
246. Vesely J, Hyza P, Ranno R, Cigna E, Monni N, Stupka I, Justan I, Dvorak Z, Novak P, Ranno S. New technique of total phalloplasty with reinnervated latissimus dorsi myocutaneous free flap in female-to-male transsexuals. *Ann Plast Surg*. 2007;**58**(5): 544–550.
247. Ranno R, Veselý J, Hýza P, Stupka I, Justan I, Dvorák Z, Monni N, Novák P, Ranno S. Neo-phalloplasty with re-innervated latissimus dorsi free flap: a functional study of a novel technique. *Acta Chir Plast*. 2007;**49**(1):3–7.

doi: 10.1210/jc.2017-01658

248. Garcia MM, Christopher NA, De Luca F, Spilotros M, Ralph DJ. Overall satisfaction, sexual function, and the durability of neophallus dimensions following staged female to male genital gender confirming surgery: the Institute of Urology, London U.K. experience. *Transl Androl Urol*. 2014;**3**(2):156–162.
249. Chen H-C, Gedebou TM, Yazar S, Tang Y-B. Prefabrication of the free fibula osteocutaneous flap to create a functional human penis using a controlled fistula method. *J Reconstr Microsurg*. 2007;**23**(3):151–154.
250. Hoebeke PB, Decaestecker K, Beysens M, Opdenakker Y, Lumen N, Monstrey SM. Erectile implants in female-to-male transsexuals: our experience in 129 patients. *Eur Urol*. 2010;**57**(2):334–341.
251. Hage JJ. Metaidoioplasty: an alternative phalloplasty technique in transsexuals. *Plast Reconstr Surg*. 1996;**97**(1):161–167.
252. Cohanzad S. Extensive metoidioplasty as a technique capable of creating a compatible analogue to a natural penis in female transsexuals. *Aesthetic Plast Surg*. 2016;**40**(1):130–138.
253. Selvaggi G, Hoebeke P, Ceulemans P, Hamdi M, Van Landuyt K, Blondeel P, De Cuypere G, Monstrey S. Scrotal reconstruction in female-to-male transsexuals: a novel scrotoplasty. *Plast Reconstr Surg*. 2009;**123**(6):1710–1718.
254. Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014;**48**(6):362–367.
255. Wolter A, Diedrichson J, Scholz T, Arens-Landwehr A, Liebau J. Sexual reassignment surgery in female-to-male transsexuals: an algorithm for subcutaneous mastectomy. *J Plast Reconstr Aesthet Surg*. 2015;**68**(2):184–191.
256. Richards C, Barrett J. The case for bilateral mastectomy and male chest contouring for the female-to-male transsexual. *Ann R Coll Surg Engl*. 2013;**95**(2):93–95.
257. Sutcliffe PA, Dixon S, Akehurst RL, Wilkinson A, Shippam A, White S, Richards R, Caddy CM. Evaluation of surgical procedures for sex reassignment: a systematic review. *J Plast Reconstr Aesthet Surg*. 2009;**62**(3):294–306, discussion 306–308.
258. Selvaggi G, Elander A. Penile reconstruction/formation. *Curr Opin Urol*. 2008;**18**(6):589–597.
259. Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One*. 2011;**6**(2):e16885.
260. Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller MD, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril*. 2009;**92**(5):1685–1689.e3.
261. Papadopulos NA, Lellé JD, Zavlin D, Herschbach P, Henrich G, Kovacs L, Ehrenberger B, Kluger AK, Machens HG, Schaff J. Quality of life and patient satisfaction following male-to-female sex reassignment surgery. *J Sex Med*. 2017;**14**(5):721–730.
262. Simonsen RK, Hald GM, Kristensen E, Giraldi A. Long-term follow-up of individuals undergoing sex-reassignment surgery: somatic morbidity and cause of death. *Sex Med*. 2016;**4**(1):e60–e68.
263. Djordjevic ML, Bizic MR, Duisin D, Bouman MB, Buncamper M. Reversal Surgery in regretful male-to-female transsexuals after sex reassignment surgery. *J Sex Med*. 2016;**13**(6):1000–1007.
264. Liberopoulos EN, Florentin M, Mikhailidis DP, Elisaf MS. Compliance with lipid-lowering therapy and its impact on cardiovascular morbidity and mortality. *Expert Opin Drug Saf*. 2008;**7**(6):717–725.
265. Forbes SS, Stephen WJ, Harper WL, Loeb M, Smith R, Christoffersen EP, McLean RF. Implementation of evidence-based practices for surgical site infection prophylaxis: results of a pre- and postintervention study. *J Am Coll Surg*. 2008;**207**(3):336–341.
266. Davis PJ, Spady D, de Gara C, Forgie SE. Practices and attitudes of surgeons toward the prevention of surgical site infections: a provincial survey in Alberta, Canada. *Infect Control Hosp Epidemiol*. 2008;**29**(12):1164–1166.

Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

Cynthia A. Stuenkel, Susan R. Davis, Anne Gompel, Mary Ann Lumsden, M. Hassan Murad, JoAnn V. Pinkerton, and Richard J. Santen

University of California, San Diego, Endocrine/Metabolism (C.A.S.), La Jolla, California 92093; Monash University, School of Public Health and Preventive Medicine (S.R.D.), Melbourne 03004, Australia; Université Paris Descartes, Hôpitaux Universitaires Port Royal-Cochin Unit de Gynécologie Endocrnienne (A.G.), Paris 75014, France; University of Glasgow School of Medicine (M.A.L.), Glasgow G31 2ER, Scotland; Mayo Clinic, Division of Preventive Medicine (M.H.M.), Rochester, Minnesota 55905; University of Virginia, Obstetrics and Gynecology (J.V.P.), Charlottesville, Virginia 22908; and University of Virginia Health System (R.J.S.), Charlottesville, Virginia 22903

Objective: The objective of this document is to generate a practice guideline for the management and treatment of symptoms of the menopause.

Participants: The Treatment of Symptoms of the Menopause Task Force included six experts, a methodologist, and a medical writer, all appointed by The Endocrine Society.

Evidence: The Task Force developed this evidenced-based guideline using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews of published data and considered several other existing meta-analyses and trials.

Consensus Process: Multiple e-mail communications, conference calls, and one face-to-face meeting determined consensus. Committees of The Endocrine Society, representatives from endorsing societies, and members of The Endocrine Society reviewed and commented on the drafts of the guidelines. The Australasian Menopause Society, the British Menopause Society, European Menopause and Andropause Society, the European Society of Endocrinology, and the International Menopause Society (co-sponsors of the guideline) reviewed and commented on the draft.

Conclusions: Menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms and other symptoms of the climacteric. Benefits may exceed risks for the majority of symptomatic postmenopausal women who are under age 60 or under 10 years since the onset of menopause. Health care professionals should individualize therapy based on clinical factors and patient preference. They should screen women before initiating MHT for cardiovascular and breast cancer risk and recommend the most appropriate therapy depending on risk/benefit considerations. Current evidence does not justify the use of MHT to prevent coronary heart disease, breast cancer, or dementia. Other options are available for those with vasomotor symptoms who prefer not to use MHT or who have contraindications because these patients should not use MHT. Low-dose vaginal estrogen and ospemifene provide effective therapy for the genitourinary syndrome of menopause, and vaginal moisturizers and lubricants are available for those not choosing hormonal therapy. All postmenopausal women should embrace appropriate lifestyle measures. **(*J Clin Endocrinol Metab* 100: 3975–4011, 2015)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received May 7, 2015. Accepted August 28, 2015.
First Published Online October 7, 2015

Abbreviations: BZA, bazedoxifene; CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DVT, deep vein thrombosis; EPT, estrogen plus progestogen therapy; ET, estrogen therapy; GSM, genitourinary syndrome of menopause; HR, hazard ratio; MetS, metabolic syndrome; MHT, menopausal hormone therapy; MI, myocardial infarction; MPA, medroxyprogesterone acetate; OTC, over the counter; PE, pulmonary embolism; POI, primary ovarian insufficiency; QOL, quality of life; RCT, randomized controlled trial; SERM, selective estrogen receptor modulator; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; VMS, vasomotor symptoms; VTE, venous thromboembolism; VVA, vulvovaginal atrophy.

Summary of Recommendations

1.0 Diagnosis and symptoms of menopause

1.1 We suggest diagnosing menopause based on the clinical criteria of the menstrual cycle. (2|⊕⊕◯◯)

1.2 If establishing a diagnosis of menopause is necessary for patient management in women having undergone a hysterectomy without bilateral oophorectomy or presenting with a menstrual history that is inadequate to ascertain menopausal status, we suggest making a presumptive diagnosis of menopause based on the presence of vasomotor symptoms (VMS) and, when indicated, laboratory testing that includes replicate measures of FSH and serum estradiol. (2|⊕⊕◯◯)

2.0 Health considerations for all menopausal women

2.1 When women present during the menopausal transition, we suggest using this opportunity to address bone health, smoking cessation, alcohol use, cardiovascular risk assessment and management, and cancer screening and prevention. (Ungraded best practice statement)

3.0 Hormone therapy for menopausal symptom relief

3.1 Estrogen and progestogen therapy

3.1a For menopausal women < 60 years of age or < 10 years past menopause with bothersome VMS (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take menopausal hormone therapy (MHT), we suggest initiating estrogen therapy (ET) for those without a uterus and estrogen plus progestogen therapy (EPT) for those with a uterus. (2|⊕⊕◯◯)

Cardiovascular risk

3.1b For women < age 60 or < 10 years past menopause onset considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of cardiovascular disease (CVD) and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|⊕⊕◯◯)

3.1c For women at high risk of CVD, we suggest initiating nonhormonal therapies to alleviate bothersome VMS (with or without climacteric symptoms) over MHT. (2|⊕⊕◯◯)

3.1d For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus, because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. (2|⊕⊕◯◯)

Venous thromboembolic events

3.1e For women at increased risk of venous thromboembolism (VTE) who request MHT, we recommend a nonoral route of ET at the lowest effective dose, if not contraindicated (1|⊕⊕◯◯); for women with a uterus, we recommend a progestogen (for example, progesterone and dydrogestone) that is neutral on coagulation parameters. (1|⊕⊕⊕◯)

Breast cancer

3.1f For women considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|⊕⊕◯◯)

3.1g For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, we suggest nonhormonal therapies over MHT to alleviate bothersome VMS. (2|⊕⊕◯◯)

Tailoring MHT

3.1h We suggest a shared decision-making approach to decide about the choice of formulation, starting dose, the route of administration of MHT, and how to tailor MHT to each woman's individual situation, risks, and treatment goals. (Ungraded best practice statement)

Custom-compounded hormones

3.1i We recommend using MHT preparations approved by the US Food and Drug Administration (FDA) and comparable regulating bodies outside the United States and recommend against the use of custom-compounded hormones. (Ungraded best practice statement)

3.2 Conjugated equine estrogens with bazedoxifene

3.2 For symptomatic postmenopausal women with a uterus and without contraindications, we suggest the combination of conjugated equine estrogens (CEE)/bazedoxifene (BZA) (where available) as an option for relief of VMS and prevention of bone loss. (2|⊕⊕⊕◯)

3.3 Tibolone

3.3a For women with bothersome VMS and climacteric symptoms and without contraindications, we suggest tibolone (in countries where available) as an alternative to MHT. (2|⊕⊕◯◯)

3.3b We recommend against adding tibolone to other forms of MHT. (1|⊕⊕◯◯)

3.3c We recommend against using tibolone in women with a history of breast cancer. (1|⊕⊕◯◯)

doi: 10.1210/jc.2015-2236

3.4 Clinical management of patients taking hormone therapies

Monitoring during therapy

3.4a For women with persistent unscheduled bleeding while taking MHT, we recommend evaluation to rule out pelvic pathology, most importantly, endometrial hyperplasia and cancer. (1|⊕⊕⊕◯)

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing EPT and emphasizing the importance of adhering to age-appropriate breast cancer screening. (1|⊕⊕⊕◯)

3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. (Ungraded best practice statement)

3.4d For young women with primary ovarian insufficiency (POI), premature or early menopause, without contraindications, we suggest taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. (2|⊕⊕◯◯)

Stopping considerations

3.4e For women preparing to discontinue MHT, we suggest a shared decision-making approach to elicit individual preference about adopting a gradual taper vs abrupt discontinuation. (2|⊕⊕◯◯)

4.0 Nonhormonal therapies for VMS

4.0 For postmenopausal women with mild or less bothersome hot flashes, we suggest a series of steps that do not involve medication, such as turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress. (2|⊕⊕◯◯)

4.1 Nonhormonal prescription therapies for VMS

4.1a For women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, we recommend selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) or gabapentin or pregabalin (if there are no contraindications). (1|⊕⊕⊕◯)

4.1b For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the nonhormonal prescription therapies, SSRIs/SNRIs or gabapentin or pregabalin, we suggest a trial of clonidine (if there are no contraindications). (2|⊕⊕◯◯)

4.2 Over-the-counter and alternative nonhormonal therapies for VMS

4.2 For women seeking relief of VMS with over-the-counter (OTC) or complementary medicine therapies, we suggest counseling regarding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3-fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis. (2|⊕⊕◯◯)

5.0 Treatment of genitourinary syndrome of menopause

5.1 Vaginal moisturizers and lubricants

5.1a For postmenopausal women with symptoms of vulvovaginal atrophy (VVA), we suggest a trial of vaginal moisturizers to be used at least twice weekly. (2|⊕⊕◯◯)

5.1b For women who do not produce sufficient vaginal secretions for comfortable sexual activity, we suggest vaginal lubricants. (2|⊕⊕◯◯)

5.2 Vaginal estrogen therapies

5.2a For women without a history of hormone- (estrogen) dependent cancers who are seeking relief from symptoms of genitourinary syndrome of menopause (GSM) (including VVA) that persist despite using vaginal lubricants and moisturizers, we recommend low-dose vaginal ET. (1|⊕⊕⊕◯)

Practice statement

5.2b In women with a history of breast or endometrial cancer, who present with symptomatic GSM (including VVA), that does not respond to nonhormonal therapies, we suggest a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET. (Ungraded best practice statement)

5.2c For women taking raloxifene, without a history of hormone- (estrogen) dependent cancers, who develop symptoms of GSM (including VVA) that do not respond to nonhormonal therapies, we suggest adding low-dose vaginal ET. (2|⊕⊕◯◯)

5.2d For women using low-dose vaginal ET, we suggest against adding a progestogen (ie, no need for adding progestogen to prevent endometrial hyperplasia). (2|⊕◯◯◯)

5.2e For women using vaginal ET who report postmenopausal bleeding or spotting, we recommend prompt evaluation for endometrial pathology. (1|⊕⊕◯◯)

5.3 Ospemifene

5.3a For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, we suggest a trial of ospemifene. (2|⊕⊕⊕◯)

5.3b For women with a history of breast cancer presenting with dyspareunia, we recommend against ospemifene. (1|⊕◯◯◯)

Method of Development of Evidence-based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of The Endocrine Society deemed management of menopause a priority area in need of a practice guideline and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force commissioned three systematic reviews of the literature to inform its key recommendations. The Task Force used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence using the recommendations of the GRADE system. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" or "we recommend against" and the number 1, and weak recommendations use the phrase "we suggest" or "we suggest against" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values the panelists considered when making the recommendation. In some instances, there are remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions. In this guideline, the Task Force made several statements to emphasize the importance of shared decision making, general preventive care measures, and basic principles of women's health. These were labeled as ungraded best practice statements. Direct evidence for these statements was either unavailable or not systematically appraised and was considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles, and these statements should not be considered as graded recommendations (3).

The 2013 Appraisal of Guidelines for Research and Evaluation II (AGREEII) criteria (23 items) were satisfied, with three exceptions. Item 5 stipulates that the views and preferences of the target population (patients, public, etc) have been sought. The Task Force did not conduct specific polling/outreach to the public in anticipation of this guideline. Item 14 states that a procedure for updating the guideline is provided. This process has not been formalized. Item 20 suggests that the potential resource implications of applying the recommendations have been considered. The Task Force did not include cost analysis of risk assessment tools or prescription drug therapies.

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before the members are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the CGS before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Commissioned systematic reviews

The Task Force formulated three questions for systematic reviews to provide evidence supporting this guideline. The first compared the effect of oral vs transdermal es-

doi: 10.1210/jc.2015-2236

trogens on the risk of venous and arterial thrombotic events. Low-quality evidence derived from 15 observational studies suggested that, compared with transdermal MHT, oral MHT was associated with increased risk of VTE, deep vein thrombosis (DVT), and possibly stroke, but not myocardial infarction (MI) (4). The second question evaluated the effect of MHT on mortality. Data from 43 randomized controlled trials (RCTs) demonstrated no association between all-cause mortality, regardless of hormone type, the presence of pre-existing heart disease, or length of follow-up (5). Meta-analysis of 2 RCTs in which MHT was started at a *mean* age less than 60 and 3 RCTs in which MHT was started less than10 years after menopause suggested possible reduction of mortality with MHT. The third question compared the effect of MHT with natural progesterone vs synthetic progestins on breast cancer risk. Low-quality evidence from two observational studies suggested that natural progesterone may be associated with a reduced risk for breast cancer compared with synthetic progestins, but data were insufficient to draw a firm conclusion.

Introduction and background

VMS, hot flashes, and night sweats, are the hallmarks of menopause, although not all women experience these symptoms. Other climacteric symptoms include sleep disturbance (6, 7), arthralgia (7–9), and vaginal dryness and dyspareunia (7, 10, 11). It is less clear whether anxiety, irritability, depression, palpitations, skin dryness, loss of libido, and fatigue can be attributed to menopause (7, 9, 12). Symptoms frequently start in the years before the final menstrual period and can last, with unpredictable duration, from a few years to more than 13 years (13–16).

ET has long been recognized as the most effective treatment for the relief of bothersome vasomotor and vaginal symptoms associated with menopause. However, prescriptions for MHT declined considerably after the 2002 publication of the Women's Health Initiative (WHI) RCT. This study determined that for postmenopausal women (average age, 63 y), oral CEE alone after hysterectomy (17), or coupled with daily medroxyprogesterone acetate (MPA) in women with a uterus (18), was associated with risks disproportionate to preventive benefits (17, 18). During ensuing years, a consensus arose that most healthy symptomatic women, without contraindications and closer to the time of menopause (<10 y after menopause onset or age <60 y), were appropriate candidates for MHT for symptom relief (19, 20). Post hoc WHI analyses and observational data suggest that benefits exceed risks in most of these women. At this juncture, women in the United States and some other countries have a broader range of therapeutic choices than ever before, including: MHT dose, type, and route of administration; new selective estrogen receptor modulators (SERMs) as solo or combination therapies; and expanded choices of nonhormonal prescription medications. In this guideline, we emphasize safety in identifying which late perimenopausal and recently postmenopausal women are candidates for various therapeutic agents. Considerations include the risks and benefits of each available therapy, the expected duration of treatment, the intensity of monitoring during therapy, and most importantly, individualizing the course of therapy to reflect the specific characteristics of the patient who is making decisions regarding symptom management.

This guideline covers the full spectrum of therapies for relief of the most common and bothersome menopausal symptoms (Figure 1). (The detailed management of early menopause transition, primary ovarian insufficiency, and prevention of osteoporosis and fracture are considered beyond the current scope.) Choice of therapy is ideally based on available evidence regarding safety and efficacy and is generally a shared decision including both patient and provider. The treatment selected should be tailored to the individual patient and will vary according to each woman's symptom severity, age, medical profile, personal preference, and estimated benefit/risk ratio. The impact of severe menopausal symptoms on quality of life (QOL) can be substantial, and there are instances in which a woman with a history of coronary heart disease (CHD) or breast cancer, for example, will choose to accept a degree of risk that might otherwise be considered to outweigh the benefits of MHT. An accepted philosophy is that a fully informed patient should be empowered to make a decision that best balances individual QOL benefits against potential health risks (21).

1.0 Diagnosis and symptoms of menopause

1.1 We suggest diagnosing menopause based on the clinical criteria of the menstrual cycle. (2⊕⊕○○)

1.2 If establishing a diagnosis of menopause is necessary for patient management in women having undergone a hysterectomy without bilateral oophorectomy or presenting with a menstrual history that is inadequate to ascertain menopausal status, we suggest making a presumptive diagnosis of menopause based on the presence of VMS and, when indicated, laboratory testing that includes replicate measures of FSH and serum estradiol. (2⊕⊕○○)

Technical remark

Table 1 summarizes other etiologies of secondary amenorrhea to be considered in the differential diagnosis.

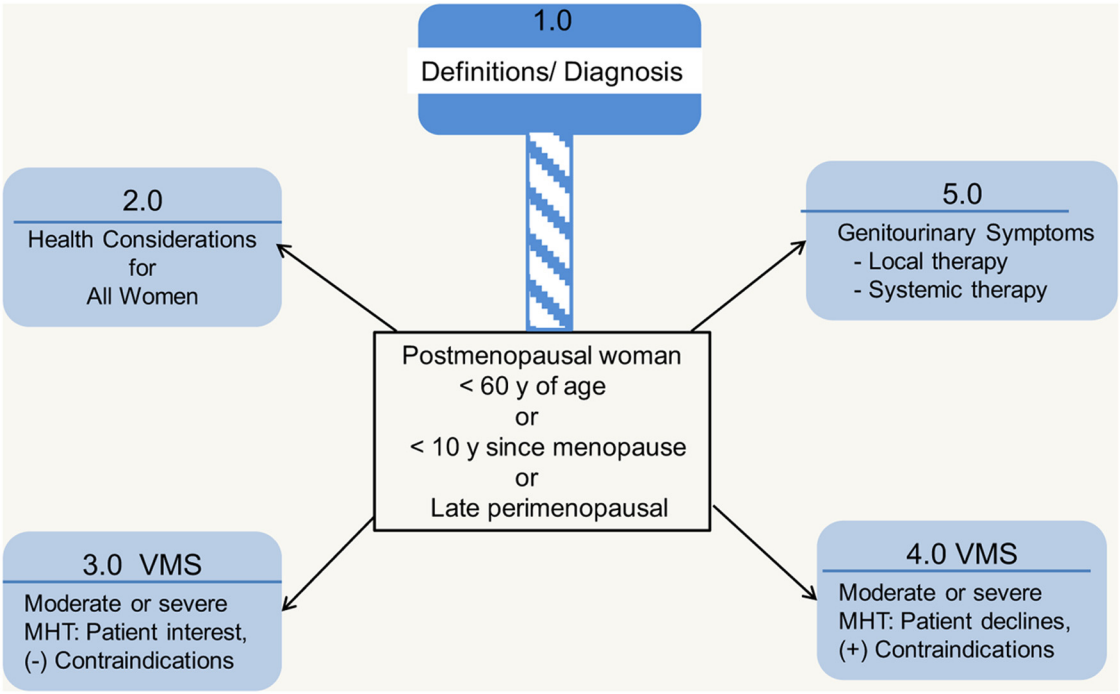


Figure 1. Approach to menopause guideline. Numbers correspond to section of text addressing selected clinical issue.

Diagnosis

Table 1 lists definitions of the clinical spectrum of menopause. In a woman with an intact uterus, menopause is a clinical diagnosis based upon cessation of menses for at least 12 months. Sex steroids, gonadotropins, inhibin B, or anti-Mullerian hormone measurements do not further inform the diagnosis, do not indicate precisely when the final menstrual period will occur, and will not influence management unless a woman is seeking fertility. In women having undergone a hysterectomy but not bilateral oophorectomy, elevated FSH levels and estradiol concentrations < 20 pg/mL on several occasions support but do not

Table 1. Definitions of Spectrum of Menopause

Menopause	Clinical status after the final menstrual period, diagnosed retrospectively after cessation of menses for 12 mo in a previously cycling woman and reflecting complete or nearly complete permanent cessation of ovarian function and fertility.
Spontaneous menopause	Cessation of menses that occurs at an average age of 51 y in the absence of surgery or medication (316–318).
Menopausal transition (or perimenopause)	An interval preceding the menopause characterized by variations in menstrual cycle length and bleeding pattern, mood shifts, vasomotor, and vaginal symptoms and with rising FSH levels and falling anti-Mullerian hormone and inhibin B levels, which starts during the late reproductive stage and progresses during the menopause transition (15, 319).
Climacteric	The phase in the aging of women marking the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.
Climacteric syndrome	When the climacteric is associated with symptomatology.
Menopause after hysterectomy without oophorectomy	Spontaneous cessation of ovarian function without the clinical signal of cessation of menses.
Induced menopause	Cessation of ovarian function induced by chemotherapy, radiotherapy, or bilateral oophorectomy.
Early menopause	Cessation of ovarian function occurring between ages 40 and 45 in the absence of other etiologies for secondary amenorrhea (pregnancy, hyperprolactinemia, and thyroid disorders).
POI	Loss of ovarian function before the age of 40 y with waxing and waning course and potential resumption of menses, conception, and pregnancy (320). The prevalence of POI is approximately 1% (321) and is differentiated into idiopathic, autoimmune (associated with polyglandular autoimmune syndromes), metabolic disorders, and genetic abnormalities (including fragile X premutation).

doi: 10.1210/jc.2015-2236

confirm the diagnosis. A distinction between the late perimenopause transition, marked by episodes of > 60 days of amenorrhea and increasing severity of VMS (15), and early postmenopause cannot be made on the sole basis of hormone measurements. With radiotherapy- or chemotherapy-induced menopause, it is important to recognize that ovarian function may resume after 12 months of amenorrhea (22), depending on the age of the woman and the dose and duration of treatment (22). For POI, persistent FSH elevation in women < age 40 provides a tentative diagnosis (Table 1).

Signs and symptoms

Vasomotor symptoms

Prevalence. Hot flashes (also called hot flushes) occur in approximately 75% of postmenopausal women in the United States (23). In the Study of Women Across the Nation (SWAN), after controlling for age, education, health, and economic strain, researchers found that US Caucasian women report more psychosomatic symptoms, African American and Hispanic women report more VMS, and Asian women report more somatic complaints (16, 24). Notably, across countries and ethnic backgrounds, the percentage of women reporting hot flashes varies (25–27). In a cross-sectional study of premenopausal women (mean age, 48 y), one-third reported "ever" experiencing hot flashes (28). A comparison between VMS experienced during the premenopause vs the postmenopause may be informative when counseling a postmenopausal woman regarding symptom relief, although to our knowledge, the presence and frequency of premenopausal hot flashes have not been studied as being predictive of response to therapy in the postmenopause. Persistence of hot flashes may also vary depending upon when in the menopausal transition VMS were first noted. In SWAN, earlier onset of VMS was associated with longer postmenopausal duration (16).

Clinical manifestations. Hot flashes typically begin as the sudden sensation of heat centered on the upper chest and face. When moderate or severe, the hot flash rapidly becomes generalized, lasts from 2 to 4 minutes, and can be associated with profuse perspiration, palpitations, or anxiety. Triggers include spicy food or alcohol. At night, vasomotor instability manifests as hot flashes or night sweats, which may represent different physiological mechanisms. The differential diagnosis includes several entities distinguishable by clinical features (Table 2). New-onset VMS in older (age, ≥ 65 y) postmenopausal women may be associated with, but not necessarily causally related to, increased risk of major CHD and all-cause mortality (29).

Table 2. Conditions That May Cause or Mimic Vasomotor Events and That Can Be Distinguished From Menopausal Symptoms by History, Examination, and Investigations, as Indicated

Hormone excess
Thyroid hormone excess
Carcinoid syndrome (flushing without sweating)
Pheochromocytoma (hypertension, flushing, and profuse sweating)
Dietary factors
Alcohol
Spicy food
Food additives (eg, monosodium glutamate, sulfites)
Pharmaceuticals
Chronic opioid use
Opiate withdrawal
SSRIs (may cause sweats)
Nicotinic acid (intense warmth, itching lasting up to 30 min)
Calcium channel blockers
Medications that block estrogen action or biosynthesis
Chronic infection (increased body temperature)
Other medical conditions
Postgastric surgery dumping syndrome
Mastocytosis and mast cell disorders (usually with gastrointestinal symptoms)
Some cancers: medullary carcinoma of the thyroid, pancreatic islet-cell tumors, renal cell carcinoma, lymphoma
Anxiety disorders

Association with sleep. In polysomnography studies, nocturnal hot flashes are more common during the first 4 hours of sleep, whereas subsequent rapid eye movement sleep suppresses hot flashes, arousals, and awakenings (30). A recent study that induced estrogen deficiency in healthy premenopausal women with a GnRH agonist directly demonstrated that hot flashes are associated with three factors: 1) an increase in episodes of waking after sleep-onset; 2) a decrease in perceived sleep efficiency; and 3) a statistically significant correlation between nocturnal VMS and sleep disruption (31). Although these data are informative, it has not been substantiated whether they apply in naturally postmenopausal women with continuously high gonadotropins. An important contributing factor is aging, which likely is also involved in sleep disturbances in menopausal women.

Mechanisms. VMS appear to involve the central nervous system (32) because: 1) hot flashes occur simultaneously with, but are not caused by, LH pulses (33, 34); and 2) research has shown an association with the neuroregulators kisspeptin, neurokinin B, and dynorphin (35). Alterations of thermoregulatory systems are mechanistically involved because women with hot flashes exhibit a narrowing of the thermoregulatory-neutral zone (32). Whereas premenopausal women initiate mechanisms to dissipate heat when the core body temperature increases

by 0.4°C, this happens with much lower increases in temperature in menopausal women (36). Core body temperature is usually still within the normal range at the onset of the flash, but inappropriate peripheral vasodilatation with increased digital and cutaneous blood flow and perspiration results in rapid heat loss and a fall in core body temperature (32). Shivering may occur to restore the core temperature (36).

Genitourinary syndrome of menopause

This new term "genitourinary syndrome of menopause" (GSM) combines the conditions of VVA and urinary tract dysfunction (Table 3) (37). VVA most often presents in the late postmenopausal stage, when VMS may have abated (15). When VVA is severe, women may have discomfort wearing tight-fitting clothing or while sitting or exercising. Sexual activity is not required for patients to experience vaginal or genital discomfort. Urinary symptoms— dysuria, urinary frequency, and recurrent urinary tract infections—increase in severity with time since menopause.

Other signs and symptoms

The menopausal decline of estradiol increases bone resorption and contributes to fractures (38).

Possible related signs and symptoms

Research has suggested (but not proven) a direct relationship between menopause and mood changes, mild depressive symptoms, anxiety, irritability, arthralgias, loss of libido, palpitations, skin dryness, fatigue, and reduction in QOL (38, 39). As opposed to the conclusions in the 2005 National Institutes of Health State of the Science consensus regarding the uncertain relationship between mood and menopause, more recent longitudinal studies now support an association of the menopause transition with depressed mood, major depressive episodes, and anxiety.

Table 3. Genitourinary Syndrome of Menopause

Symptoms
Vulvar pain, burning, or itching
Vaginal dryness
Vaginal discharge
Dyspareunia
Spotting or bleeding after intercourse
Dysuria, urinary frequency, urgency
Recurrent urinary tract infections
Signs, external genitalia
Decreased labial size
Loss of vulvar fat pads
Vulvar fissures
Receded or phimotic clitoris
Prominent urethra with mucosal eversion or prolapse
Signs, vagina
Introital narrowing
Loss of elasticity with constriction
Thin vaginal epithelial lining
Loss of mature squamous epithelium
Pale or erythematous appearance
Petechiae, ulcerations, or tears
Alkaline pH (>5.5)
Infection (yellow or greenish discharge)

Derived from D. J. Portman et al: Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Menopause*. 2014;21:1063–1068 (37), with permission.

2.0 Health considerations for all menopausal women

2.1 When women present during the menopausal transition, we suggest using this opportunity to address bone health, smoking cessation, alcohol use, cardiovascular risk assessment and management, and cancer screening and prevention. (Ungraded best practice statement)

Evidence

The menopause transition, a portal to the second half of life, is a critical window to reassess lifestyle, recognize ongoing and potential health concerns, and encourage a proactive approach to future well-being, regardless of menopausal symptoms. To decrease morbidity and mortality from CVD and cancer and maintain QOL, optimizing diet and exercise to maintain healthy weight are important measures, as are counseling regarding alcohol use and smoking cessation and identifying and treating hypertension, glucose intolerance, and dyslipidemias (40, 41).

Adequate intake of calcium and vitamin D, along with limiting alcohol consumption will minimize bone loss and reduce the risk of falls and fractures (42). For postmenopausal women < 65 years of age and at high risk of osteoporosis, dual-energy x-ray absorptiometry assessment of bone mineral density contributes to risk assessment. ET for the relief of menopausal symptoms prevents bone loss and reduces fracture risk (43). Women without VMS and at significant risk of osteoporosis can discuss the merits of ET for bone preservation. Recent guidelines address bone-specific therapies (43).

3.0 Hormone therapy for menopausal symptom relief

3.1 Estrogen and progestogen therapy

3.1a For menopausal women < 60 years of age or < 10 years past menopause with bothersome VMS (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take MHT, we suggest initiating ET for those without a uterus and EPT for those with a uterus. (2⊕⊕◯◯)

doi: 10.1210/jc.2015-2236

Evidence

In postmenopausal women, ET improves menopause-associated (climacteric) symptoms (eg, VMS, genitourinary symptoms, sleep disturbance, menopause-associated anxiety and depressive symptoms, and arthralgias). ET also reduces menopause-related bone loss, lowers the risk of fragility fractures in older women, and reduces the incidence of self-reported diabetes. In addition, combined EPT reduced the risk of colorectal cancer and, in cumulative follow-up of the WHI, endometrial cancer (38, 44).

MHT is not appropriate for all symptomatic menopausal women (Figure 2). There are no commonly recognized lists of absolute or relative contraindications to MHT as published in professional society guidelines. And whereas US product labeling (regulated by the FDA) does include contraindications to MHT (Table 4), caution is also advised for women with certain additional medical conditions (Table 4). Risk/benefit assessment is the most important consideration, and QOL may be an important issue in a decision to recommend MHT. Women with conditions precluding MHT (Table 4) who are unwilling to take MHT, or at substantial risk for breast cancer or CVD, can consider nonhormonal options for symptom relief (*Section 4.0*).

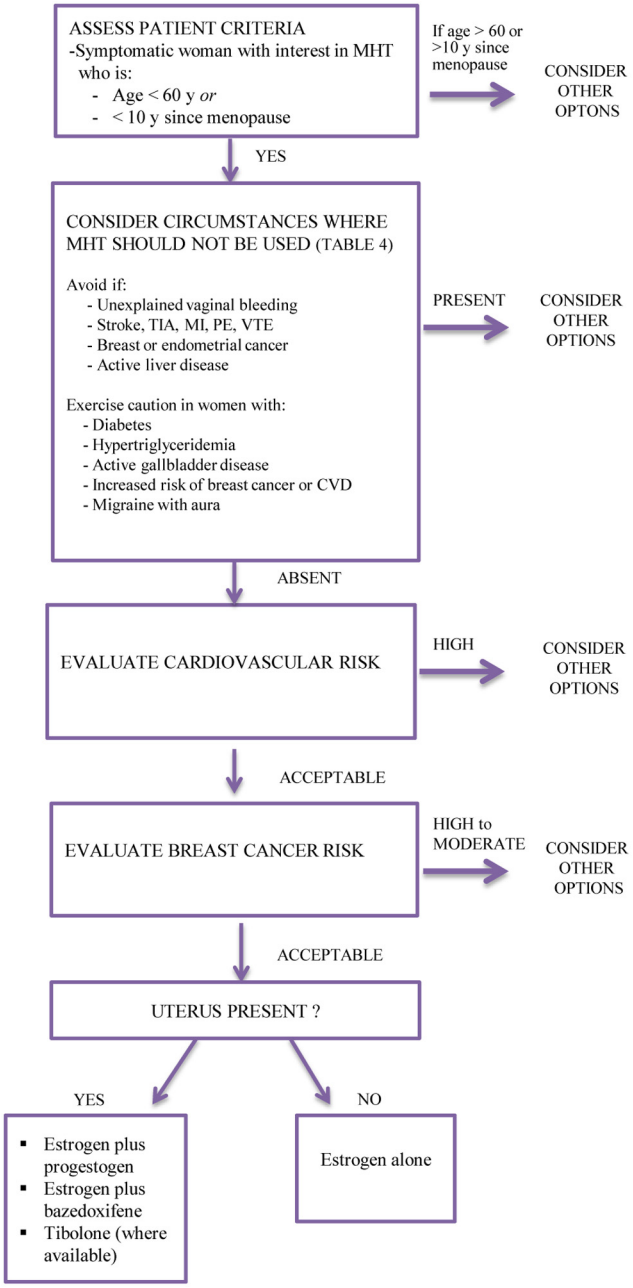


Figure 2. Approach to the patient with VMS contemplating MHT. TIA, transient ischemic attack.

Risks and benefit overview

Healthcare providers and patients should choose MHT based on individual risks and benefits utilizing a shared

Table 4. Specific Cautions to Use of Systemic MHT or SERMs[a,b] for Treatment of Menopausal Symptoms

In general, ET should not be used in women with any of the following conditions:
Undiagnosed abnormal genital bleeding
Known, suspected, or history of cancer of the breast
Known or suspected estrogen-dependent neoplasia including endometrial cancer
Active DVT, pulmonary embolism, or history of these conditions
Active arterial thromboembolic disease (for example, stroke, MI) or a history of these conditions
Known anaphylactic reaction or angioedema in response to any ingredient in the medication[c]
Known liver impairment or disease
Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders[c]
Known or suspected pregnancy
Caution should also be exercised in women with:
Gallbladder disease (oral ET)
Hypertriglyceridemia (>400 mg/d) (oral ET)
Diabetes
Hypoparathyroidism (risk of hypocalcemia)
Benign meningioma
Intermediate or high risk of breast cancer
High risk of heart disease
Migraine with aura (oral ET)
Other conditions[d]

[a] Also apply to conjugated estrogens/BZA, ospemifene, and tibolone therapies.

[b] Advice not to use estrogens in the specific conditions listed is based on FDA recommendations and package labeling in the United States. The advice to exercise caution is based on a review of the literature (including package labeling) and not dictums generally included in various Menopause Society guidelines. Because these guidelines are meant to be used internationally, it should be noted that these considerations may vary from country to country.

[c] Specific to CEE ± combination with BZA.

[d] Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

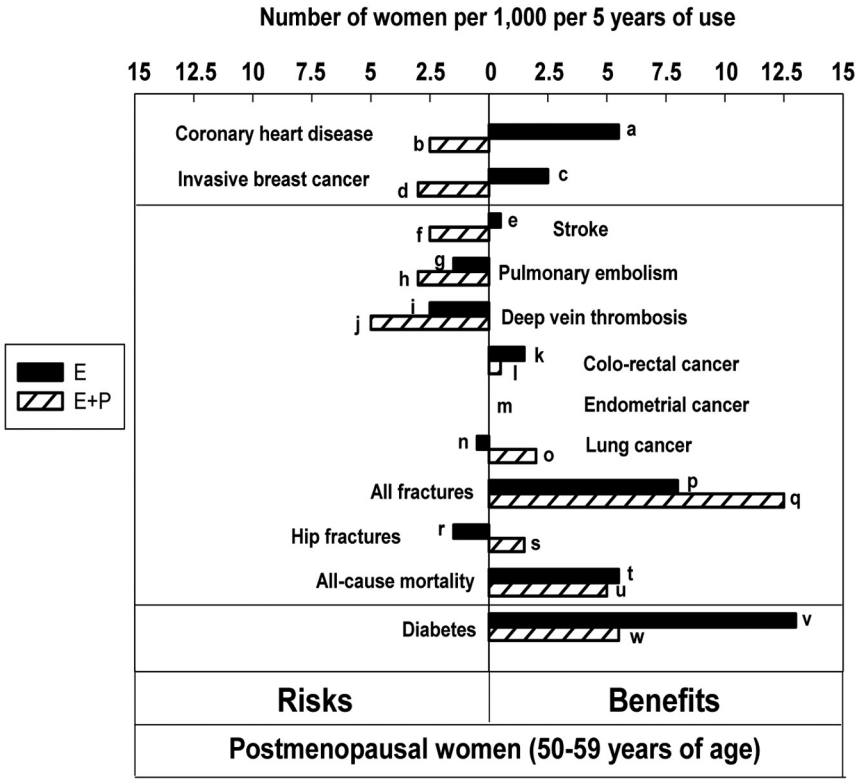


Figure 3. Updated summary of the effects of orally administered CEE alone or combined with MPA in women ages 50–59 years during intervention phase of WHI. One set of analyses examined the risks and benefits of these agents in women ages 50–59 years. This figure plots these data, which are expressed here as excess risks and benefits per 1000 women using MHT for 5 years. Because women deciding to use MHT are more likely to continue this for a period of years rather than 1 year, this figure is constructed according to that assumption. WHI studies were not powered for age-related subset analyses, and none of the data presented in the figure are statistically significant. Nonetheless, this figure represents the best estimates that are available at the present time and are likely more reliable than similar estimates based on observational studies as reported previously in The Endocrine Society Scientific Statement (38). The HR (95% CI) values for the bars in the figure are listed here with reference to the alphabetical designations shown next to the bars: a, HR, 0.60 (0.35–1.04); b, HR, 1.34 (0.82–2.19); c, HR, 0.82 (0.50–1.34); d, HR, 1.21 (0.81–1.80); e, HR, 0.99 (0.53–1.85); f, HR, 1.51 (0.81–2.82); g, HR, 1.53 (0.63–3.75); h, HR, 2.05 (0.89–4.71); i, HR, 1.66 (0.76–3.67); j, HR, 3.01 (1.36–6.66); k, HR, 0.71 (0.30–1.67); l, HR, 0.79 (0.29–2.18); m, HR, 1.00 (ns-ns); n, HR, 1.12 (0.45–2.75); o, HR, 0.62 (0.30–1.29); p, HR, 0.90 (0.72–1.11); q, HR, 0.82 (0.68–1.00); r, HR, 5.01 (0.59–42.9); s, HR, 0.17 (0.02–1.45); t, HR, 0.70 (0.46–1.09); u, HR, 0.67 (0.43–1.04); v, HR, 0.83 (0.67–1.04); and w, HR, 0.85 (0.66–1.09). [RJ Santen, et al: Competency in menopause management: whither goest the internist? *J Womens Health (Larchmt)*. 2014;23(4): 281–285, courtesy of Mary Ann Liebert, Inc].

decision-making approach. Current recommendations suggest that the initiation of MHT should generally be limited to women < 60 years of age or < 10 years after menopause onset. Accordingly, data are needed to estimate risks and benefits in this specific population. No adequately powered RCTs with clinical outcomes have been specifically conducted with younger, symptomatic women, however, and data for women < 50 years old are limited. The best available evidence comes from subgroup analyses of WHI data, which provide information specifically in women 50 to 59 years of age or < 10 years since menopause onset. Because of the number of women participants ages 50 to 59 (5520 in the combined therapy arm and 3313 in the estrogen-alone arm), and the low event rate for MI and stroke in this age group, such data provide trends but few statistically significant differences. Findings from observational studies, case reports, and clinical expertise, both from the United States and other countries, provide additional sources of evidence regarding younger postmenopausal women.

Estimations of risks and benefits previously published in The Endocrine Society's 2010 Scientific Statement utilized both observational and RCT data. However, updated outcomes from the WHI are now available. Accordingly, the updated reanalysis of the WHI (44) is considered by many to provide the best available data on risks and benefits in women ages 50 to 59, but not in those younger than age 50. The 2010 Statement expresses attributable (excess) benefits and risks as the number of affected women/1000 users/5 years of therapy, assuming that most women initiating MHT will consider therapy for 5 years. Maintaining this format, the risks and benefits (as reported in the WHI and reflecting the specific oral therapies studied) are presented in Figure 3 and are not repeated in the text of this guideline. These data, representing the effects of CEE with or without MPA, cannot be extrapolated to other MHT regimens. However, in the absence of RCTs with other specific agents, they provide the most conservative estimates. Notably, the baseline risk of most adverse events is lower in younger vs older women and results in lower attributable risk although relative risks may be similar among various age groups. The converse is also true for benefits, such as fracture reduction.

Benefits of MHT

Vasomotor symptoms

ET is the most effective treatment for VMS and improving QOL in symptomatic women (38). In a dose-dependent manner, MHT reduces hot flash frequency by approximately 75% and severity by 87%, compared with 50% with placebo (38, 45, 46).

doi: 10.1210/jc.2015-2236

Genitourinary syndrome of menopause

Systemic estrogen administration effectively treats VVA and improves symptoms of overactive bladder and recurrent urinary tract infections (47, 48). With lower doses of systemic MHT, vaginal symptoms may persist and local therapy may be needed (*Section 5*).

Sleep disruption

Large placebo-controlled trials reported significantly fewer sleep disturbances with MHT use (44), but additional data are required for definitive conclusions.

Anxiety and depressive symptoms

Anxiety symptoms increase during the menopause transition and are associated with an increased likelihood of a major depressive disorder (49). ET may improve mild-to-moderate depressive symptoms during or shortly after the menopause transition, whereas antidepressant therapy remains appropriate treatment for major depression (50, 51).

Arthralgia

Joint pain or stiffness and general aches or pains were improved in women receiving EPT (38, 44, 52). Joint pain increased slightly after discontinuation of treatment (44).

Potential preventive benefits of menopausal hormone therapy

Although studies have suggested certain preventive benefits, the U.S. Preventive Services Task Force (53) and many expert groups (40, 54–56) recommend against MHT for primary or secondary disease prevention, whereas other experts disagree (57).

Bone loss and fracture. RCTs, observational studies, and meta-analyses consistently report reduction in bone loss with ET (38). The updated WHI analysis reports a significant reduction in vertebral fractures and a borderline significant reduction for all fractures with EPT in women ages 50 to 59 years (Figure 3); this effect was greater than with ET (44). Benefit may also be dose-related (38).

Type 2 diabetes. RCTs (58–60) and large observational studies (61, 62) reported that MHT reduced the prevalence of self-reported diabetes by 14 to 19% (44), an effect that did not persist after therapy was discontinued (44).

Colorectal cancer. In clinical trials, EPT was associated with a nonsignificant lower incidence of colorectal cancer in women ages 50 to 59 (44). Cancers that did occur in women receiving EPT, however, were diagnosed at a more advanced stage when all age groups were considered (64). The reduction in cancer during active therapy did not persist after discontinuation (44).

Endometrial cancer. During 13 years of cumulative follow-up of the WHI, combined CEE and MPA was associated with a 35% reduction in endometrial cancer in women ages 50 to 59 years (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.37–1.12) (44). This finding may be unique to the specific type, dose, and regimen utilized.

Risks of MHT

Endometrial cancer

Unopposed ET increases the risk of endometrial hyperplasia and cancer (38, 65, 66), whereas concurrent progestogen therapy (Table 5) for at least 12 days per month reduces this risk (18, 44, 67) and is recommended for all women with a uterus. Continuous combined CEE and MPA was associated with a reduced risk of endometrial cancer over 13 years of cumulative follow-up (44). After 6 to 10 years, sequential regimens may be associated with a 2-fold increased risk of endometrial cancer, particularly in thin women (38). Micronized progesterone and dydrogesterone, in combination with estrogen, have been associated with an approximate 2-fold increase in endometrial cancer when continued beyond 5 years in a large observational study (68). In contrast, one RCT comparing micronized progesterone with MPA (3 y) (69), a second RCT comparing micronized progesterone with chlormadinone acetate (18 mo) (70), and a third trial of single-tablet formulation of cyclical estradiol-dydrogesterone (2 y) (71) each demonstrated endometrial safety. The difference in outcome may reflect enhanced patient compliance with progestogen therapies when formulated in combination. Limited information is available about the safety of long cycle intermittent use of progestogens, but concern has been raised about increased risk of endometrial cancer (72, 73).

The levonorgestrel intrauterine device (not approved for a postmenopausal indication in the United States, but widely used in other countries and, increasingly, off-label in United States) appears effective at minimizing hyperplasia and endometrial cancer risk, especially in obese women (74–76).

Breast cancer

Estrogen therapy. Most, but not all, observational studies report an increased breast cancer risk with oral or transdermal estradiol when initiated in recently menopausal women (77–79). This increase occurs as a function of duration of ET (38, 80–82) with a linear trend in the largest study (83). Insufficient numbers of patients may confound

Table 5. Commonly Prescribed Hormone Therapies

Preparation	Doses	Comments
Systemic estrogen therapies[a]		
Oral estrogen tablets		
Micronized E2	0.5, 1.0, 2.0 mg/d	
Estradiol valerate[b]	1.5 mg/d	
CEE	0.3, 0.45, 0.625 mg/d	Higher doses available Preparation used in WHI
Transdermal estrogens		
Estradiol patch	0.025 to 0.1 mg once or twice weekly depending on preparation 0.014 mg/wk	Corresponds to 0.5 to 2.0 mg estradiol tablets Diffusion can be different from one patch to another Preserved bone in women >60 y old
Estradiol percutaneous gel	0.25–1.5 mg qd	Corresponds to 0.5 to 2.0 mg estradiol tablets Can be transferred to persons and pets by skin contact
Estradiol transdermal spray	1.5 mg qd	Estradiol via spray Can be transferred to persons and pets by skin contact
Vaginal ring		
Estradiol acetate	0.05–0.10 mg/d	Systemic levels of estradiol provide relief of VMS; 90-d duration/ring
Progestogen therapies		
Oral progestin tablets		
Medroxyprogesterone acetate	2.5, 5, 10 mg/d	Utilized in WHI
Norethindrone	0.35 mg/d	
Neta	5.0 mg/d	
Megestrol acetate	20, 40 mg/d	
Dydrogesterone[b]	10 mg/d	
Chlormadinone acetate[b]	5, 10 mg/d	
Medrogestone[b]	5 mg/d	
Nomegestrol acetate[b]	3.75, 5 mg/d	
Promegestone[b]	0.125, 0.25, 0.5 mg/d	
Oral progesterone capsule		
Micronized progesterone	100, 200 mg/d	In peanut oil; avoid if peanut allergy. May cause drowsiness and should be taken at bedtime
Intrauterine system progestin[c]		
LNorg	20 μg released/d 6 μg/d	IUD for 5-y use IUD for 3-y use
Vaginal gel progesterone[c]	4%, 8%	45- or 90-mg applicator
Combination hormone therapies		
Oral		
CEE + MPA	0.3–0.625 mg/1.5–5 mg/d	Cyclic or continuous
E2 + Neta	0.5–1 mg/0.1–0.5 mg/d	Continuous
E2 + drospirenone	0.5–1 mg/0.25–1 mg/d	Continuous
E2 + norgestimate	1 mg/0.09 mg/d	Cycle 3 d E alone, 3 d E + progesterone
E2 + dydrogesterone[b]	1–2 mg/5–10 mg/d	Cyclic and continuous
E2 + cyproterone acetate[b]	2 mg/1 mg/d	Continuous
E2 + MPA[b]	1–2 mg/2–10 mg/d	Continuous
CEE + BZA[d]	0.45 mg/20 mg/d	Continuous
Transdermal		
E2 + Neta	50 μg/0.14–0.25 mg/patch	Twice weekly
E2 + LNorg	45 μg/0.015 mg/patch	Once weekly

Abbreviations: IUD, intrauterine device; E, estrogen; E2, 17-β estradiol; LNorg, levonorgestrel; Neta, norethindrone acetate or norethisterone acetate; qd, once daily.

[a] Not all preparations and doses are available in all countries.

[b] Only available outside the United States.

[c] Not approved in the United States for endometrial protection when administered with postmenopausal estrogen.

[d] Approved indications in the United States include treatment of moderate to severe VMS associated with menopause and prevention of postmenopausal osteoporosis. In the European Union, the indications state: treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 mo since the last menses) for whom treatment with progestin-containing therapy is not appropriate. The experience treating women older than 65 years is limited.

doi: 10.1210/jc.2015-2236

the interpretation of these data on ET alone (ie, type II statistical error). It is possible that in observational studies mammographic surveillance differed between users and nonusers of MHT. The finding of increased risk in recently menopausal women is controversial, however. In women in the WHI ages 50 to 59 or < 10 years after menopause onset, CEE did not increase risk (44, 84). The statistically significant 21% reduction of invasive breast cancer in the 13-year cumulative follow-up of all women in the estrogen-alone arm of the WHI was of similar magnitude in each age group (44), but some analyses have suggested less reduction or an increase in risk among women starting ET close to menopause (77, 85).

The presence or absence of obesity confounds the interpretation of existing data. The aromatase enzyme, which increases with obesity, results in enhanced endogenous estrogen production, which may minimize the additional effects of exogenous ET. The insulin resistance associated with obesity also confounds the relationship between obesity and breast cancer risk (86). Therefore, increased breast cancer risk with ET in non-US studies might reflect differing levels of obesity between US and European populations. CEE and estradiol may also have differential effects as suggested by in vitro (87) and primate (88) studies. In summary, the risk of breast cancer from estrogen alone, taken for 5 years, appears to be small.

Combined EPT. Studies examining the effects of combined therapy report a consistent increase in breast cancer risk (38, 89, 90). It should be noted that the original WHI study did not report any increase overall in women who had not previously used MHT (hormone naive), but data on this issue are not available for women ages 50 to 59 or < 10 years postmenopausal (18, 91), and there are no reported follow-up data for the hormone-naive women. In women ages 50 to 59 in the WHI, the excess risk of invasive breast cancer during the intervention phase persisted 7 years after the cessation of EPT, with 4.5 excess cases/1000 over 5 years (HR, 1.34; 95% CI, 1.03–1.75) (44). Studies have reported similar findings with most other estrogen/progestogen combinations (38, 89, 92). However, observational data suggest that progesterone or dydrogesterone (5, 89) may be associated with a lower risk, but further studies are required to confirm this. Observational studies also report a greater risk when EPT is started close to menopause (79, 85, 93) and with continuous rather than with cyclic regimens (78, 82, 94).

Lung cancer

In the 50- to 59-year age group in the WHI study, the incidence of lung cancer was not significantly increased or decreased in either treatment arm (44).

Ovarian cancer

In the 50- to 59-year age group of the WHI, the HR of ovarian cancer with EPT was 0.30 (two vs six cases; 95% CI, 0.06–1.47), with 1.5 fewer cases/1000 per 5 years of treatment (44). No data have been reported for ET. A controversial meta-analysis of 52 observational studies (95–97) showed an increase of 0.52 cases/1000 in women starting MHT (no difference in risk between ET and EPT) at age 50 and continuing therapy for 5 years. Risk persisted 5 years after stopping MHT, with 0.37 cases/1000 in the same women when ages 55 to 59 (95). Of note, the overall risk of ovarian cancer with EPT in the WHI (HR, 1.41), although not statistically significant, was comparable to findings in the meta-analysis, as was the rate in the cumulative follow-up (HR, 1.24). Based on current data, adequately powered RCTs are needed to fully ascertain ovarian cancer risk in symptomatic, recently postmenopausal women.

Coronary heart disease

Estrogen therapy. The age at initiation of ET influences risk. In the WHI, there was a trend toward a reduction in CHD and total MI in women aged 50 to 59 years at trial enrollment (44). Composite outcomes, including revascularization (98) and coronary artery calcium scores (99), were lower with ET than with placebo.

Observational studies of ET suggest the potential for CHD benefit in some women, although a number of biases might have contributed to those conclusions (100). In summary, ET does not increase CHD risk in women starting therapy at ages < 60 years and may possibly reduce this risk.

Although observational studies suggest that a dermal route of ET may carry a lower risk of MI (101, 102), a meta-analysis reported no significant difference in CHD outcomes between oral and transdermal MHT (4). No associations with estrogen dose were reported (101, 102).

Combined EPT. Age at initiation of EPT does not appear to influence the relative risk of CHD, based on the most recent WHI data (44) and a meta-analysis (4). In women in the WHI aged 50 to 59, there was a trend toward excess risk of CHD, but no increased risk was apparent in women < 10 years since menopause onset (44). These findings and those of several recent studies have been controversial. A randomized osteoporosis trial that did not have CHD as a predefined primary endpoint reported that 10 years of MHT treatment in women < 50 years old at study onset was associated with the reduction of a composite safety endpoint (death, hospital admission for MI, or heart failure) (103). This study has been criticized for its composite index and nonblinded nature. A primary pre-

vention RCT of recently (< 3 y) postmenopausal women ages 42 to 58 failed to detect a difference in progression of atherosclerosis (as assessed by carotid intima-medial thickness and coronary artery calcium determinations) after 4 years of therapy (104) but may have been underpowered to detect significant differences (ie, type II error). In summary, EPT does not appear to be associated with an increased risk of CHD among women close to the onset of menopause, and if any risk elevation is present in women younger than 60 years, its magnitude is small. A definitive conclusion regarding CHD risk requires an appropriately powered RCT.

Stroke

Researchers reported a nonsignificant trend toward an increase in stroke risk with EPT in women ages 50 to 59 in the WHI (44) but did not report an adverse effect with ET. When examined by years since menopause, ET increased stroke risk in women < 10 years since menopause (6.5 women/1000 over 5 y) (44). The differences between these two groups might reflect the difficulty in establishing time of menopause in women with a hysterectomy.

No RCTs have evaluated stroke risk according to estrogen type, dose, or route of administration. Some observational studies suggest that transdermal estradiol in doses ≤ 50 μg may confer a lower risk compared with higher dose transdermal or oral therapies (4, 105). Other studies are conflicting regarding effects of estrogen type (102, 106) and dose (101, 105, 107). In summary, MHT may confer a small risk of stroke.

Venous thromboembolic events

Estrogen therapy. RCTs demonstrate that oral ET increases VTE risk in women ages 50 to 59 (44). These data are supported by observational studies (106, 108, 109). Risk declined after discontinuing therapy (44). Observational studies (108–112) and meta-analyses (4, 113) suggest that transdermal ET does not increase VTE risk, even in women with thrombophilia or obesity (114–117). In an observational study, oral CEE was associated with a 2-fold increase in VTE compared with oral estradiol (106).

Combined EPT. The WHI trial found an association between EPT and both DVT and pulmonary embolism (PE) in women ages 50 to 59 (44). Risks resolved when therapy was discontinued. Observational studies suggest that formulations containing MPA and normethytestosterone derivatives appear to be associated with greater risk than other progestogens (108, 109, 111). A recent meta-analysis comparing ET and EPT did not report any statistically significant differences in risk (4).

Gallbladder disease

No data are available specifically for women ages 50 to 59; conclusions regarding gallbladder disease rely on overall findings of the WHI. ET resulted in 29 excess cases/1000 women over 5 years (44). This risk did not persist after discontinuation (44, 118). With EPT, the excess risk was 23 women/1000 (44), similar to another trial (119). Risk persisted at least 5 years after cessation of EPT (44, 120). Observational studies report increased risk with oral, but not transdermal, estradiol (121, 122) and increased dose and duration (120, 123).

Incontinence

Stress urinary incontinence, urge urinary incontinence, and mixed urinary incontinence increase in women taking oral ET and EPT (124, 125). An increased risk may persist after discontinuation (44).

Uncertain benefits of hormone therapy

Mortality

A meta-analysis of RCTs demonstrated no significant effect on all-cause mortality with MHT use, but these data included women < and > 60 years of age (5). A recent Cochrane collaboration review reported a 30% relative risk reduction (HR, 0.70; 95% CI, 0.52–0.95) of all-cause mortality in women starting MHT < 10 years since menopause (or < age 60) (127). Comparison of the ET and EPT groups in the WHI suggested a stronger trend by age group among those on ET, with a statistically significant trend by age in the ET trial but not in the EPT trial (44). Observational studies (128–130) reported a reduction in mortality with MHT, as did one small RCT with composite endpoints (103). This is consistent with meta-analyses that reported a 30–40% mortality reduction (131, 132). In summary, further data are required for definitive conclusions about mortality in younger women.

Dementia

Observational studies suggest a possible benefit of MHT if started in younger women closer to menopause (133), as opposed to the detrimental effects reported in clinical trials when MHT is initiated in women > 65 years old (134). Some studies of postmenopausal women treated with estradiol reported an improvement in verbal memory and executive function (135–138), whereas other studies did not associate CEE therapy with cognitive improvement (139, 140). Definitive conclusions about MHT in women < age 60, therefore, are lacking.

Individual baseline risk assessment and therapeutic decisions

Evaluating risk facilitates individual counseling and decisions regarding MHT for symptom relief (Figure 2).

doi: 10.1210/jc.2015-2236

However, no clinical trial evidence is available to support the practice of incorporating risk assessment instruments for quantifying cardiovascular (CHD, stroke, and VTE) and breast cancer risks among women considering MHT. Nevertheless, we feel that risk assessment instruments are useful to facilitate decision-making regarding MHT.

Cardiovascular risk

3.1b For women < age 60 or < 10 years past menopause onset considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of CVD and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2⊕⊕◯◯)

3.1c For women at high risk of CVD, we suggest initiating nonhormonal therapies to alleviate bothersome VMS (with or without climacteric symptoms) over MHT. (2⊕⊕◯◯)

Technical remarks

High risk includes known MI, cerebrovascular disease, and peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, chronic kidney disease, and 10-year CVD risk > 10% (40).

3.1d For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. (2⊕⊕◯◯)

Evidence

Cardiovascular risk

Results showing fewer excess CHD and stroke events when MHT was initiated in younger rather than older study participants in the WHI (141) provide the foundation for the widely accepted consensus that MHT should be initiated primarily in younger women (age < 60 y) close in time (< 10 y) to menopause onset, when women likely have less baseline atherosclerosis (19, 20). The population prevalence of obesity, hypertension, dyslipidemia, and diabetes continues to increase. Accordingly, baseline CVD risk evaluation is important in women considering MHT. As reviewed in recent statements, CHD and stroke are associated with a wide range of risk factors, many unique to women (40, 41). Notably, a prior history of CHD conveys the highest risk of subsequent MI and stroke (142). We feel that methods to integrate these factors to categorize individual risk as minimal, moderate, and high are useful and can be accomplished qualitatively by clinical judgment or quantitatively by risk assessment tools.

Country- and population-specific CVD risk calculators are available to quantify individual risk per local guidelines (143). However, specific cutoffs for the safe use of MHT have not been formally validated, and practice differs from country to country.

The Menopause Decision-Support Algorithm (63) starts with calculating the American College of Cardiology (ACC)/American Heart Association (AHA) 10-year CVD risk (144), then stratifies by years since menopause to suggest appropriateness of MHT (Table 6) (63). For a woman at intermediate risk, family history, coronary artery calcium score, C-reactive protein, and ankle-brachial index can further stratify risk (144); inflammatory markers and lipid ratios predict treatment-related CHD events (145).

Metabolic syndrome. The metabolic syndrome (MetS) is associated with higher risk of cardiovascular events and breast and colon cancers (146). In a nested case-control study in the WHI, women with MetS at baseline were twice as likely to have CHD events while taking oral MHT as with placebo (147). In contrast, women without MetS had no increase in CHD risk on MHT. Transdermal estradiol with micronized progesterone might have less deleterious metabolic effects than oral therapies, but there are no RCTs that have evaluated the safety of these preparations in women with MetS.

Diabetes. Diabetes is considered by the AHA to be a CHD risk equivalent (40), which would suggest that women with diabetes should not take MHT. However, clinical trial evidence of CVD outcomes associated with MHT in women with diabetes is mostly lacking. Some diabetic women were included in RCTs (Heart and Estrogen/Progestin Replacement Study [19%]; WHI [4.4–7.7%]), but these trials were not powered to assess differences in CVD

Table 6. Evaluating CVD Risk in Women Contemplating MHT

	Years Since Menopause Onset	
10-y CVD Risk	**<5 y**	**6 to 10 y**
Low (<5%)	MHT ok	MHT ok
Moderate (5–10%)	MHT ok (choose transdermal)	MHT ok (choose transdermal)
High (>10%)[a]	Avoid MHT	Avoid MHT

CVD risk calculated by ACC/AHA Cardiovascular Risk Calculator (144). Methods to calculate risk and risk stratification vary among countries. Derived from J. E. Manson: Current recommendations: what is the clinician to do? *Fertil Steril.* 2014;101:916–921 (63), with permission. © Elsevier Inc.

[a] High risk includes known MI, stroke, peripheral artery disease, etc.

outcomes. A few short-term RCTs have evaluated glucose control in diabetic women taking a variety of MHT preparations and showed either no effect or improved control (148). The evidence at this time is inadequate to make firm recommendations. An individualized approach to treating menopausal symptoms could be considered, with a low threshold to recommend nonhormonal therapies, particularly in women with concurrent CVD. However, some diabetic women, after careful evaluation of cardiovascular risk, may be candidates for MHT, preferably transdermal estrogen and micronized progesterone or another less metabolically active progestogen.

Venous thromboembolic events

3.1e For women at increased risk of VTE who request MHT, we recommend a nonoral route of ET at the lowest effective dose, if not contraindicated (1|⊕⊕◯◯); for women with a uterus, we recommend a progestogen (for example, progesterone and dydrogestone) that is neutral on coagulation parameters. (1|⊕⊕⊕◯)

Evidence

Obesity, age, and thrombophilia are associated with increased risk of VTE. An approximately 2-fold increased risk of VTE (both DVT and PE) with oral MHT is similar among women at low, intermediate, or high risk (149, 150). Accordingly, the attributable risk of MHT will be higher in those at high or intermediate baseline risk.

A prior history of VTE confers the highest risk. If the patient has a known inherited coagulation defect, such as Factor V Leiden, oral ET or EPT should be avoided because research has shown a high risk of VTE recurrence (114). A history of VTE due to pregnancy, oral contraceptives, unknown etiology, or blood clotting disorders poses a contraindication to any ET, whereas VTE due to past immobility, surgery, or bone fracture would be a contraindication to oral but not necessarily transdermal MHT (151). In some countries, a history of any VTE is a contraindication to oral but not low-dose transdermal ET.

Breast cancer

3.1f For women considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|⊕⊕◯◯)

3.1g For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, we suggest nonhormonal therapies over MHT to alleviate bothersome VMS. (2|⊕⊕◯◯)

Technical remarks

High or intermediate risk includes calculated level of risk that would qualify for risk-reducing medications.

Evidence

There are no established clear criteria for recommending (or avoiding) MHT based on a woman's risk of breast cancer. Nonsignificant trends from the WHI suggest that the relative risk of breast cancer in association with MHT remains stable or increases in the 5-year Gail model breast risk categories of < 1.25 vs ≥ 1.75. On this basis, the excess or attributable risk should increase in women at higher categories of risk (90, 152). As another consideration, it seems prudent not to recommend MHT for women whose risk meets the criteria for breast cancer prevention with SERMs or aromatase inhibitors. The U.S. Preventive Services 2013 Task Force recommends that women with a 5-year risk of $\geq 3\%$ should be considered for preventive therapy with tamoxifen or raloxifene (126), whereas the American Society of Clinical Oncology guidelines suggest discussing such therapy in women with a risk of $\geq 1.67\%$ (153), consistent with enrollment criteria of breast cancer prevention trials. Prevention recommendations differ outside the United States. Another consideration is to take into account the data suggesting that breast cancer risk is associated with combined estrogen/progestogen use, but less so, if at all, with CEE alone.

We suggest one potential algorithm for MHT counseling, extrapolated from breast cancer prevention trial enrollment criteria (Table 7); however, it is not validated in clinical trials or widely utilized. This algorithm requires the assessment of breast cancer risk, which can be accomplished by qualitative methods or preferably with readily available quantitative risk assessment tools. The National Cancer Institute Breast Cancer Risk Assessment Tool pro-

Table 7. Breast Cancer Risk Cutoffs for Counseling Before Recommending MHT[a]

Risk Category[a]	5-y NCI or IBIS Breast Cancer Risk Assessment, %	Suggested Approach
Low	<1.67	MHT ok
Intermediate	1.67–5	Caution[b]
High	>5	Avoid

Abbreviations: IBIS, International Breast Intervention Study; NCI, National Cancer Institute.

[a] Categories here are newly defined for these guidelines and based on recommendations published for use of antiestrogens for breast cancer prevention (126, 153, 322, 323). The assumption is that candidates for breast cancer prevention with antiestrogens should not be candidates for initiating MHT. Method to calculate risk varies among countries.

[b] Caution indicates need for detailed counseling regarding anticipated benefits and risks of MHT with strong consideration of nonhormonal therapies for symptom relief, and possible consideration of chemopreventive strategies for women who meet suggested criteria.

doi: 10.1210/jc.2015-2236

vides a standardized online risk calculator for 5-year risk of invasive breast cancer (154). The International Breast Intervention Study calculator predicts 10-year and lifetime risk (155, 156). For women with strong family histories of breast cancer, several other methods are available (155). Although these provide useful predictive information, all are limited by only moderate discriminatory accuracy (155). Mammographic breast density, when added to these methods, may emerge as an important objective risk for women contemplating MHT (157–159).

Although a history of breast cancer is considered by most to be a contraindication to MHT, the severity of menopausal symptoms, the compromise in QOL experienced by breast cancer survivors, and limitations of nonhormonal therapies for relief of VMS present a persistent clinical challenge. As recently summarized, it is not possible from currently available studies to draw firm conclusions regarding the risks of MHT in this population (38), but adding estrogen seems counterintuitive when current breast cancer therapies interrupt or decrease estrogen levels. Future studies taking into account estrogen receptor status, time since diagnosis and therapy, mastectomy status, and risks for breast cancer recurrence might better inform decision-making.

Tailoring menopausal hormone therapy

3.1h We suggest a shared decision-making approach to decide about the choice of formulation, starting dose, the route of administration of MHT, and how to tailor MHT to each woman's individual situation, risks, and treatment goals. (Ungraded best practice statement)

Clinicians prescribe estrogen alone for women without a uterus. Starting dosages are generally lower than those in the WHI (Table 5), and the overarching principle is to use the lowest effective dose with upward titration based on clinical response. Clinicians usually do not measure estradiol levels to monitor therapy except when symptoms do not improve with escalating doses, particularly after changing the mode of administration from oral to transdermal. For younger women with surgical menopause or those with POI who are accustomed to higher baseline endogenous estradiol levels, clinicians often prescribe higher starting doses of ET (eg, transdermal estradiol, 100 μg), and then slowly lower the dose as tolerated. When women with premature menopause approach the age of natural menopause, the reassessment and tapering of MHT dose seems reasonable.

Estrogen preparations

Oral estrogens. Estradiol tablets or conjugated estrogens (synthetic or equine) are convenient, are studied most extensively, and alleviate climacteric symptoms in a dose-dependent fashion. CEE, derived from pregnant mares' urine and used for decades, contain more than 200 compounds with varying estrogenic potency (160). Oral micronized estradiol and other oral estrogen preparations may result in up to 5-fold higher levels of circulating estrone and 10- to 20-fold higher estrone sulfate than transdermally administered estradiol at comparable or even higher doses. The biological effects of these estrone and estrone-sulfate increments are unknown (161–163).

Cutaneous and transdermal estradiol. Cutaneous and transdermal estradiol, administered via percutaneous gels, sprays, emulsions, or transdermal patches, have a similar efficacy as oral ET in reducing climacteric symptoms and are easily tailored to the individual (164, 165). The primary advantage of transdermal ET is to alleviate the first-pass hepatic metabolic effect (166) of oral estrogens resulting in a procoagulant effect and increases in SHBG, thyroid-binding globulin, cortisol-binding globulin (167, 168), triglycerides, and markers of inflammation such as C-reactive protein (167, 169).

Transdermal therapies, at low doses, are preferable for women with a VTE risk, as evidenced by a recent meta-analysis commissioned for these guidelines (4), and they may also be preferable in patients with hypertension, hypertriglyceridemia, obesity, MetS, diabetes, or a history of gallbladder disease. Clinicians should keep in mind that there are no existing head-to-head RCTs with clinical outcomes that compare transdermal with oral therapies.

Vaginal delivery of systemic estrogens. Estradiol acetate vaginal rings, delivering 50 or 100 μg of estradiol daily (Table 5), provide consistent systemic estradiol levels for 3 months per ring insertion. They are indicated for treatment of moderate to severe VMS and VVA due to menopause (170, 171). High-dose vaginal creams containing estradiol or CEE (ie, 1–2 g) also result in systemic estrogen levels. Concomitant progestogen is needed with these preparations to abrogate endometrial stimulation. We discuss low-dose vaginal ETs for the specific treatment of GSM in *Section 5.0*.

Progestogen administration

In women with a uterus, a progestogen must be added to prevent endometrial hyperplasia and cancer. The various formulations (Table 5) are administered in two regimens. The combined sequential regimen includes estrogen for 20 to 25 days and a progestogen for 12 to 15 days each month. This approach is preferred for recently menopausal woman who are prone to breakthrough bleeding during the first year or two of therapy. The combined continuous regimen utilizes both an estrogen and pro-

gestogen daily on a continuous basis. Clinicians can administer progestogen orally, transdermally by patch, vaginally, or by intrauterine administration (172). The levonorgestrel intrauterine device minimizes systemic progestogen absorption, but increased blood levels do occur, and one observational study reported higher breast cancer incidence (173).

Progestogen alone. For those who do not tolerate ET, progestogens can relieve VMS. In RCTs, oral synthetic progestogens (Table 5) (174, 175) and micronized progesterone (176) were effective. Clinical outcome trials are lacking in women with breast cancer; thus, progestogen therapy is best avoided, except under limited circumstances in these patients, because the effect on recurrence is unclear (80).

Custom-compounded hormones

3.1i We recommend using MHT preparations approved by the FDA and comparable regulating bodies outside the United States and recommend against the use of custom-compounded hormones. (Ungraded best practice statement)

Evidence

A number of FDA-approved hormonal therapies are "biochemically identical" to endogenous estradiol and progesterone and are preferred to custom-compounded options. Custom-compounded hormone therapies have become increasingly popular but are not recommended because the manufacturing process lacks FDA oversight (177). Clinical trials documenting the efficacy and safety of compounded progesterone for endometrial protection are lacking. Proponents of custom-compounded hormone therapies often advise measuring salivary hormone levels to monitor therapy. However, scientific evidence is lacking to justify salivary measurements due to inter- and intra-assay variability, variable salivary flow rates dependent upon hydration, food intake, and other factors, and the inability to predict the pharmacokinetics of a custom-compounded hormone dose in a manner that would allow for valid salivary sampling.

3.2 Conjugated equine estrogens with bazedoxifene

3.2 For symptomatic postmenopausal women with a uterus and without contraindications, we suggest the combination of CEE/BZA (where available) as an option for relief of VMS and prevention of bone loss. (2⊕⊕⊕○)

Evidence

The combination of CEE with the SERM/BZA (available in the United States and licensed in the European Union) relieves VMS and vaginal atrophy and reduces bone resorption in women with a uterus; it provides an alternative to progestogen therapy for women averse to vaginal bleeding, breast tenderness, or altered mood. A series of RCTs up to 2 years in duration evaluated effects of CEE/BZA (0.45 mg/20 mg, the approved dose) compared with MHT (CEE 0.45 mg/MPA 1.5 mg) (178–180).

Benefits

Vasomotor symptoms. The number and severity of moderate-to-severe VMS were significantly decreased at 12 weeks; hot flash frequency was reduced by 74% compared with 51% for placebo, and hot flash severity was reduced up to 54%. Hot flash reduction was sustained at 12 months ($P < .05$) (181).

Bone loss. Bone loss at the lumbar spine and hip was prevented in postmenopausal women at risk for osteoporosis (182), as reflected by reduction of serum bone turnover markers and enhancement of bone mineral density vs placebo (180, 181). At 12 months, CEE/BZA was less effective at the lumbar spine than CEE/MPA (180). Fracture data are lacking.

Vaginal effects. Treating postmenopausal women ages 40 to 65 with VVA at baseline (183) improved vaginal maturation at 12 weeks (181). Women reported a lower incidence of dyspareunia.

Quality of life. Secondary endpoints included improvements in sleep, health-related QOL, and improved treatment satisfaction (184, 185). In RCTs, both CEE/BZA and CEE/MPA improved sleep disturbance and time to fall asleep (185).

Safety considerations

Breast. The incidence of breast pain and tenderness was similar for CEE/BZA and placebo (185–187) and was less than with CEE/MPA. After 1 year of therapy with CEE/BZA, mammographic breast density was not appreciably different than with placebo, whereas it increased with CEE/MPA (184). In trials up to 2 years, the rates of breast cancer (reported as adverse events, not clinical outcomes) were not sufficient to assess risk or benefit (186, 187).

Endometrium. Cumulative amenorrhea rates for CEE/BZA were comparable with placebo and greater than for CEE/MPA (188). At 2 years, the incidence of neither endometrial hyperplasia nor endometrial cancer was increased (180, 189).

Potential risks

Adverse events. Although an osteoporosis trial found a 2-fold risk of VTE with BZA 20-mg therapy alone (190),

doi: 10.1210/jc.2015-2236

there was no additive effect on VTE when BZA was combined with CEE, although adequately powered studies are necessary (181). In trials of up to 2 years in women ages 40 to 65, rates of cardiovascular events, cancers (breast, endometrial, ovarian), and mortality were similar to placebo (191), but studies were underpowered to draw firm conclusions regarding these endpoints.

3.3 Tibolone

3.3a For women with bothersome VMS and climacteric symptoms and without contraindications, we suggest tibolone (in countries where available) as an alternative to MHT. (2|⊕⊕◯◯)

3.3b We recommend against adding tibolone to other forms of MHT. (1|⊕⊕◯◯)

3.3c We recommend against using tibolone in women with a history of breast cancer. (1|⊕⊕◯◯)

Evidence

Tibolone belongs to the group of normethyltestosterone progestogen derivatives and has metabolites that exhibit estrogenic, progestogenic, and androgenic effects (192). This agent (193) is available in many countries outside of the United States at doses of 1.25–2.5 mg/d.

Benefits

Menopausal symptoms. Tibolone alleviates VMS with equivalent or lesser potency than conventional MHT. Tibolone also improves sleep, mood, and urogenital atrophy and may improve libido (194–197).

Bone loss and fracture. Tibolone prevents postmenopausal bone loss and osteoporotic fractures in women with osteoporosis (198, 199), but is not approved for this purpose because of the increased risk of stroke in older women with osteoporosis initiating therapy at ages ≥ 60 years (199).

Possible risks

Endometrium. There is no endometrial thickening (197) or increase in myoma with tibolone (200). A Cochrane analysis concluded that there was no clear evidence of endometrial cancer with tibolone therapy (seven RCTs, n = 8152; odds ratio, 1.98; 95% CI, 0.73–5.32) (194).

Thrombosis and CVD. In an observational study (110), tibolone did not increase the risk of thrombosis. In an RCT of older women with osteoporosis, tibolone increased stroke (199).

Breast and colon cancers. The incidence of breast tenderness is low (around 3%), (201, 202), and neither mammographic density nor invasive breast cancer was increased; however, the risk of colon cancer was decreased (199, 201). An RCT of women with a history of breast cancer, after a median follow-up of 3.1 years, reported a higher rate of breast cancer recurrence with tibolone (HR, 1.40; 95% CI, 1.14–1.70) (203). The study reported the greatest increase for women taking an aromatase inhibitor (HR, 2.42; 95% CI, 1.01–5.79).

3.4 Clinical management of patients taking hormone therapies

Monitoring during therapy

3.4a For women with persistent unscheduled bleeding while taking MHT, we recommend evaluation to rule out pelvic pathology, most importantly, endometrial hyperplasia and cancer. (1|⊕⊕⊕◯)

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing EPT and emphasizing the importance of adhering to age-appropriate breast cancer screening. (1|⊕⊕⊕◯)

Technical remarks

Regular clinical follow-up, initially, within 1 to 3 months after starting MHT, and then every 6 to 12 months, depending upon the individual (and health care system), allows for monitoring efficacy and side effects (abdominal/pelvic pain, mastalgia, metrorrhagia, weight gain, mood changes, blood pressure), and if necessary, making treatment adjustments (Table 8).

Duration of therapy

3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. (Ungraded best practice statement)

Technical remarks

Most published recommendations suggest using MHT for the shortest duration possible, but strong evidence is lacking to support this recommendation. Current proposed limits on duration of therapy are informed by large intervention trials (5 to 7 y) with extended follow-up for 13 years (44). Regarding duration of use, these data suggest that risk rates for breast cancer and CVD increase with age and time since menopause, although the risks with ET appear to be less than with EPT. Ovarian cancer risk may also increase relative to duration of MHT (95). We conclude, and guidelines from other societies concur, that clinicians and patients should reassess MHT continuation yearly and discuss the risks (and individual benefits) beyond 5 years (55, 56). Patients likely to consider

Table 8. Clinical Caveats During Treatment With MHT

Symptom/Condition When MHT Started	Approach to Resolution
Persistent, intolerable VMS	Switch mode of administration or adjust dose of estrogen and/or progestogen.
Hot flashes that persist after treatment adjustment	Consider another etiology of flashes (Table 2). Ensure absorption: if transdermal, consider serum estradiol determination.
Bleeding: approach depends on time since menopause, MHT regimen, duration of therapy, duration and character of bleeding	Sequential regimen may be more appropriate for recently menopausal (<2 y), because unscheduled bleeding with continuous combined MHT can be problematic. Persistent irregular bleeding (>6 mo) should be evaluated for endometrial pathology; if obese, diabetic, or having family history for endometrial cancer, evaluate sooner. Atrophic endometrium in women more remote from menopause may respond to increased estrogen dose if otherwise appropriate.
Breast tenderness	Usually responds to a reduction in estrogen dose or change in progestogen preparation. CEE/BZA may improve symptoms. Changing to tibolone may be helpful in women who develop mastalgia on conventional MHT.
Baseline TG level >200 mg/dL	Review family history and seek contributing factors. Transdermal ET is preferred. If oral estrogen is selected, monitor serum TG levels 2 wk after starting therapy.
Hypothyroid on thyroid replacement	Monitor TSH 6 to 12 wk after starting oral MHT; T_4 dose may need to be increased (209).

Abbreviation: TG, triglycerides.

continuing therapy include those who fail an attempt to stop EPT, who are at high risk for fracture, or for whom alternative therapies are not appropriate.

3.4d For young women with POI, premature, or early menopause, without contraindications, we suggest taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. (2⊕⊕◯◯)

Stopping considerations

3.4e For women preparing to discontinue MHT, we suggest a shared decision-making approach to elicit individual preference about adopting a gradual taper vs abrupt discontinuation. (2⊕⊕◯◯)

Evidence

A number of studies have compared methods (ie, taper protocols vs abrupt cessation) to facilitate the discontinuation of MHT (204–207) and have detected no differences. Therefore, the approach to discontinuation is an individual choice. Anecdotally, some women find that a very low dose of ET maintains adequate symptom relief and well-being and prefer that to complete discontinuation.

Menopausal symptoms and joint pain can recur when MHT is discontinued (44). Depending on the severity of the symptoms, women may elect to restart MHT, perhaps at a lower dose, or seek relief with nonhormonal therapies. Accelerated bone loss was reported after the discontinuation of MHT, whereas in contrast, bone density is stable for some years after discontinuing bisphosphonate therapy. Bisphosphonates, however, remain in bone indefinitely, and most expert groups do not recommend initiating bisphosphonate therapy for osteoporosis prevention in women aged 50 to 59. Adverse effects such as osteonecrosis of the jaw and atypical femur fractures, while rare, increase with the duration of therapy. Furthermore, as opposed to reports from observational studies (208), in the long-term follow-up of the WHI, hip fracture rates did not increase during 5 to 7 years of observation after MHT was discontinued (44). Breast cancer risk after 5 years of EPT in the WHI persisted 7 years after discontinuation. A large meta-analysis of observational studies found a persistent risk of ovarian cancer up to a decade after discontinuing MHT (95). Urinary incontinence persisted after oral MHT was discontinued; however, the percentage of affected women was approximately one-third less than during active treatment (44). MHT discontinuation may result in symptoms of VVA (*Section 5.0*), and when oral therapy is discontinued, glucose, cholesterol, triglycerides, calcium, and TSH (209) levels may change.

4.0 Nonhormonal therapies for VMS

4.0 For postmenopausal women with mild or less bothersome hot flashes, we suggest a series of steps that do not involve medication, such as turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress. (2⊕⊕◯◯)

doi: 10.1210/jc.2015-2236

Evidence

As hot flashes result from alterations of the thermoregulatory neutral zone, shedding layers of clothing, using fans, keeping the bedroom cool (30), avoiding alcohol and spicy foods, and reducing stress may be effective. Being overweight or obese is a risk factor for VMS (26, 210, 211), and weight loss may reduce hot flash frequency (212, 214).

4.1 Nonhormonal prescription therapies for VMS

4.1a For women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, we recommend SSRIs/SNRIs or gabapentin or pregabalin (if there are no contraindications). (1|⊕⊕⊕◯)

Evidence

The interpretation of hot flash efficacy studies requires an appreciation of an important confounding factor. There is a strong, consistently reported placebo effect, which averages 30% (range, 4–57%; Figure 4) and occurs more often in women with high anxiety and stress scores (215–220). Clinical trials of paroxetine, venlafaxine, desvenlafaxine, citalopram, and escitalopram demonstrate statistically significant efficacy with a reduction of frequency of hot flashes ranging from 25 to 69% (Figure 4). The composite score of hot flash frequency and severity is reduced by 27–61%. Other agents such as sertraline and fluoxetine are associated with non-statistically significant trends toward the reduction of hot flashes and inconsistent results (221–223).

Meta-analyses and a Cochrane review concluded that SSRIs and SNRIs exert mild-to-moderate effects to reduce hot flashes in women with a history of breast cancer (217, 224–227). Each of these agents appears to have similar efficacy in breast cancer survivors as in healthy menopausal women, although studies are small (213, 217, 228–234). Caution is advised in the use of paroxetine in patients taking tamoxifen because paroxetine markedly interferes with the metabolism of tamoxifen to its metabolite, endoxifen (221, 222, 224, 235–237).

The only FDA-approved agent in this class is low-dose paroxetine mesylate, but others have been used off-label in the United States. No direct trials are available to determine the relative efficacy of one over another. We describe suggested daily doses, efficacy, side effects, and contraindications in Figure 4. In general, the evidence suggests that these agents are effective and well tolerated.

Gabapentin

Four RCTs confirmed moderate efficacy in relieving hot flashes (238–241). On the basis of clinical experience, women whose hot flashes occur primarily at night respond well to a single bedtime dose. Individual dose requirements vary widely, as determined by empiric dose escalation, and range from 300 to 1200 mg. Gabapentin effects as a sedative and a reducer of vasomotor instability work well together when used at bedtime because sedating side effects dissipate by morning. However, when used during the day, gabapentin may result in a level of lethargy that is not tolerable.

Pregabalin

In one 6-week RCT, pregabalin (75–150 mg twice daily) decreased mean hot flash scores by 65 and 71%, compared with 50% by placebo (242), and was reasonably well tolerated.

Choice of SSRI/SNRI vs gabapentin/pregabalin

A randomized, crossover, multicenter trial that compared recommended doses of venlafaxine vs gabapentin, 300 mg three times a day (243), reported that both agents reduced hot flash scores by 66%, but two-thirds of patients preferred venlafaxine over gabapentin. The quality of this comparative evidence is low due to imprecision.

Relative efficacy of nonhormonal prescription therapies vs estrogens

A limited number of head-to-head RCTs have compared varying estrogen doses, preparations, and routes of administration with nonhormonal agents (213, 240, 244). None of the RCTs established statistically significant superiority of one treatment regimen over another. However, when these and other published data are taken into account (213, 217, 236, 245), the limited evidence available suggests that standard-dose MHT is more effective than nonhormonal agents.

4.1b For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the nonhormonal prescription therapies SSRIs/SNRIs or gabapentin or pregabalin, we suggest a trial of clonidine (if there are no contraindications). (2|⊕⊕◯◯)

Evidence

Clonidine

Several RCTs demonstrated that this α-2-adrenergic receptor agonist reduced hot flashes, but less effectively than the SSRI/SNRIs, gabapentin, and pregabalin, and with more side effects (Figure 4) (217, 236). Clonidine transdermal patches are preferred over tablets because of more stable blood levels.

4.2 OTC and alternative nonhormonal therapies for VMS

4.2 For women seeking relief of VMS with OTC or complementary medicine therapies, we suggest counseling re-

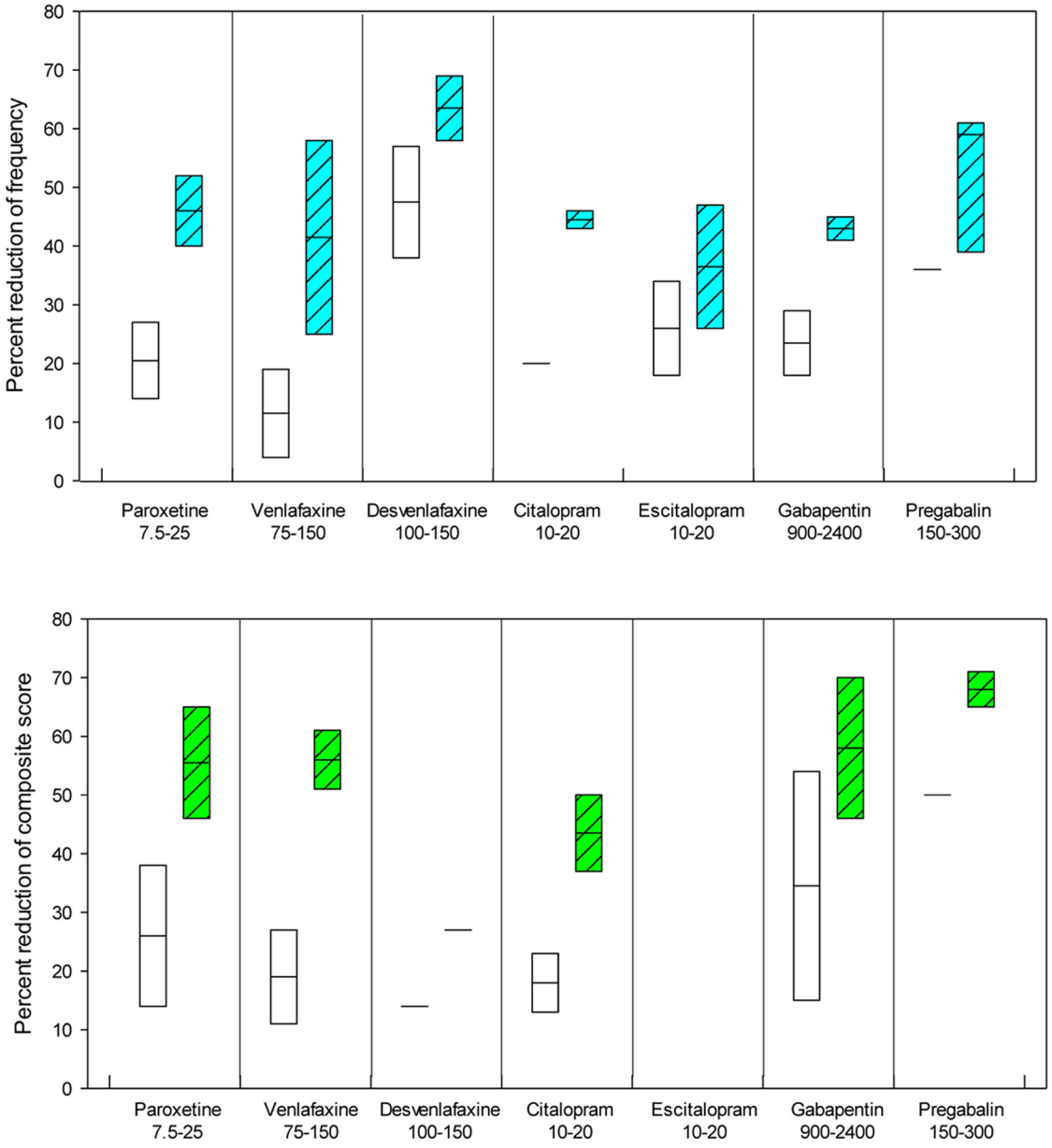


Figure 4. Hot flash frequency and composite score with nonhormonal prescription therapies for relief of VMS. Upper panel, Effect on frequency of VMS; lower panel, effect on composite score (severity times frequency; best representation of effect); open bars, placebo; colored bars, therapies; length of bars, ranges in studies; horizontal bar, means. All of these agents are generally well tolerated (226). Hypersensitivity or prior adverse drug reactions to each of these agents represent contraindications. For the SSRI/SNRIs, prior neuroleptic syndrome, serotonin syndrome, and concurrent use of monoamine oxidase inhibitors are also contraindications. SSRI/SNRIs should be used with caution in patients with bipolar disease, uncontrolled seizures, hepatic or renal insufficiency, uncontrolled hyponatremia, concurrent use of other SSRI/SNRIs, or poorly controlled hypertension. These agents uncommonly induce suicidal thoughts within the first few months of treatment. Preliminary evidence suggests a possible increase in risk of bone fracture. Gabapentin and pregabalin may increase suicidal thoughts and behaviors, cause drowsiness or dizziness, and impair balance and coordination. Pregabalin may impair memory and concentration. Clonidine is contraindicated in patients with low blood pressure and may cause lightheadedness, hypotension, headache, and constipation; sudden cessation of treatment can be associated with significant increments in blood pressure (63).

garding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3 fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis. (2|⊕⊕◯◯)

Evidence

Clinical trials with these agents have reported inconsistent efficacy over placebo, but individual patients may experience benefit (Table 9). The MSFLASH trial showed that omega-3 fatty acids do not improve VMS (246). In a randomized trial of 187 symptomatic menopausal women, clinical hypnosis was associated with a 74.2% reduction in hot flashes compared with a 17.1% reduction in women randomized to structured attention control ($P < .001$) (247). The phytoestrogens are nonsteroidal compounds that have both estrogenic and anti-

doi: 10.1210/jc.2015-2236

Table 9. Alternative Therapies for Treatment of VMS

Agents	Comments	Refs.
Agents with inconsistent reports of benefit		
Genistein	Purified isoflavone ±Estrogenically active Breast safety not established	324–336
Daidzein	Purified isoflavone ±Estrogenically active Breast safety not established	324–336
S-equol	Metabolite of daidzein	337
Nonpurified isoflavones	Breast safety not established	338
Flaxseed		225, 236, 328, 339–341
Red clover	Breast safety not established	225, 236, 328, 339–341
High-dose extracted or synthesized phytoestrogen		225, 236, 328, 339–341
Dietary soy	Agreement about breast safety	248
Vitamin E	10% benefit in some studies	217, 342, 343
Reports with predominantly no benefit		
Black cohosh	Some short-term trials report benefit, most report no benefit Breast safety not established Reports of liver toxicity	225, 344–352
Omega-3 fatty acids	No benefit in MSFLASH trial	246
Acupuncture	Not effective when compared to "sham acupuncture" controls	353–356
Exercise	Exercise with sweating may increase hot flashes	357
Other complementary approaches	Ginseng, dong quai, wild yam, progesterone creams, traditional Chinese herbs, reflexology, magnetic devices	225, 332
Agents requiring further study		
Stellate ganglion block	Need further RCTs to establish lack of complications	358
Guided relaxation	Stress management, deep breathing, paced respiration, guided imagery, mindfulness training	217, 225, 247, 359–365
Hypnosis	Recent studies suggest efficacy	247
Cognitive behavior modification	Recent studies suggest efficacy with trained practitioners	366, 367

estrogenic properties. Caution is advised because some of these agents, when consumed as supplements, can exert estrogenic effects, a concern in breast cancer survivors although dietary soy appears to have no adverse effects on breast cancer prognosis (248).

5.0 Treatment of genitourinary syndrome of menopause

5.1 Vaginal moisturizers and lubricants

5.1a For postmenopausal women with symptoms of VVA, we suggest a trial of vaginal moisturizers to be used at least twice weekly. (2⊕⊕◯◯)

Evidence

Vaginal moisturizers (eg, polycarbophil-based moisturizer, hyaluronic acid-based preparations, and a pectin-based preparation), when used regularly (at least twice weekly), may provide an effective nonhormonal approach to alleviating symptoms of vaginal atrophy. However, studies have been small, mostly open-labeled, and limited to 12 weeks (249–257). Although helpful, these approaches are not likely as effective as vaginal ET. Vaginal moisturizers have not been shown to reduce urinary tract symptoms or asymptomatic bacteriuria. Use of a vaginal moisturizer may not eliminate the need for a vaginal lubricant during intercourse.

5.1b For women who do not produce sufficient vaginal secretions for comfortable sexual activity, we suggest vaginal lubricants. (2⊕⊕◯◯)

Evidence

Vaginal lubricants are used to enhance the sexual experience in women with symptoms of VVA by alleviating vaginal dryness and preventing dyspareunia (258). Lubricants do not treat the underlying problem and only briefly alleviate symptoms. Several OTC options are available. Because data do not demonstrate the superiority of one to another, women can experiment with these products. Olive oil is also effective (259). Petroleum jelly has been associated with an increased rate of bacterial vaginosis (260).

5.2 Vaginal estrogen therapies

5.2a For women without a history of hormone- (estrogen) dependent cancers who are seeking relief from symptoms of GSM (including VVA) that persist despite using

vaginal lubricants and moisturizers, we recommend low-dose vaginal ET. (1|⊕⊕⊕○)

Evidence

A 2006 Cochrane meta-analysis of vaginal estrogens (261) compared 19 efficacy trials and found that all products effectively alleviated symptoms, but study differences limited comparisons among agents. As a guiding principle, we recommend using the lowest effective dose.

RCTs of low-dose vaginal estrogen products (262–267) report rapid improvement of vaginal symptoms (vaginal dryness or dyspareunia) and urinary symptoms (dysuria and urge incontinence) within 2 to 3 weeks. Objective improvements continue at 12 weeks and are maintained to 1 year. Limited evidence suggests that vaginal ET may prevent recurrent urinary tract infections (268, 269) and overactive bladder (270, 271). No clear proof exists that vaginal ET prevents or improves pelvic prolapse (272), but it may be advantageous preoperatively (273). Adverse effects include potential transfer to partner via penile or oral absorption and, with vaginal creams, residue on undergarments.

Vaginal estrogens

Vaginal estrogen preparations have been categorized as: 1) low, 2) intermediate, and 3) systemic doses (274) (Table 10). By using the lowest effective doses, systemic absorption is minimized. During the initiation of therapy, vaginal atrophy may enhance systemic absorption, although not all studies demonstrate this effect (267, 275). When vaginal epithelium is restored (after several weeks of ET), systemic absorption may decrease (276, 277).

Low-dose therapies

Low-dose vaginal ring. Low-dose vaginal rings result in estradiol levels that remain within the normal postmenopausal range; however, bone resorption and lipid levels decrease, suggesting possible systemic effects (278, 279). Insertion and removal at 3-month intervals may be difficult, the ring can be sensed during intercourse, and it can be expelled, particularly in women who have undergone a hysterectomy (265).

Vaginal estradiol tablets. The 10-μg tablet provides standard twice weekly dosing, relieves vaginal symptoms by 8 weeks, and is effective for at least 52 weeks (263, 275, 280, 281). Therapy is initiated with daily administration for 2 weeks, and then twice weekly thereafter. Vaginal placement of the tablet may provide less introital benefit than creams.

Promestriene (estradiol diether). This is a low-dose estrogen used outside the United States. Evidence is limited to studies of poor quality and very few RCTs (282).

Intermediate-dose vaginal estrogen

The 25-μg estradiol tablets increase plasma estradiol from 3.1 ± 0.83 to 19.8 ± 6.1 pg/mL by 7 days (283). An RCT of CEE vaginal cream ≥ 0.3 mg applied daily or twice weekly reported an improvement in VVA by 12 weeks that was sustained for 52 weeks without reports of endometrial effects (266). Intermediate-dose estradiol and CEE creams provide flexibility of dosing, allow treatment from the introitus to the vaginal apex, and provide the emollient effect of vehicle. Some systemic absorption exists (284, 285).

Table 10. Classification of Government-Approved Vaginal Estrogens

Type	Dose	Serum Estradiol Level
Low dose		<20 pg/mL
Silastic estradiol vaginal ring	7.5 μg	
Estradiol vaginal tablet	10 μg	
Promestriene (estradiol diether) ovule[a]	10 mg	
Estriol ovule[a]	0.5 mg	
Estriol + progesterone + *Lactobacillus Doderleini* ovule[a]	0.2 mg + 2 mg + 341 mg	
Promestriene cream[a]	3 mg	
Estriol cream[a]	0.015–0.03 mg	
Intermediate dose		>20 pg/mL
CEE vaginal cream >0.3-mg dose		5–50 pg/mL
Estradiol vaginal tablet 25 μg[b]		Some >20 pg/mL
High dose (systemic)		35–200 pg/mL
Estradiol vaginal ring	50 and 100 μg	
Vaginal estradiol	>0.5 mg	
Vaginal CEE	>0.5 mg[c]	

[a] Not approved or recommended in United States.

[b] No longer available in United States.

[c] Predominantly estrone sulfate; LH suppression reflects systemic absorption.

doi: 10.1210/jc.2015-2236

Systemic-dose vaginal estrogen

CEE 0.625- to 2.5-mg vaginal cream, administered daily, results in systemic effects as evidenced by LH and FSH suppression (285). No RCT data are available regarding the FDA-approved dosing of estradiol 2- to 4-g vaginal cream, administered daily for 1 to 2 weeks, followed by a maintenance dosage of 1 g, one to three times a week.

Other hormonal agents

Estriol vaginal preparations (gels and suppositories) are manufactured and government regulated in a number of countries outside the United States. Estriol is considered a low-affinity estrogen and, despite increased plasma concentration after repeated vaginal administration, is not considered to have substantial systemic effects (286, 287).

Adverse events

Because serum estradiol levels during therapy usually fall within the normal postmenopausal range, the risk profile with low-dose vaginal ET is expected to be lower than with systemic ET (288). However, long-term endometrial safety data are lacking, and 1 year is the maximum duration of RCTs of vaginal ET (261). Side effects include vulvovaginal candidiasis (289, 290) and, with higher dosing and systemic absorption, vaginal bleeding and breast pain (289). Increased CVD or VTE risk has not been reported (261). This may reflect an actual neutral effect due to the absence of a first-pass hepatic effect by vaginal estrogens, or that studies of women at high CVD or VTE risk are lacking (281). Available evidence does not support the boxed warning on low-dose vaginal estrogen regarding an increased risk of CHD, stroke, VTE, dementia, and breast cancer, and efforts to modify the labeling of these products are in progress (288).

Practice statement

5.2b In women with a history of breast or endometrial cancer, who present with symptomatic GSM (including VVA), that does not respond to nonhormonal therapies, we suggest a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET. (Ungraded best practice statement)

Evidence

Breast cancer

Whether small increases in circulating estrogens from low-dose vaginal estrogen can stimulate the growth of residual breast cancer cells (280, 291–293) remains an unanswered question. However, for women taking aromatase inhibitors, the effectiveness of which depends upon blocking up to 95% of estrogen synthesis and reducing circulating estradiol levels to < 1 pg/mL (250), caution is raised because minimal amounts of estrogen can be absorbed with low-dose vaginal ET. In a cohort case-control study of 13 479 breast cancer survivors taking adjuvant tamoxifen or aromatase inhibitor therapy for at least 1 year, after 3.5 years of concurrent administration of the low-dose estrogen ring or 10-μg vaginal tablet, breast cancer recurrence did not increase (relative risk, 0.78; 95% CI, 0.48–1.25) (294). These data are insufficient, however, to conclude safety and to recommend this approach.

Endometrial cancer

The effect of low-dose vaginal ET on endometrial cancer recurrence is unknown. The only RCT attempting to evaluate the effect of systemic ET on recurrence rate and survival in women after surgery for stage I or II endometrial cancer was closed prematurely without complete enrollment (295). In the absence of RCT findings to guide practice recommendations, the decision to use ET remains controversial and involves assessing the severity of postmenopausal symptoms and tumor characteristics (296, 297).

5.2c For women taking raloxifene, without a history of hormone- (estrogen) dependent cancers, who develop symptoms of GSM (including VVA) that do not respond to nonhormonal therapies, we suggest adding low-dose vaginal ET. (2⊕⊕◯◯)

Evidence

Raloxifene has neutral vaginal effects (298–300). In two clinical trials, vaginal, but not oral (301) ET, was safely used to treat vaginal symptoms in women taking raloxifene without untoward endometrial effects (302, 303).

5.2d For women using low-dose vaginal ET, we suggest against adding a progestogen (ie, no need for adding progestogen to prevent endometrial hyperplasia). (2⊕◯◯◯)

5.2e For women using vaginal ET who report postmenopausal bleeding or spotting, we recommend prompt evaluation for endometrial pathology. (1⊕⊕◯◯)

Evidence

Bleeding or spotting in a woman using only vaginal estrogens is uncommon in the absence of endometrial pathology. The 2006 Cochrane review of 19 studies found no significant difference among vaginal creams, tablets, or rings in terms of endometrial thickness or hyperplasia or in the proportion of women with adverse events (261). Recent 1-year-long studies of vaginal CEE cream and low-dose vaginal estradiol tablets revealed no cases of endometrial hyperplasia or cancer as determined by endometrial biopsy (263, 266, 304). Vaginal administration of

estradiol tablets, when placed in the upper third of the vagina, may result in a uterine first-pass effect resulting in a higher degree of uterine stimulation (305–309). It is unknown whether endometrial proliferation, hyperplasia, or cancer can occur after long-duration treatment (> 1 y) or in women with risk factors (late menopause, higher body mass index, higher dosing). For women at higher risk of endometrial cancer, surveillance using transvaginal ultrasound, followed by endometrial biopsy if endometrial thickening is present, may be prudent. Intermittent (possibly annual) progestogen withdrawal may be considered to assess endometrial status (261, 280).

5.3 Ospemifene

5.3a For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, we suggest a trial of ospemifene. (2|⊕⊕⊕◯)

5.3b For women with a history of breast cancer presenting with dyspareunia, we recommend against ospemifene. (1|⊕◯◯◯)

Evidence

Benefits

Not all women are comfortable using vaginal ET, and women may prefer an oral medication specifically indicated for dyspareunia.

Vaginal symptoms and sexual function. Two 12-week RCTs of ospemifene reported improvements in pH and vaginal maturation index, severity of dyspareunia (310, 311), and standardized measures of sexual function (including desire, arousal, orgasm, and satisfaction) (312). Two year-long studies (313, 314) demonstrated sustained vaginal benefits.

Risks

Vasomotor symptoms. The most common adverse effect was VMS (7.2% of women taking ospemifene compared with 2% taking placebo) (314).

Cardiovascular. Ospemifene involves risk of VTE (315) and is contraindicated in women at risk for venous or arterial thrombosis or stroke. In safety studies, incidence rates for thromboembolic stroke, hemorrhagic stroke, and DVT were 0.72, 1.45, and 1.45/1000, respectively, in women receiving ospemifene 60 mg vs 1.04, 0, and 1.04/1000, respectively, in women assigned to placebo (310).

Endometrium. No cases of endometrial carcinoma have been reported. Studies reported endometrial thickening of ≥ 5 mm at a rate of 60.1/1000 women per year of therapy with ospemifene vs 21.2/1000 women per year of therapy with placebo. The incidence of proliferative endometrium (weakly plus active plus disordered) was 86.1/1000 women with ospemifene vs 13.3/1000 with placebo (315). The incidence of uterine polyps was 5.9 cases/1000 women with ospemifene vs 1.8/1000 women with placebo (315).

Breast. Data on breast density or breast cancer risk are lacking. Estrogen-dependent neoplasia is a contraindication.

Future research

There are numerous gaps in our knowledge regarding menopause symptoms. Some of these include a lack of the most basic understanding of what causes hot flashes, questions regarding the potential link between VMS and CVD in older vs younger postmenopausal women, and a poor understanding of the relationships between menopause and sleep and hormonal transitions and mood, which have significant social and economic implications. Given the uncertainties regarding the precise neuroendocrine events that cause VMS, developing specific targeted therapies is challenging. Establishing appropriate animal models and expanding recent research involving the neuroregulators kisspeptin, neurokinin B, and dynorphin may help develop new effective treatments (35).

Management of the transition to menopause remains uncharted territory. The SWAN and the Melbourne Women's Midlife Health Project provide extensive epidemiological, physiological, and descriptive data characterizing reproductive changes that occur during the transition to menopause. However, clinical management decisions are often based on the extrapolation of observational data collected from studies conducted in younger, reproductive age women. RCTs of frequently prescribed therapies, such as oral contraceptives, MHT, and measures to control mood, with clinical outcomes relevant to women of relatively advanced age are sorely needed to confidently advise patients regarding the safest and most effective therapies to use during this transition.

Managing the loss of ovarian function in premenopausal women due to surgery, the range of disorders manifesting as POI, or the sequelae of treatment for breast cancer and other malignancies remains challenging. This is due to a dearth of quality data assessing the long-term risks and benefits of MHT or other options for symptom relief and prevention of chronic diseases in these groups. Fertility issues can be managed with modern assisted reproductive technology, but we fall short on adequately managing estrogen deficiency. Pressing questions remain

doi: 10.1210/jc.2015-2236

regarding optimal treatment preparation, dosing and regimens, and the merits of long-term MHT, even in women without menopausal symptoms. International registries and clinical trials are overdue to address the long-reaching implications of these important issues.

The most persistent question for naturally postmenopausal women is how to balance menopausal symptom relief with the prevention of chronic diseases of aging such as CHD, osteoporotic fractures, and dementia. ET has long been hypothesized to meet this goal, although conclusive evidence remains elusive, and questions persist regarding the interaction between EPT and these outcomes, as well as breast cancer. Observational data suggesting differences in VTE risk and other CVD outcomes continue to accumulate, suggesting a significant need for adequately powered clinical trials comparing the safety and efficacy of oral with transdermal therapies in younger, recently postmenopausal women.

Finally, new SERM therapies (alone and partnered with estrogens) are promising, but larger, longer trials are needed to fully characterize the benefit/risk profiles of these new treatments and inform the clinician as to which patients stand to benefit the most from their use.

Financial Disclosures of the Task Force*

Financial Disclosure of Task Force:* Cynthia A. Stuenkel, MD. (chair)—Financial or business/organizational interests: North American Menopause Society (Chair, Exam Committee), National Women's Law Center-Well Women's Project; Significant financial interest or leadership position: none declared. Susan R. Davis, MBBS, PhD—Financial or Business/Organizational Interests: International Menopause Society, North American Menopause Society, Menopause, Maturitas, Climacteric, Trimel Pharmaceuticals Canada, Lawley Pharmaceuticals Australia, Abbott Pharmaceuticals; Significant Financial Interest or Leadership Position: International Menopause Society, National Health and Medical Research Council, Australia, Bupa Health Foundation. Anne Gompel, MD, PhD—Financial or Business/Organizational Interests: European Society for Contraception, European Society of Endocrinology, Groupe d'Etude sur la Ménopause et le Vieillissement Hormonal, Société Française de Sénologie et Pathologie Mammaire; Significant financial interest or leadership position: none declared. Mary Ann Lumsden, MD, PhD—Financial or Business/Organizational Interests: —Financial or Business/Organizational Interests: International Menopause Society, British Menopause Society; Significant Financial Interest or Leadership Position: National Institute of Health and Clinical Excellence. M. Hassan Murad, M.D., M.P.H.** —Financial or business/organizational interests: Mayo Clinic, Division of Preventive Medicine; Significant financial interest or leadership position: none declared. JoAnn V. Pinkerton, MD—Financial or business/organizational interests: North American Menopause Society, Menopause Journal, OBG Management, Climacteric Journal, Journal of Women's Health, University of Virginia Board of Visitors (Noven Pharmaceuticals, Pfizer, Inc., Shionogi, Therapeutics MD), University of Virginia Clinical Trials (Therapeutics MD); Significant Financial Interest or Leadership Position: North American Menopause Society, Academy of Women's Health, South Atlantic Association of ObGyn. Richard J. Santen, MD—Financial or business/organizational interests: American Society of Clinical Oncology, Up-to-Date (Author/Honorarium); Significant Financial Interest or Leadership Position: Pfizer (Advisory Board, Research Grant).

* Financial, business, and organizational disclosures of the Task Force cover the year prior to publication. Disclosures prior to this time period are archived.

** Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

Acknowledgments

Special thanks are extended to Drs. David F. Archer, Gloria A. Bachmann, Henry Burger, Roger A. Lobo, Charles L. Loprinzi, JoAnn E. Manson, Kathryn A. Martin, Nanette F. Santoro, Hugh S. Taylor, and Nelson B. Watts for careful review and thoughtful suggestions.

Address all correspondence and requests for reprints to: The Endocrine Society, 2055 L Street NW, Suite 600, Washington, DC 20036. E-mail: govt-prof@endocrine.org; Phone: 202–971-3636. Send commercial reprint requests for orders over 100 to: https://www.endocrine.org/corporate-relations/commercial-reprints. Send commercial reprint requests for orders under 100 to: Society Services, E-mail: society services@endocrine.org; Phone: 202–971-3636; Fax: 202–736-9705.

Cosponsoring Associations: The Australasian Menopause Society, the British Menopause Society, European Menopause and Andropause Society, the European Society of Endocrinology, and the International Menopause Society.

References

1. **Atkins D, Best D, Briss PA, et al.** Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490.
2. **Swiglo BA, Murad MH, Schünemann HJ, et al.** A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab*. 2008;93:666–673.

3. **Guyatt GH, Schünemann HJ, Djulbegovic B, Akl EA.** Guideline panels should not GRADE good practice statements. *J Clin Epidemiol*. 2015;68:597–600.
4. **Mohammed K, Benkhadra K, et al.** Oral vs. transdermal estrogen and the risk of venous and arterial thrombotic events: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. (To be submitted 2015).
5. **Benkhadra KM, Nofal AA, Carranza Leon BG, Alahdab F, Abu Dabrh AM.** Menopausal hormonal therapy and mortality: a systematic review and meta-analysis. *J Clin Endocrinol Metab* (to be submitted 2015).
6. **Tom SE, Kuh D, Guralnik JM, Mishra GD.** Self-reported sleep difficulty during the menopausal transition: results from a prospective cohort study. *Menopause*. 2010;17:1128–1135.
7. **Mishra GD, Kuh D.** Health symptoms during midlife in relation to menopausal transition: British prospective cohort study. *BMJ*. 2012;344:e402.
8. **Syed Alwi SA, Lee PY, Awi I, Mallik PS, Md Haizal MN.** The menopausal experience among indigenous women of Sarawak, Malaysia. *Climacteric*. 2009;12:548–556.
9. **Liu M, Wang Y, Li X, et al.** A health survey of Beijing middle-aged registered nurses during menopause. *Maturitas*. 2013;74:84–88.
10. **Nappi RE, Davis SR.** The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI. *Climacteric*. 2012;15:267–274.
11. **Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG.** A prospective population-based study of menopausal symptoms. *Obstet Gynecol*. 2000;96:351–358.
12. **Freeman EW, Sammel MD, Lin H.** Temporal associations of hot flashes and depression in the transition to menopause. *Menopause*. 2009;16:728–734.
13. **Herber-Gast GC, Mishra GD, van der Schouw YT, Brown WJ, Dobson AJ.** Risk factors for night sweats and hot flushes in midlife: results from a prospective cohort study. *Menopause*. 2013;20(9):953–959.
14. **Freeman EW.** Hot flushes and the menopause: how long should they be expected to last? *Maturitas*. 2014;78:153–154.
15. **Harlow SD, Gass M, Hall JE, et al.** Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012;97:1159–1168.
16. **Avis NE, Crawford SL, Greendale G, et al.** Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med*. 2015;175:531–539.
17. **Anderson GL, Limacher M, Assaf AR, et al.** Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701–1712.
18. **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333.
19. **Stuenkel CA, Gass ML, Manson JE, et al.** A decade after the women's health initiative–the experts do agree. *J Clin Endocrinol Metab*. 2012;97:2617–2618.
20. **de Villiers TJ, Gass ML, Haines CJ, et al.** Global consensus statement on menopausal hormone therapy. *Maturitas*. 2013;74:391–392.
21. **Santen R, Pritchard K, Burger H.** The consensus conference on treatment of estrogen deficiency symptoms in women surviving breast cancer. *Obstet Gynecol Surv*. 1998;53:S1–S83.
22. **Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N.** Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol*. 1999;17:2365–2370.
23. **Woods NF, Mitchell ES.** Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med*. 2005;118(suppl 12B):14–24.
24. **Avis NE, Stellato R, Crawford S, et al.** Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med*. 2001;52:345–356.
25. **Freeman EW, Sherif K.** Prevalence of hot flushes and night sweats around the world: a systematic review. *Climacteric*. 2007;10:197–214.
26. **Gartoulla P, Islam MR, Bell RJ, Davis SR.** Prevalence of menopausal symptoms in Australian women at midlife: a systematic review. *Climacteric*. 2014;17:529–539.
27. **Islam MR, Gartoulla P, Bell RJ, Fradkin P, Davis SR.** Prevalence of menopausal symptoms in Asian midlife women: a systematic review. *Climacteric*. 2015;18:157–176.
28. **Reed SD, Lampe JW, Qu C, et al.** Premenopausal vasomotor symptoms in an ethnically diverse population. *Menopause*. 2014;21:153–158.
29. **Szmuilowicz ED, Manson JE, Rossouw JE, et al.** Vasomotor symptoms and cardiovascular events in postmenopausal women. *Menopause*. 2011;18:603–610.
30. **Freedman RR, Roehrs TA.** Effects of REM sleep and ambient temperature on hot flash-induced sleep disturbance. *Menopause*. 2006;13:576–583.
31. **Joffe H, Crawford S, Economou N, et al.** A gonadotropin-releasing hormone agonist model demonstrates that nocturnal hot flashes interrupt objective sleep. *Sleep*. 2013;36:1977–1985.
32. **Freedman RR.** Hot flashes: behavioral treatments, mechanisms, and relation to sleep. *Am J Med*. 2005;118(suppl 12B):124–130.
33. **Casper RF, Yen SS, Wilkes MM.** Menopausal flushes: a neuroendocrine link with pulsatile luteinizing hormone secretion. *Science*. 1979;205:823–825.
34. **Tataryn IV, Meldrum DR, Lu KH, Frumar AM, Judd HL.** LH, FSH and skin temperature during the menopausal hot flash. *J Clin Endocrinol Metab*. 1979;49:152–154.
35. **Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ.** Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flushes. *Front Neuroendocrinol*. 2013;34:211–227.
36. **Casper RF, Yen SS.** Neuroendocrinology of menopausal flushes: an hypothesis of flush mechanism. *Clin Endocrinol (Oxf)*. 1985;22:293–312.
37. **Portman DJ, Gass ML, Vulvovaginal Atrophy Terminology Consensus Conference Panel.** Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Menopause*. 2014;21:1063–1068.
38. **Santen RJ, Allred DC, Ardoin SP, et al.** Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab*. 2010;95:s1–s66.
39. **The Study of Women's Health Across the Nation.** SWAN Research Findings Publication List. Pages 1–37. Updated September 7, 2015. http://www.swanstudy.org/publications/swan-research-findings/. Accessed September 15, 2015.
40. **Mosca L, Benjamin EJ, Berra K, et al.** Effectiveness-based guidelines for the prevention of cardiovascular disease in women–2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123:1243–1262.
41. **Bushnell C, McCullough LD, Awad IA, et al.** Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1545–1588.
42. **National Osteoporosis Foundation.** *2014 Clinician's Guide to Prevention and Treatment of Osteoporosis*. http://nof.org/files/nof/public/content/file/2791/upload/919.pdf. Accessed April 12, 2014.
43. **Cosman F, de Beur SJ, LeBoff MS, et al.** Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25:2359–2381.
44. **Manson JE, Chlebowski RT, Stefanick ML, et al.** Menopausal hormone therapy and health outcomes during the intervention and

doi: 10.1210/jc.2015-2236

extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310:1353–1368.
45. **Maclennan AH, Broadbent JL, Lester S, Moore V.** Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev*. 2004;4:CD002978.
46. **Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH.** Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril*. 2001;75:1065–1079.
47. **Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L.** Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol*. 1998;92:722–727.
48. **Perrotta C, Aznar M, Mejia R, Albert X, Ng CW.** Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev*. 2008;2:CD005131.
49. **Kravitz HM, Schott LL, Joffe H, Cyranowski JM, Bromberger JT.** Do anxiety symptoms predict major depressive disorder in midlife women? The Study of Women's Health Across the Nation (SWAN) Mental Health Study (MHS). *Psychol Med*. 2014;44:2593–2602.
50. **Soares CN.** Mood disorders in midlife women: understanding the critical window and its clinical implications. *Menopause*. 2014;21:198–206.
51. **Worsley R, Davis SR, Gavrilidis E, et al.** Hormonal therapies for new onset and relapsed depression during perimenopause. *Maturitas*. 2012;73:127–133.
52. **Barnabei VM, Cochrane BB, Aragaki AK, et al.** Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. *Obstet Gynecol*. 2005;105:1063–1073.
53. **Moyer VA, U.S. Preventive Services Task Force.** Menopausal hormone therapy for the primary prevention of chronic conditions: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013;158:47–54.
54. **Marjoribanks J, Farquhar C, Roberts H, Lethaby A.** Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev*. 2012;7:CD004143.
55. **North American Menopause Society.** The 2012 hormone therapy position statement of: The North American Menopause Society. *Menopause*. 2012;19:257–271.
56. ACOG Practice Bulletin No. 141: management of menopausal symptoms. *Obstet Gynecol*. 2014;123:202–216.
57. **Lobo RA, Davis SR, De Villiers TJ, et al.** Prevention of diseases after menopause. *Climacteric*. 2014;17:540–556.
58. **Kanaya AM, Herrington D, Vittinghoff E, et al.** Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/Progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2003;138:1–9.
59. **Margolis KL, Bonds DE, Rodabough RJ, et al.** Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia*. 2004;47:1175–1187.
60. **Bonds DE, Lasser N, Qi L, et al.** The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. *Diabetologia*. 2006;49:459–468.
61. **Manson JE, Rimm EB, Colditz GA, et al.** A prospective study of postmenopausal estrogen therapy and subsequent incidence of non-insulin-dependent diabetes mellitus. *Ann Epidemiol*. 1992;2:665–673.
62. **de Lauzon-Guillain B, Fournier A, Fabre A, et al.** Menopausal hormone therapy and new-onset diabetes in the French Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort. *Diabetologia*. 2009;52:2092–2100.
63. **Manson JE.** Current recommendations: what is the clinician to do? *Fertil Steril*. 2014;101:916–921.
64. **Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al.** Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med*. 2004;350:991–1004.
65. **Weiss NS, Szekely DR, Austin DF.** Increasing incidence of endometrial cancer in the United States. *N Engl J Med*. 1976;294:1259–1262.
66. **Mack TM, Pike MC, Henderson BE, et al.** Estrogens and endometrial cancer in a retirement community. *N Engl J Med*. 1976;294:1262–1267.
67. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA*. 1995;273:199–208.
68. **Fournier A, Dossus L, Mesrine S, et al.** Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992–2008. *Am J Epidemiol*. 2014;180:508–517.
69. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA*. 1996;275:370–375.
70. **Jondet M, Maroni M, Yaneva H, Brin S, Peltier-Pujol F, Pélissier C.** Comparative endometrial histology in postmenopausal women with sequential hormone replacement therapy of estradiol and, either chlormadinone acetate or micronized progesterone. *Maturitas*. 2002;41:115–121.
71. **Ferenczy A, Gelfand MM, van de Weijer PH, Rioux JE.** Endometrial safety and bleeding patterns during a 2-year study of 1 or 2 mg 17 β-estradiol combined with sequential 5–20 mg dydrogesterone. *Climacteric*. 2002;5:26–35.
72. **Pukkala E, Tulenheimo-Silfvast A, Leminen A.** Incidence of cancer among women using long versus monthly cycle hormonal replacement therapy, Finland 1994–1997. *Cancer Causes Control*. 2001;12:111–115.
73. **Jaakkola S, Lyytinen HK, Dyba T, Ylikorkala O, Pukkala E.** Endometrial cancer associated with various forms of postmenopausal hormone therapy: a case control study. *Int J Cancer*. 2011;128:1644–1651.
74. **Wildemeersch D, Pylyser K, De Wever N, Pauwels P, Tjalma W.** Endometrial safety after 5 years of continuous combined transdermal estrogen and intrauterine levonorgestrel delivery for postmenopausal hormone substitution. *Maturitas*. 2007;57:205–209.
75. **Orbo A, Vereide A, Arnes M, Pettersen I, Straume B.** Levonorgestrel-impregnated intrauterine device as treatment for endometrial hyperplasia: a national multicentre randomised trial. *BJOG*. 2014;121:477–486.
76. **Morelli M, Di Cello A, Venturella R, Mocciaro R, D'Alessandro P, Zullo F.** Efficacy of the levonorgestrel intrauterine system (LNG-IUS) in the prevention of the atypical endometrial hyperplasia and endometrial cancer: retrospective data from selected obese menopausal symptomatic women. *Gynecol Endocrinol*. 2013;29:156–159.
77. **Beral V, Reeves G, Bull D, Green J, Million Women Study Collaborators.** Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst*. 2011;103:296–305.
78. **Bakken K, Fournier A, Lund E, et al.** Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2011;128:144–156.
79. **Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F.** Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? *J Clin Oncol*. 2009;27:5138–5143.
80. **Beral V, Million Women Study Collaborators.** Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362:419–427.
81. **Chen WY, Manson JE, Hankinson SE, et al.** Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med*. 2006;166:1027–1032.

82. **Saxena T, Lee E, Henderson KD, et al.** Menopausal hormone therapy and subsequent risk of specific invasive breast cancer subtypes in the California Teachers Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19:2366–2378.
83. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;350:1047–1059.
84. **Anderson GL, Chlebowski RT, Aragaki AK, et al.** Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol*. 2012;13:476–486.
85. **Prentice RL, Manson JE, Langer RD, et al.** Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. *Am J Epidemiol*. 2009;170:12–23.
86. **Goodwin PJ, Stambolic V.** Obesity and insulin resistance in breast cancer–chemoprevention strategies with a focus on metformin. *Breast*. 2011;20(suppl 3):S31–S35.
87. **Song Y, Santen RJ, Wang JP, Yue W.** Effects of the conjugated equine estrogen/bazedoxifene tissue-selective estrogen complex (TSEC) on mammary gland and breast cancer in mice. *Endocrinology*. 2012; 153:5706–5715.
88. **Wood CE, Clarkson TB, Chen H, et al.** Comparative effects of oral conjugated equine estrogens and micronized 17β-estradiol on breast proliferation: a retrospective analysis. *Menopause*. 2008; 15:890–898.
89. **Fournier A, Berrino F, Clavel-Chapelon F.** Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat*. 2008; 107:103–111.
90. **Chlebowski RT, Anderson GL, Gass M, et al.** Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. 2010;304:1684–1692.
91. **Anderson GL, Chlebowski RT, Rossouw JE, et al.** Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas*. 2006;55: 103–115.
92. **Lyytinen H, Dyba T, Pukkala E, Ylikorkala O.** Do the dose or route of administration of norethisterone acetate as a part of hormone therapy play a role in risk of breast cancer: national-wide case-control study from Finland. *Int J Cancer*. 2010;127:185–189.
93. **Chlebowski RT, Manson JE, Anderson GL, et al.** Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. *J Natl Cancer Inst*. 2013;105:526–535.
94. **Cordina-Duverger E, Truong T, Anger A, et al.** Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France. *PLoS One*. 2013; 8:e78016.
95. **Collaborative Group On Epidemiological Studies Of Ovarian Cancer, Beral V, Gaitskell K, et al.** Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet*. 2015;385:1835–1842.
96. **Gompel A, Burger H.** A commentary on a recent update of the ovarian cancer risk attributable to menopausal hormone therapy. *Climacteric*. 2015;18:376–378.
97. **Davis SR, Baber R.** Reproductive endocrinology: menopausal hormone therapy-ovarian cancer risk revisited. *Nat Rev Endocrinol*. 2015;11:322–323.
98. **Hsia J, Langer RD, Manson JE, et al.** Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med*. 2006;166:357–365.
99. **Manson JE, Allison MA, Rossouw JE, et al.** Estrogen therapy and coronary-artery calcification. *N Engl J Med*. 2007;356:2591–2602.
100. **Barrett-Connor E, Grady D.** Hormone replacement therapy, heart disease, and other considerations. *Annu Rev Public Health*. 1998; 19:55–72.
101. **Løkkegaard E, Andreasen AH, Jacobsen RK, Nielsen LH, Agger C, Lidegaard Ø.** Hormone therapy and risk of myocardial infarction: a national register study. *Eur Heart J*. 2008;29:2660–2668.
102. **Shufelt CL, Merz CN, Prentice RL, et al.** Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study. *Menopause*. 2014;21:260–266.
103. **Schierbeck LL, Rejnmark L, Tofteng CL, et al.** Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ*. 2012;345:e6409.
104. **Harman SM, Black DM, Naftolin F, et al.** Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med*. 2014;161:249–260.
105. **Renoux C, Dell'aniello S, Garbe E, Suissa S.** Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ*. 2010;340:c2519.
106. **Smith NL, Blondon M, Wiggins KL, et al.** Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. *JAMA Intern Med*. 2014;174:25–31.
107. **Grodstein F, Manson JE, Stampfer MJ, Rexrode K.** Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med*. 2008; 168:861–866.
108. **Canonico M, Oger E, Plu-Bureau G, et al.** Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation*. 2007;115:840–845.
109. **Sweetland S, Beral V, Balkwill A, et al.** Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. *J Thromb Haemost*. 2012;10:2277–2286.
110. **Renoux C, Dell'Aniello S, Suissa S.** Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost*. 2010;8:979–986.
111. **Canonico M, Fournier A, Carcaillon L, et al.** Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol*. 2010;30:340–345.
112. **Roach RE, Lijfering WM, Helmerhorst FM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A.** The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. *J Thromb Haemost*. 2013;11:124–131.
113. **Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY.** Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ*. 2008;336:1227–1231.
114. **Høibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrøm E, Sandset PM.** Increased risk of recurrent venous thromboembolism during hormone replacement therapy–results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost*. 2000;84:961–967.
115. **Olié V, Plu-Bureau G, Conard J, Horellou MH, Canonico M, Scarabin PY.** Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. *Menopause*. 2011; 18:488–493.
116. **Straczek C, Oger E, Yon de Jonage-Canonico MB, et al.** Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. *Circulation*. 2005;112:3495–3500.
117. **Canonico M, Oger E, Conard J, et al.** Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. *J Thromb Haemost*. 2006;4:1259–1265.

doi: 10.1210/jc.2015-2236

118. **Cirillo DJ, Wallace RB, Rodabough RJ, et al.** Effect of estrogen therapy on gallbladder disease. *JAMA*. 2005;293:330–339.
119. **Simon JA, Hunninghake DB, Agarwal SK, et al.** Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med*. 2001;135:493–501.
120. **Grodstein F, Colditz GA, Stampfer MJ.** Postmenopausal hormone use and cholecystectomy in a large prospective study. *Obstet Gynecol*. 1994;83:5–11.
121. **Liu B, Beral V, Balkwill A, et al.** Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. *BMJ*. 2008;337:a386.
122. **Racine A, Bijon A, Fournier A, et al.** Menopausal hormone therapy and risk of cholecystectomy: a prospective study based on the French E3N cohort. *CMAJ*. 2013;185:555–561.
123. **Hart AR, Luben R, Welch A, Bingham S, Khaw KT.** Hormone replacement therapy and symptomatic gallstones - a prospective population study in the EPIC-Norfolk cohort. *Digestion*. 2008;77:4–9.
124. **Hendrix SL, Cochrane BB, Nygaard IE, et al.** Effects of estrogen with and without progestin on urinary incontinence. *JAMA*. 2005;293:935–948.
125. **Steinauer JE, Waetjen LE, Vittinghoff E, et al.** Postmenopausal hormone therapy: does it cause incontinence? *Obstet Gynecol*. 2005;106:940–945.
126. **Moyer VA, U.S, Preventive Services Task Force.** Medications to decrease the risk for breast cancer in women: recommendations from the U.S. Preventive Task Force Recommendation Statement. *Ann Intern Med*. 2013;159(10):698–708. http://www.ncbi.nlm.nih.gov/pubmed/24061412 "Annals of internal medicine"
127. **Boardman HM, Hartley L, Eisinga A, et al.** Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev*. 2015;3:CD002229.
128. **Grodstein F, Stampfer MJ, Colditz GA, et al.** Postmenopausal hormone therapy and mortality. *N Engl J Med*. 1997;336:1769–1775.
129. **Berglind IA, Andersen M, Citarella A, Linder M, Sundström A, Kieler H.** Hormone therapy and risk of cardiovascular outcomes and mortality in women treated with statins. *Menopause*. 2015;22:369–376.
130. **Mikkola TS, Tuomikoski P, Lyytinen H, et al.** Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. *Menopause*. 2015;22(9):976–983.
131. **Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE.** Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *Am J Med*. 2009;122:1016–1022.e1.
132. **Salpeter SR, Walsh JM, Greyber E, Ormiston TM, Salpeter EE.** Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med*. 2004;19:791–804.
133. **Maki PM.** Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. *Menopause*. 2013;20:695–709.
134. **Shumaker SA, Legault C, Rapp SR, et al.** Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289:2651–2662.
135. **Carlson MC, Zandi PP, Plassman BL, et al.** Hormone replacement therapy and reduced cognitive decline in older women: the Cache County Study. *Neurology*. 2001;57:2210–2216.
136. **Jacobs DM, Tang MX, Stern Y, et al.** Cognitive function in non-demented older women who took estrogen after menopause. *Neurology*. 1998;50:368–373.
137. **Sherwin BB, Tulandi T.** "Add-back" estrogen reverses cognitive deficits induced by a gonadotropin-releasing hormone agonist in women with leiomyomata uteri. *J Clin Endocrinol Metab*. 1996;81:2545–2549.
138. **Phillips SM, Sherwin BB.** Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology*. 1992;17:485–495.
139. **Kang JH, Weuve J, Grodstein F.** Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. *Neurology*. 2004;63:101–107.
140. **Espeland MA, Rapp SR, Shumaker SA, et al.** Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2959–2968.
141. **Rossouw JE, Prentice RL, Manson JE, et al.** Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297:1465–1477.
142. **Rosamond W, Flegal K, Furie K, et al.** Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117:e25–e146.
143. **Kariuki JK, Stuart-Shor EM, Leveille SG, Hayman LL.** Evaluation of the performance of existing non-laboratory based cardiovascular risk assessment algorithms. *BMC Cardiovasc Disord*. 2013;13:123.
144. **Goff DC Jr, Lloyd-Jones DM, Bennett G, et al.** 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49–S73.
145. **Rossouw JE, Cushman M, Greenland P, et al.** Inflammatory, lipid, thrombotic, and genetic markers of coronary heart disease risk in the Women's Health Initiative trials of hormone therapy. *Arch Intern Med*. 2008;168:2245–2253.
146. **Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D.** Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care*. 2012;35:2402–2411.
147. **Wild RA, Wu C, Curb JD, et al.** Coronary heart disease events in the Women's Health Initiative hormone trials: effect modification by metabolic syndrome: a nested case-control study within the Women's Health Initiative randomized clinical trials. *Menopause*. 2013;20:254–260.
148. **Szmuilowicz ED, Stuenkel CA, Seely EW.** Influence of menopause on diabetes and diabetes risk. *Nat Rev Endocrinol*. 2009;5:553–558.
149. **Curb JD, Prentice RL, Bray PF, et al.** Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med*. 2006;166:772–780.
150. **Cushman M, Kuller LH, Prentice R, et al.** Estrogen plus progestin and risk of venous thrombosis. *JAMA*. 2004;292:1573–1580.
151. **Manson JE, Bassuk SS.** The menopause transition and postmenopausal hormone therapy. In: Longo DL, Fauci AS, Kasper DL, et al. *Harrison's Principles of Internal Medicine*. New York, NY: McGraw Hill; 2012;3040–3045.
152. **Stefanick ML, Anderson GL, Margolis KL, et al.** Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA*. 2006;295:1647–1657.
153. **Visvanathan K, Hurley P, Bantug E, et al.** Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013;31:2942–2962.
154. **National Cancer Institute.** Breast Cancer Risk Assessment Tool. http://www.cancer.gov/bcrisktool/. Accessed April 12, 2015.
155. **Amir E, Freedman OC, Seruga B, Evans DG.** Assessing women at high risk of breast cancer: a review of risk assessment models. *J Natl Cancer Inst*. 2010;102:680–691.
156. **Tyrer J, Duffy SW, Cuzick J.** A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med*. 2004;23:1111–1130.

157. **Kerlikowske K, Cook AJ, Buist DS, et al.** Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. *J Clin Oncol*. 2010;28:3830–3837.
158. **Hou N, Hong S, Wang W, Olopade OI, Dignam JJ, Huo D.** Hormone replacement therapy and breast cancer: heterogeneous risks by race, weight, and breast density. *J Natl Cancer Inst*. 2013;105:1365–1372.
159. **Chen J, Pee D, Ayyagari R, et al.** Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. *J Natl Cancer Inst*. 2006;98:1215–1226.
160. **Bhavnani BR.** Pharmacokinetics and pharmacodynamics of conjugated equine estrogens: chemistry and metabolism. *Proc Soc Exp Biol Med*. 1998;217:6–16.
161. **Torres-Santiago L, Mericq V, Taboada M, et al.** Metabolic effects of oral versus transdermal 17β-estradiol (E_2): a randomized clinical trial in girls with Turner syndrome. *J Clin Endocrinol Metab*. 2013;98:2716–2724.
162. **Slater CC, Hodis HN, Mack WJ, Shoupe D, Paulson RJ, Stanczyk FZ.** Markedly elevated levels of estrone sulfate after long-term oral, but not transdermal, administration of estradiol in postmenopausal women. *Menopause*. 2001;8:200–203.
163. **Nachtigall LE, Raju U, Banerjee S, Wan L, Levitz M.** Serum estradiol-binding profiles in postmenopausal women undergoing three common estrogen replacement therapies: associations with sex hormone-binding globulin, estradiol, and estrone levels. *Menopause*. 2000;7:243–250.
164. **Nelson HD.** Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. *JAMA*. 2004;291:1610–1620.
165. **Crandall C.** Low-dose estrogen therapy for menopausal women: a review of efficacy and safety. *J Womens Health (Larchmt)*. 2003;12:723–747.
166. **Mauvais-Jarvis P, Bercovici JP.** Hormone therapy by percutaneous route. Physiological bases. Clinical applications [in French]. *Therapeutique*. 1972;48:403–406.
167. **Vehkavaara S, Silveira A, Hakala-Ala-Pietilä T, et al.** Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. *Thromb Haemost*. 2001;85:619–625.
168. **Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M.** Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol*. 1997;17:3071–3078.
169. **Loeper J, Loeper MJ, Ohlghiesser C, de Lignières B, Mauvais-Jarvis P.** The influence of estrogen therapy on triglycerides. Importance of the choice of substance and the route of administration (author's translation) [in French]. *Nouv Presse Med*. 1977;6:2747–2750.
170. **Speroff L.** Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. *Obstet Gynecol*. 2003;102:823–834.
171. **Al-Azzawi F, Buckler HM, United Kingdom Vaginal Ring Investigator Group.** Comparison of a novel vaginal ring delivering estradiol acetate versus oral estradiol for relief of vasomotor menopausal symptoms. *Climacteric*. 2003;6:118–127.
172. **Jaakkola S, Lyytinen H, Pukkala E, Ylikorkala O.** Endometrial cancer in postmenopausal women using estradiol-progestin therapy. *Obstet Gynecol*. 2009;114:1197–1204.
173. **Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Pukkala E.** Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. *Obstet Gynecol*. 2014;124:292–299.
174. **Schiff I, Tulchinsky D, Cramer D, Ryan KJ.** Oral medroxyprogesterone in the treatment of postmenopausal symptoms. *JAMA*. 1980;244:1443–1445.
175. **Prior JC, Nielsen JD, Hitchcock CL, Williams LA, Vigna YM, Dean CB.** Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy. *Clin Sci*. 2007;112:517–525.
176. **Hitchcock CL, Prior JC.** Oral micronized progesterone for vasomotor symptoms–a placebo-controlled randomized trial in healthy postmenopausal women. *Menopause*. 2012;19:886–893.
177. **The Endocrine Society.** The Endocrine Society re-issues position statement on bioidentical hormones. Press release. https://www.endocrine.org/news-room/press-release-archives/2009/society reissuespositionstatementonbioidenticalhormones. Published February 5, 2009. Accessed February 13, 2015.
178. **Sharifi M, Lewiecki EM.** Conjugated estrogens combined with bazedoxifene: the first approved tissue selective estrogen complex therapy. *Expert Rev Clin Pharmacol*. 2014;7:281–291.
179. **Mirkin S, Komm BS, Pan K, Chines AA.** Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. *Climacteric*. 2013;16:338–346.
180. **Pinkerton JV, Harvey JA, Lindsay R, et al.** Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. *J Clin Endocrinol Metab*. 2014;99:E189–E198.
181. **Lobo RA, Pinkerton JV, Gass ML, et al.** Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. *Fertil Steril*. 2009;92:1025–1038.
182. **Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G.** Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril*. 2009;92:1045–1052.
183. **Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH.** A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. *Menopause*. 2010;17:281–289.
184. **Utian W, Yu H, Bobula J, Mirkin S, Olivier S, Pickar JH.** Bazedoxifene/conjugated estrogens and quality of life in postmenopausal women. *Maturitas*. 2009;63:329–335.
185. **Abraham L, Pinkerton JV, Messig M, Ryan KA, Komm BS, Mirkin S.** Menopause-specific quality of life across varying menopausal populations with conjugated estrogens/bazedoxifene. *Maturitas*. 2014;78:212–218.
186. **Pinkerton JV, Harvey JA, Pan K, et al.** Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. *Obstet Gynecol*. 2013;121:959–968.
187. **Harvey JA, Pinkerton JV, Baracat EC, Shi H, Chines AA, Mirkin S.** Breast density changes in a randomized controlled trial evaluating bazedoxifene/conjugated estrogens. *Menopause*. 2013;20:138–145.
188. **Mirkin S, Archer DF, Taylor HS, Pickar JH, Komm BS.** Differential effects of menopausal therapies on the endometrium. *Menopause*. 2014;21:899–908.
189. **Pickar JH, Yeh IT, Bachmann G, Speroff L.** Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. *Fertil Steril*. 2009;92:1018–1024.
190. **de Villiers TJ, Chines AA, Palacios S, et al.** Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. *Osteoporos Int*. 2011;22:567–576.
191. **Komm BS, Thompson JR, Mirkin S.** Cardiovascular safety of conjugated estrogens plus bazedoxifene: meta-analysis of the SMART trials. *Climacteric*. 2015;18:503–511.
192. **Kloosterboer HJ.** Intracrinology: the secret of the tissue-specificity of tibolone. *J Br Menopause Soc*. 2000;6:23–27.
193. **Tiefert MA, Roy H, Moudrianakis EN.** Binding of adenine nucleotides and pyrophosphate by the purified coupling factor of photophosphorylation. *Biochemistry*. 1977;16:2396–2404.
194. **Formoso G, Perrone E, Maltoni S, et al.** Short and long term effects

doi: 10.1210/jc.2015-2236

of tibolone in postmenopausal women. *Cochrane Database Syst Rev*. 2012;2:CD008536.
195. **Davis SR.** The effects of tibolone on mood and libido. *Menopause*. 2002;9:153–155.
196. **Botsis D, Kassanos D, Kalogirou D, Antoniou G, Vitoratos N, Karakitsos P.** Vaginal ultrasound of the endometrium in postmenopausal women with symptoms of urogenital atrophy on low-dose estrogen or tibolone treatment: a comparison. *Maturitas*. 1997;26:57–62.
197. **Swanson SG, Drosman S, Helmond FA, Stathopoulos VM.** Tibolone for the treatment of moderate to severe vasomotor symptoms and genital atrophy in postmenopausal women: a multicenter, randomized, double-blind, placebo-controlled study. *Menopause*. 2006;13:917–925.
198. **Delmas PD, Davis SR, Hensen J, Adami S, van Os S, Nijland EA.** Effects of tibolone and raloxifene on bone mineral density in osteopenic postmenopausal women. *Osteoporos Int*. 2008;19:1153–1160.
199. **Cummings SR, Ettinger B, Delmas PD, et al.** The effects of tibolone in older postmenopausal women. *N Engl J Med*. 2008;359:697–708.
200. **Fedele L, Bianchi S, Raffaelli R, Zanconato G.** A randomized study of the effects of tibolone and transdermal estrogen replacement therapy in postmenopausal women with uterine myomas. *Eur J Obstet Gynecol Reprod Biol*. 2000;88:91–94.
201. **Hammar M, Christau S, Nathorst-Böös J, Rud T, Garre K.** A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. *Br J Obstet Gynaecol*. 1998;105:904–911.
202. **Hammar ML, van de Weijer P, Franke HR, et al.** Tibolone and low-dose continuous combined hormone treatment: vaginal bleeding pattern, efficacy and tolerability. *BJOG*. 2007;114:1522–1529.
203. **Kenemans P, Bundred NJ, Foidart JM, et al.** Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol*. 2009;10:135–146.
204. **Haskell SG, Bean-Mayberry B, Gordon K.** Discontinuing postmenopausal hormone therapy: an observational study of tapering versus quitting cold turkey: is there a difference in recurrence of menopausal symptoms? *Menopause*. 2009;16:494–499.
205. **Suffoletto JA, Hess R.** Tapering versus cold turkey: symptoms versus successful discontinuation of menopausal hormone therapy. *Menopause*. 2009;16:436–437.
206. **Aslan E, Bagis T, Kilicdag EB, Tarim E, Erkanli S, Kuscu E.** How best is to discontinue postmenopausal hormone therapy: immediate or tapered? *Maturitas*. 2007;56:78–83.
207. **Haimov-Kochman R, Barak-Glantz E, Arbel R, et al.** Gradual discontinuation of hormone therapy does not prevent the reappearance of climacteric symptoms: a randomized prospective study. *Menopause*. 2006;13:370–376.
208. **Karim R, Dell RM, Greene DF, Mack WJ, Gallagher JC, Hodis HN.** Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization. *Menopause*. 2011;18:1172–1177.
209. **Arafah BM.** Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med*. 2001;344:1743–1749.
210. **Thurston RC, Sowers MR, Chang Y, et al.** Adiposity and reporting of vasomotor symptoms among midlife women: the study of women's health across the nation. *Am J Epidemiol*. 2008;167:78–85.
211. **Thurston RC, Sowers MR, Sternfeld B, et al.** Gains in body fat and vasomotor symptom reporting over the menopausal transition: the study of women's health across the nation. *Am J Epidemiol*. 2009;170:766–774.
212. **Huang AJ, Subak LL, Wing R, et al.** An intensive behavioral weight loss intervention and hot flushes in women. *Arch Intern Med*. 2010;170:1161–1167.
213. **Joffe H, Guthrie KA, LaCroix AZ, et al.** Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. *JAMA Intern Med*. 2014;174:1058–1066.
214. **Kroenke CH, Caan BJ, Stefanick ML, et al.** Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. *Menopause*. 2012;19:980–988.
215. **van Die MD, Teede HJ, Bone KM, Reece JE, Burger HG.** Predictors of placebo response in a randomized, controlled trial of phytotherapy in menopause. *Menopause*. 2009;16:792–796.
216. **Villaseca P.** Non-estrogen conventional and phytochemical treatments for vasomotor symptoms: what needs to be known for practice. *Climacteric*. 2012;15:115–124.
217. **Rada G, Capurro D, Pantoja T, et al.** Non-hormonal interventions for hot flushes in women with a history of breast cancer. *Cochrane Database Syst Rev*. 2010;9:CD004923.
218. **Albertazzi P.** Non-estrogenic approaches for the treatment of climacteric symptoms. *Climacteric*. 2007;10(suppl 2):115–120.
219. **Loprinzi CL, Barton DL, Sloan JA, et al.** Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. *Menopause*. 2008;15:655–660.
220. **Guttuso T Jr.** Effective and clinically meaningful non-hormonal hot flash therapies. *Maturitas*. 2012;72:6–12.
221. **Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF.** Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. *Obstet Gynecol*. 2007;109:823–830.
222. **Kerwin JP, Gordon PR, Senf JH.** The variable response of women with menopausal hot flashes when treated with sertraline. *Menopause*. 2007;14:841–845.
223. **Loprinzi CL, Sloan JA, Perez EA, et al.** Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol*. 2002;20:1578–1583.
224. **Loprinzi CL, Sloan J, Stearns V, et al.** Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. *J Clin Oncol*. 2009;27:2831–2837.
225. **Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD.** Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. *Arch Intern Med*. 2006;166:1453–1465.
226. **Shams T, Firwana B, Habib F, et al.** SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. *J Gen Intern Med*. 2014;29:204–213.
227. **Sun Z, Hao Y, Zhang M.** Efficacy and safety of desvenlafaxine treatment for hot flashes associated with menopause: a meta-analysis of randomized controlled trials. *Gynecol Obstet Invest*. 2013;75:255–262.
228. **Bardia A, Novotny P, Sloan J, Barton D, Loprinzi C.** Efficacy of nonestrogenic hot flash therapies among women stratified by breast cancer history and tamoxifen use: a pooled analysis. *Menopause*. 2009;16:477–483.
229. **Stearns V, Beebe KL, Iyengar M, Dube E.** Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA*. 2003;289:2827–2834.
230. **Stearns V, Slack R, Greep N, et al.** Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol*. 2005;23:6919–6930.
231. **Loprinzi CL, Kugler JW, Sloan JA, et al.** Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet*. 2000;356:2059–2063.
232. **Evans ML, Pritts E, Vittinghoff E, McClish K, Morgan KS, Jaffe RB.** Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial. *Obstet Gynecol*. 2005;105:161–166.
233. **Carpenter JS, Storniolo AM, Johns S, et al.** Randomized, double-

blind, placebo-controlled crossover trials of venlafaxine for hot flashes after breast cancer. *Oncologist*. 2007;12:124–135.
234. **Simon JA, Portman DJ, Kaunitz AM, et al.** Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause*. 2013;20:1027–1035.
235. **Kalay AE, Demir B, Haberal A, Kalay M, Kandemir O.** Efficacy of citalopram on climacteric symptoms. *Menopause*. 2007;14:223–229.
236. **Nelson HD, Vesco KK, Haney E, et al.** Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA*. 2006;295:2057–2071.
237. **Freeman EW, Guthrie KA, Caan B, et al.** Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA*. 2011;305:267–274.
238. **Guttuso T Jr, Kurlan R, McDermott MP, Kieburtz K.** Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol*. 2003;101:337–345.
239. **Butt DA, Lock M, Lewis JE, Ross S, Moineddin R.** Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. *Menopause*. 2008;15:310–318.
240. **Reddy SY, Warner H, Guttuso T Jr, et al.** Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. *Obstet Gynecol*. 2006;108:41–48.
241. **Pandya KJ, Morrow GR, Roscoe JA, et al.** Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet*. 2005;366:818–824.
242. **Loprinzi CL, Qin R, Balcueva EP, et al.** Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. *J Clin Oncol*. 2010;28:641–647.
243. **Bordeleau L, Pritchard KI, Loprinzi CL, et al.** Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. *J Clin Oncol*. 2010;28:5147–5152.
244. **Aguirre W, Chedraui P, Mendoza J, Ruilova I.** Gabapentin vs. low-dose transdermal estradiol for treating post-menopausal women with moderate to very severe hot flushes. *Gynecol Endocrinol*. 2010;26:333–337.
245. **Notelovitz M, Mattox JH.** Suppression of vasomotor and vulvovaginal symptoms with continuous oral 17β-estradiol. *Menopause*. 2000;7:310–317.
246. **Cohen LS, Joffe H, Guthrie KA, et al.** Efficacy of omega-3 for vasomotor symptoms treatment: a randomized controlled trial. *Menopause*. 2014;21:347–354.
247. **Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ.** Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. *Menopause*. 2013;20:291–298.
248. **Caan BJ, Natarajan L, Parker B, et al.** Soy food consumption and breast cancer prognosis. *Cancer Epidemiol Biomarkers Prev*. 2011;20:854–858.
249. **Loprinzi CL, Abu-Ghazaleh S, Sloan JA, et al.** Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. *J Clin Oncol*. 1997;15:969–973.
250. **Biglia N, Peano E, Sgandurra P, et al.** Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. *Gynecol Endocrinol*. 2010;26:404–412.
251. **van der Laak JA, de Bie LM, de Leeuw H, de Wilde PC, Hanselaar AG.** The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerised cytometry. *J Clin Pathol*. 2002;55:446–451.
252. **Nachtigall LE.** Comparative study: Replens versus local estrogen in menopausal women. *Fertil Steril*. 1994;61:178–180.
253. **Bygdeman M, Swahn ML.** Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. *Maturitas*. 1996;23:259–263.
254. **Fiorilli A, Molteni B, Milani M.** Successful treatment of bacterial vaginosis with a policarbophil-carbopol acidic vaginal gel: results from a randomised double-blind, placebo-controlled trial. *Eur J Obstet Gynecol Reprod Biol*. 2005;120:202–205.
255. **Le Donne M, Caruso C, Mancuso A, et al.** The effect of vaginally administered genistein in comparison with hyaluronic acid on atrophic epithelium in postmenopause. *Arch Gynecol Obstet*. 2011;283:1319–1323.
256. **Ekin M, Yaşar L, Savan K, et al.** The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. *Arch Gynecol Obstet*. 2011;283:539–543.
257. **Caswell M, Kane M.** Comparison of the moisturization efficacy of two vaginal moisturizers: pectin versus polycarbophil technologies. *J Cosmet Sci*. 2002;53:81–87.
258. **Jozkowski KN, Herbenick D, Schick V, Reece M, Sanders SA, Fortenberry JD.** Women's perceptions about lubricant use and vaginal wetness during sexual activities. *J Sex Med*. 2013;10:484–492.
259. **Juraskova I, Jarvis S, Mok K, et al.** The acceptability, feasibility, and efficacy (phase I/II study) of the OVERcome (Olive Oil, Vaginal Exercise, and MoisturizeR) intervention to improve dyspareunia and alleviate sexual problems in women with breast cancer. *J Sex Med*. 2013;10:2549–2558.
260. **Brown JM, Hess KL, Brown S, Murphy C, Waldman AL, Hezareh M.** Intravaginal practices and risk of bacterial vaginosis and candidiasis infection among a cohort of women in the United States. *Obstet Gynecol*. 2013;121:773–780.
261. **Suckling J, Lethaby A, Kennedy R.** Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev*. 2006;4:CD001500.
262. **Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M.** Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. *Obstet Gynecol*. 2008;111:67–76.
263. **Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W.** Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. *Obstet Gynecol*. 2008;112:1053–1060.
264. **Lose G, Englev E.** Oestradiol-releasing vaginal ring versus oestriol vaginal pessaries in the treatment of bothersome lower urinary tract symptoms. *BJOG*. 2000;107:1029–1034.
265. **Crandall C.** Vaginal estrogen preparations: a review of safety and efficacy for vaginal atrophy. *J Womens Health (Larchmt)*. 2002;11:857–877.
266. **Bachmann G, Bouchard C, Hoppe D, et al.** Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. *Menopause*. 2009;16:719–727.
267. **Santen RJ, Pinkerton JV, Conaway M, et al.** Treatment of urogenital atrophy with low-dose estradiol: preliminary results. *Menopause*. 2002;9:179–187.
268. **Raz R, Stamm WE.** A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med*. 1993;329:753–756.
269. **Eriksen B.** A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol*. 1999;180:1072–1079.
270. **Nelken RS, Ozel BZ, Leegant AR, Felix JC, Mishell DR Jr.** Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. *Menopause*. 2011;18:962–966.
271. **Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A.** Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev*. 2012;10:CD001405.
272. **de Tayrac R, Sentilhes L.** Complications of pelvic organ prolapse surgery and methods of prevention. *Int Urogynecol J*. 2013;24:1859–1872.
273. **Rahn DD, Good MM, Roshanravan SM, et al.** Effects of preoperative local estrogen in postmenopausal women with prolapse: a randomized trial. *J Clin Endocrinol Metab*. 2014;99:3728–3736.

doi: 10.1210/jc.2015-2236

274. **Santen RJ.** Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. *Climacteric*. 2015;18:121–134.
275. **Eugster-Hausmann M, Waitzinger J, Lehnick D.** Minimized estradiol absorption with ultra-low-dose 10 microg 17β-estradiol vaginal tablets. *Climacteric*. 2010;13:219–227.
276. **Dorr MB, Nelson AL, Mayer PR, et al.** Plasma estrogen concentrations after oral and vaginal estrogen administration in women with atrophic vaginitis. *Fertil Steril*. 2010;94:2365–2368.
277. **Pschera H, Hjerpe A, Carlström K.** Influence of the maturity of the vaginal epithelium upon the absorption of vaginally administered estradiol-17 β and progesterone in postmenopausal women. *Gynecol Obstet Invest*. 1989;27:204–207.
278. **Naessen T, Rodriguez-Macias K, Lithell H.** Serum lipid profile improved by ultra-low doses of 17 β-estradiol in elderly women. *J Clin Endocrinol Metab*. 2001;86:2757–2762.
279. **Ballagh SA.** Vaginal hormone therapy for urogenital and menopausal symptoms. *Semin Reprod Med*. 2005;23:126–140.
280. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause*. 2013;20:888–902; quiz 903–904.
281. **Archer DF.** Efficacy and tolerability of local estrogen therapy for urogenital atrophy. *Menopause*. 2010;17:194–203.
282. **Del Pup L, Di Francia R, Cavaliere C, et al.** Promestriene, a specific topic estrogen. Review of 40 years of vaginal atrophy treatment: is it safe even in cancer patients? *Anticancer Drugs*. 2013;24:989–998.
283. **Labrie F, Cusan L, Gomez JL, et al.** Effect of one-week treatment with vaginal estrogen preparations on serum estrogen levels in postmenopausal women. *Menopause*. 2009;16:30–36.
284. **Rigg LA, Hermann H, Yen SS.** Absorption of estrogens from vaginal creams. *N Engl J Med*. 1978;298:195–197.
285. **Mandel FP, Geola FL, Meldrum DR, et al.** Biological effects of various doses of vaginally administered conjugated equine estrogens in postmenopausal women. *J Clin Endocrinol Metab*. 1983;57:133–139.
286. **van Haaften M, Donker GH, Haspels AA, Thijssen JH.** Oestrogen concentrations in plasma, endometrium, myometrium and vagina of postmenopausal women, and effects of vaginal oestriol (E3) and oestradiol (E2) applications. *J Steroid Biochem*. 1989;33:647–653.
287. **Kicovic PM, Cortes-Prieto J, Milojeviæ S, Haspels AA, Aljinovic A.** The treatment of postmenopausal vaginal atrophy with Ovestin vaginal cream or suppositories: clinical, endocrinological and safety aspects. *Maturitas*. 1980;2:275–282.
288. **Manson JE, Goldstein SR, Kagan R, et al.** Why the product labeling for low-dose vaginal estrogen should be changed. *Menopause*. 2014;21:911–916.
289. **Fischer G, Bradford J.** Vulvovaginal candidiasis in postmenopausal women: the role of hormone replacement therapy. *J Low Genit Tract Dis*. 2011;15:263–267.
290. **Dennerstein GJ, Ellis DH.** Oestrogen, glycogen and vaginal candidiasis. *Aust N Z J Obstet Gynaecol*. 2001;41:326–328.
291. **Obiorah I, Jordan VC.** Scientific rationale for postmenopause delay in the use of conjugated equine estrogens among postmenopausal women that causes reduction in breast cancer incidence and mortality. *Menopause*. 2013;20:372–382.
292. **Mastaglia SR, Bagur A, Royer M, Yankelevich D, Sayegh F, Oliveri B.** Effect of endogenous estradiol levels on bone resorption and bone mineral density in healthy postmenopausal women: a prospective study. *Climacteric*. 2009;12:49–58.
293. **Bagur A, Oliveri B, Mautalen C, et al.** Low levels of endogenous estradiol protect bone mineral density in young postmenopausal women. *Climacteric*. 2004;7:181–188.
294. **Le Ray I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S.** Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. *Breast Cancer Res Treat*. 2012;135:603–609.
295. **Barakat RR, Bundy BN, Spirtos NM, et al.** Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2006;24:587–592.
296. **Guidozzi F.** Estrogen therapy in gynecological cancer survivors. *Climacteric*. 2013;16:611–617.
297. **North American Menopause Society.** *Menopause Practice: A Clinician's Guide*. 5th ed. Cleveland, OH: North American Menopause Society; 2014:152.
298. **Vogel VG, Costantino JP, Wickerham DL, et al.** Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295:2727–2741.
299. **Land SR, Wickerham DL, Costantino JP, et al.** Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295:2742–2751.
300. **Davies GC, Huster WJ, Lu Y, Plouffe L Jr, Lakshmanan M.** Adverse events reported by postmenopausal women in controlled trials with raloxifene. *Obstet Gynecol*. 1999;93:558–565.
301. **Stovall DW, Utian WH, Gass ML, et al.** The effects of combined raloxifene and oral estrogen on vasomotor symptoms and endometrial safety. *Menopause*. 2007;14:510–517.
302. **Pinkerton JV, Shifren JL, La Valleur J, Rosen A, Roesinger M, Siddhanti S.** Influence of raloxifene on the efficacy of an estradiol-releasing ring for treating vaginal atrophy in postmenopausal women. *Menopause*. 2003;10:45–52.
303. **Parsons A, Merritt D, Rosen A, et al.** Effect of raloxifene on the response to conjugated estrogen vaginal cream or nonhormonal moisturizers in postmenopausal vaginal atrophy. *Obstet Gynecol*. 2003;101:346–352.
304. **Ulrich LS, Naessen T, Elia D, et al.** Endometrial safety of ultra-low-dose Vagifem 10 microg in postmenopausal women with vaginal atrophy. *Climacteric*. 2010;13:228–237.
305. **Cicinelli E, Di Naro E, De Ziegler D, et al.** Placement of the vaginal 17β-estradiol tablets in the inner or outer one third of the vagina affects the preferential delivery of 17β-estradiol toward the uterus or periurethral areas, thereby modifying efficacy and endometrial safety. *Am J Obstet Gynecol*. 2003;189:55–58.
306. **Tourgeman DE, Boostanfar R, Chang L, Lu J, Stanczyk FZ, Paulson RJ.** Is there evidence for preferential delivery of ovarian estradiol to the endometrium? *Fertil Steril*. 2001;75:1156–1158.
307. **Fanchin R, De Ziegler D, Bergeron C, Righini C, Torrisi C, Frydman R.** Transvaginal administration of progesterone. *Obstet Gynecol*. 1997;90:396–401.
308. **Ross D, Cooper AJ, Pryse-Davies J, Bergeron C, Collins WP, Whitehead MI.** Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women. *Am J Obstet Gynecol*. 1997;177:937–941.
309. **De Ziegler D, Bulletti C, De Monstier B, Jääskeläinen AS.** The first uterine pass effect. *Ann NY Acad Sci*. 1997;828:291–299.
310. **Portman DJ, Bachmann GA, Simon JA, Ospemifene Study Group.** Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause*. 2013;20:623–630.
311. **Bachmann GA, Komi JO, Ospemifene Study Group.** Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. *Menopause*. 2010;17:480–486.
312. **Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA.** Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. *Climacteric*. 2015;18:226–232.
313. **Simon JA, Lin VH, Radovich C, Bachmann GA, Ospemifene Study Group.** One-year long-term safety extension study of ospemifene

for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. *Menopause*. 2013;20:418–427.
314. **Simon J, Portman D, Mabey RG Jr, Ospemifene Study Group.** Long-term safety of ospemifene (52-week extension) in the treatment of vulvar and vaginal atrophy in hysterectomized postmenopausal women. *Maturitas*. 2014;77:274–281.
315. **Shionogi Inc.** Highlights of prescribing information for Osphena. http://www.shionogi.com/pdf/PI/Osphena-PI.pdf. Accessed September 15, 2015.
316. **Singh M.** Early age of natural menopause in India, a biological marker for early preventive health programs. *Climacteric*. 2012; 15:581–586.
317. **Ang SB, How CH.** Menopause: an important milestone in women's health. *Singapore Med J*. 2013;54:60–63.
318. **Gold EB, Crawford SL, Avis NE, et al.** Factors related to age at natural menopause: longitudinal analyses from SWAN. *Am J Epidemiol*. 2013;178:70–83.
319. **Hale GE, Robertson DM, Burger HG.** The perimenopausal woman: endocrinology and management. *J Steroid Biochem Mol Biol*. 2014;142:121–131.
320. **Nelson LM.** Clinical practice. Primary ovarian insufficiency. *N Engl J Med*. 2009;360:606–614.
321. **Kalantaridou SN, Davis SR, Nelson LM.** Premature ovarian failure. *Endocrinol Metab Clin North Am*. 1998;27:989–1006.
322. **Freedman AN, Yu B, Gail MH, et al.** Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. *J Clin Oncol*. 2011;29:2327–2333.
323. **Levine M, Moutquin JM, Walton R, et al.** Chemoprevention of breast cancer. A joint guideline from the Canadian Task Force on Preventive Health Care and the Canadian Breast Cancer Initiative's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. *CMAJ*. 2001;164:1681–1690.
324. **Taku K, Melby MK, Kronenberg F, Kurzer MS, Messina M.** Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. *Menopause*. 2012;19:776–790.
325. **Bolaños R, Del Castillo A, Francia J.** Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: systematic review and meta-analysis. *Menopause*. 2010;17:660–666.
326. **Jacobs A, Wegewitz U, Sommerfeld C, Grossklaus R, Lampen A.** Efficacy of isoflavones in relieving vasomotor menopausal symptoms - a systematic review. *Mol Nutr Food Res*. 2009;53:1084–1097.
327. **Eden JA.** Phytoestrogens for menopausal symptoms: a review. *Maturitas*. 2012;72:157–159.
328. **Lethaby AE, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J.** Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst Rev*. 2007;12:CD001395.
329. **Van Patten CL, Olivotto IA, Chambers GK, et al.** Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial. *J Clin Oncol*. 2002;20:1449–1455.
330. **Upmalis DH, Lobo R, Bradley L, Warren M, Cone FL, Lamia CA.** Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause*. 2000;7:236–242.
331. **Quella SK, Loprinzi CL, Barton DL, et al.** Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: a North Central Cancer Treatment Group Trial. *J Clin Oncol*. 2000;18:1068–1074.
332. **Kronenberg F, Fugh-Berman A.** Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. *Ann Intern Med*. 2002;137:805–813.
333. **Nikander E, Kilkkinen A, Metsä-Heikkilä M, et al.** A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstet Gynecol*. 2003;101:1213–1220.
334. **MacGregor CA, Canney PA, Patterson G, McDonald R, Paul J.** A randomised double-blind controlled trial of oral soy supplements versus placebo for treatment of menopausal symptoms in patients with early breast cancer. *Eur J Cancer*. 2005;41:708–714.
335. **Levis S, Strickman-Stein N, Ganjei-Azar P, Xu P, Doerge DR, Krischer J.** Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms: a randomized, double-blind trial. *Arch Intern Med*. 2011;171:1363–1369.
336. **Murkies AL, Wilcox G, Davis SR.** Clinical review 92: Phytoestrogens. *J Clin Endocrinol Metab*. 1998;83:297–303.
337. **Jenks BH, Iwashita S, Nakagawa Y, et al.** A pilot study on the effects of S-equol compared to soy isoflavones on menopausal hot flash frequency. *J Womens Health (Larchmt)*. 2012;21:674–682.
338. **North American Menopause Society.** The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010). *Menopause*. 2011;18:732–753.
339. **Dodin S, Lemay A, Jacques H, Légaré F, Forest JC, Mâsse B.** The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: a randomized, double-blind, wheat germ placebo-controlled clinical trial. *J Clin Endocrinol Metab*. 2005;90:1390–1397.
340. **Pruthi S, Qin R, Terstreip SA, et al.** A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes: North Central Cancer Treatment Group N08C7. *Menopause*. 2012;19:48–53.
341. **Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR.** Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. *JAMA*. 2003;290:207–214.
342. **Barton DL, Loprinzi CL, Quella SK, et al.** Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol*. 1998;16:495–500.
343. **Ziaei S, Kazemnejad A, Zareai M.** The effect of vitamin E on hot flashes in menopausal women. *Gynecol Obstet Invest*. 2007;64: 204–207.
344. **Newton KM, Buist DS, Keenan NL, Anderson LA, LaCroix AZ.** Use of alternative therapies for menopause symptoms: results of a population-based survey. *Obstet Gynecol*. 2002;100:18–25.
345. **Keenan NL, Mark S, Fugh-Berman A, Browne D, Kaczmarczyk J, Hunter C.** Severity of menopausal symptoms and use of both conventional and complementary/alternative therapies. *Menopause*. 2003;10:507–515.
346. **Leach MJ, Moore V.** Black cohosh (Cimicifuga spp.) for menopausal symptoms. *Cochrane Database Syst Rev*. 2012;9:CD007244.
347. **Laakmann E, Grajecki D, Doege K, zu Eulenburg C, Buhling KJ.** Efficacy of *Cimicifuga racemosa*, *Hypericum perforatum* and *Agnus* castus in the treatment of climacteric complaints: a systematic review. *Gynecol Endocrinol*. 2012;28:703–709.
348. **Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer Ch, Birkhäuser M.** *Cimicifuga racemosa* dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. *Maturitas*. 2005;51: 397–404.
349. **Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke-von Zepelin HH.** Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol*. 2005; 105:1074–1083.
350. **Verhoeven MO, van der Mooren MJ, van de Weijer PH, et al.** Effect of a combination of isoflavones and *Actaea racemosa Linnaeus* on climacteric symptoms in healthy symptomatic perimenopausal women: a 12-week randomized, placebo-controlled, double-blind study. *Menopause*. 2005;12:412–420.
351. **Pockaj BA, Gallagher JG, Loprinzi CL, et al.** Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. *J Clin Oncol*. 2006;24:2836–2841.
352. **Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J.** Treatment of vasomotor symptoms of menopause

doi: 10.1210/jc.2015-2236

with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med*. 2006;145:869–879.
353. **Kim DI, Jeong JC, Kim KH, et al.** Acupuncture for hot flushes in perimenopausal and postmenopausal women: a randomised, sham-controlled trial. *Acupunct Med*. 2011;29:249–256.
354. **Avis NE, Legault C, Coeytaux RR, et al.** A randomized, controlled pilot study of acupuncture treatment for menopausal hot flashes. *Menopause*. 2008;15:1070–1078.
355. **Cho SH, Whang WW.** Acupuncture for vasomotor menopausal symptoms: a systematic review. *Menopause*. 2009;16:1065–1073.
356. **Lee MS, Shin BC, Ernst E.** Acupuncture for treating menopausal hot flushes: a systematic review. *Climacteric*. 2009;12:16–25.
357. **Daley A, Stokes-Lampard H, Macarthur C.** Exercise for vasomotor menopausal symptoms. *Cochrane Database Syst Rev*. 2011;5: CD006108.
358. **van Gastel P, Kallewaard JW, van der Zanden M, de Boer H.** Stellate-ganglion block as a treatment for severe postmenopausal flushing. *Climacteric*. 2013;16:41–47.
359. **Carpenter JS, Burns DS, Wu J, et al.** Paced respiration for vasomotor and other menopausal symptoms: a randomized, controlled trial. *J Gen Intern Med*. 2013;28:193–200.
360. **Sood R, Sood A, Wolf SL, et al.** Paced breathing compared with usual breathing for hot flashes. *Menopause*. 2013;20:179–184.
361. **Carmody JF, Crawford S, Salmoirago-Blotcher E, Leung K, Churchill L, Olendzki N.** Mindfulness training for coping with hot flashes: results of a randomized trial. *Menopause*. 2011;18:611–620.
362. **Ayers B, Smith M, Hellier J, Mann E, Hunter MS.** Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial. *Menopause*. 2012;19:749–759.
363. **Maki PM.** New data on mindfulness-based stress reduction for hot flashes: how do alternative therapies compare with selective serotonin reuptake inhibitors? *Menopause*. 2011;18:596–598.
364. **Duijts SF, van Beurden M, Oldenburg HS, et al.** Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. *J Clin Oncol*. 2012;30:4124–4133.
365. **Freedman RR, Woodward S.** Behavioral treatment of menopausal hot flushes: evaluation by ambulatory monitoring. *Am J Obstet Gynecol*. 1992;167:436–439.
366. **Norton S, Chilcot J, Hunter MS.** Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects. *Menopause*. 2014;21:574–578.
367. **Chilcot J, Norton S, Hunter MS.** Cognitive behaviour therapy for menopausal symptoms following breast cancer treatment: who benefits and how does it work? *Maturitas*. 2014;78:56–61.
368. **Santen RJ, Stuenkel CA, Burger HG, Manson JE.** Competency in menopause management: whither goest the internist? *J Womens Health (Larchmt)*. 2014;23(4):281–285.

SPECIAL ARTICLE

The *Physicians' Desk Reference*

Problems and Possible Improvements

Jay S. Cohen, MD; Paul A. Insel, MD

The *Physicians' Desk Reference* (*PDR*) is a widely used source of drug information by American physicians and patients, but as we shall discuss, it suffers from numerous shortcomings.[1] The *PDR* is a collection of written and pictorial information that is provided and paid for by pharmaceutical manufacturers. The written material for a given drug is a compilation of data and recommendations that are identical to those in the drug's package insert. The wording and directives that are included in these package inserts (and thus in the *PDR*) represent information that the pharmaceutical companies are permitted to present following discussion and approval by the Food and Drug Administration (FDA), Rockville, Md. The *PDR* is thus a negotiated effort of commercial enterprises and governmental regulators.

Family physicians rely on the *PDR* more than any other drug information resource.[2] According to the Medical Economics Data Production Company, Montvale, NJ, which publishes the *PDR*: "Nine out of ten doctors consider the PDR to be their most used drug reference book . . . 97% of physicians say that the PDR is the book they go to when they're prescribing a drug they're not completely familiar with" (Mr Cy Caine, PDR Electronics, Medical Economics Data Production Co, oral communication, September 12, 1994). Moreover, each year, approximately 500 000 *PDR*s are sent to physicians, and about 500 000 more are sold to other professionals and to the general public.

Even so, the *PDR* has received little objective scrutiny with regard to the quality of its data. We will address the following questions: Is the information provided by the *PDR* comprehensive, current, and accurate? Does the cost-free mailing of annual editions of the *PDR*, underwritten by the drug industry, constitute a conflict of interest? Does physicians' reliance on the *PDR* influence the quality and objectivity of their knowledge of drugs, and by extension, the quality of care given to patients?

From the Departments of Psychiatry (Dr Cohen) and Pharmacology and Medicine (Dr Insel), University of California, San Diego, School of Medicine, La Jolla.

THE BASIS OF THE POPULARITY OF THE *PDR*

The popularity of the *PDR* among physicians is probably not a coincidence. First and perhaps foremost, for physicians, the *PDR* is delivered by mail free of charge. Unlike textbooks that can become quickly outdated, the *PDR* is updated by both periodic supplements during a given year and new annual editions.

The *PDR* enters the lives of physicians when they are young. The first free copy arrives during medical school. It is a powerful gift not only because it is free, but also, we believe, because receipt of the *PDR* has symbolic power, implying that a medical student is almost a physician. The result is that from the start, the *PDR* becomes identified as a natural part of being a physician. Medical students who begin clinical clerkships are often urged to consult the *PDR* to learn the brand names of drugs that preclinical pharmacology classes generally avoid teaching; yet, clinicians often favor brand names of drugs when they discuss and prescribe therapeutic agents. Moreover, the *PDR* pro-

vides information about doses—a topic that is typically ignored in preclinical teaching.

Beyond cost and convenience, there are other reasons for the popularity of the *PDR*. The format of the *PDR* is superior to many other drug information resources. The organization of the *PDR* is simplified by 3 color-coded, easily identified indexes: (1) an alphabetical list of drugs that contains both the brand and generic names, (2) a listing of drugs by therapeutic category and symptoms, and (3) an index that provides the drug manufacturers' 1-800 telephone numbers for professional support. The "Product Identification Section" (ie, glossy pages of color pictures of drug formulations) is an excellent visual-identification section. Thus, its organization and presentation make the *PDR* very "user-friendly." Package insert information in the *PDR* can thus be readily used to complement information that is provided by other sources of drug advertising.

As the *PDR* is well indexed, regularly updated, easy to use, and free, all these factors contribute to the popularity of the *PDR*. Moreover, because the *PDR* represents a compilation of package inserts that have been evaluated by the FDA, the *PDR* is perceived as government-approved information about drugs. Thus, it is commonly used to answer questions with regard to the "standard of care" of drug administration.

DEFICIENCIES IN THE *PDR*

The substance of the *PDR* lies in its "Product Information" section (ie, the manufacturer-written package inserts). It is in this largest and most important part of the book that we believe multiple problems exist: (1) In the *PDR*, dosage information and guidelines are inadequate and do not always account for interindividual variation. (2) Dosage methods that are recommended in the *PDR* are likely to be based on clinical studies that are skewed toward accelerated and higher dosing. (3) Clinically relevant low-dose information, when present, tends to be lost amid the lengthy write-ups in the *PDR*. (4) Many drug descriptions in the *PDR* provide no dosing adjustments for elderly patients. (5) Specific dosages for specific diagnoses are sometimes omitted. (6) Data with regard to side effects in the *PDR* tend to be unfocused, inaccurate, and inadequately updated. (7) The *PDR* sometimes contains outdated information.

Inadequate Dosage Information and Guidelines

It is a fundamental pharmacologic observation that normal subjects who are administered the same dose of a medication show variations in response. Depending on the drug, the range of interindividual variation in pharmacokinetics can be large, sometimes varying up to 40-fold.[3-5] If we add the factor of intraindividual variation, the implications become even greater. For this reason, textbooks of clinical pharmacology advise (and clinical experience dictates) individualization of drug dosages according to the requirements of each patient. Yet, in the guidelines in the *PDR*, many drugs are recommended in only 1 or 2 dosages and information with regard to dosing in relation to meals is not generally provided.

For example, terfenadine (Seldane) is recommended at 60 mg twice each day for all patients, regardless of factors such as age, size, gender, state of health, concomitant medications, or a history of medication intolerance. This one-size-fits-all approach might be appropriate if terfenadine were entirely benign, but substantial evidence implicates its role in life-threatening cardiac arrhythmias.[6] This side effect appears to be, in part, dose-related.[6,7] Moreover, data that preceded the marketing of terfenadine and that demonstrated effectiveness of the drug at dosages 50% lower than those recommended[8,9] are not mentioned in its *PDR* description.

Product descriptions in the *PDR* often contain brief summaries of findings from selected clinical studies that support the dosages recommended by the manufacturer. In part, this is a consequence of the regulatory environment that demands agreement between a manufacturer and the FDA with regard to the content of these descriptions. Studies that demonstrate effectiveness of lower than recommended dosages may be omitted from the *PDR*. Examples include flurazepam hydrochloride (Dalmane),[10,11] zolpidem tartrate (Ambien),[12-14] ibuprofen (Motrin),[15,16] diclofenac sodium (Voltaren),[17-20] fluoxetine hydrochloride (Prozac),[21,22] ranitidine hydrochloride (Zantac),[23-25] and omeprazole (Prilosec).[26]

Similarly, most *PDR* drug descriptions provide pharmacokinetic data on certain factors (eg, peak plasma drug levels, mean elimination half-lives); however, in many cases, these data are expressed as statistical means without confidence limits. We believe that the absence of such data may inhibit the ability of physicians to understand unusual and idiosyncratic reactions in some patients.

Guidelines for administration of medications at only 1 or 2 doses are sometimes medically irrational; yet, new drugs often are recommended in the *PDR* with this type of guideline. Perhaps this has more to do with economics than science. Drug manufacturers understand that penetrating an established market is difficult; thus, nonscientific issues may take precedence in carving out a niche for a new drug.[27]

A drug for which the formulation and dosage are easy for physicians to remember (and for patients to use) will presumably have a better chance of being prescribed than will a drug with complex dosage guidelines that may better match the range of individual variation. Although flexible dosing schedules may be more medically sound, complicated dosing schedules are harder to remember, take more time to explain to patients, and may contribute to noncompliance. Thus, flexible dosing may be a liability in a competitive market for drug prescriptions.

Basis of *PDR*-Recommended Dosage Methods

Because of economic and time considerations, Phase 1 and 2 studies may be relatively brief. For example, in the case of fluoxetine, stud-

ies were sometimes ended before this long-acting drug reached its peak blood levels.[28] Studies that have been designed to define dosage may have been conducted with subjects who are younger, healthier, and thus potentially more tolerant of pharmacologic effects than are patients. All of these factors favor higher dosages.

Recent efforts by the FDA to achieve a more balanced gender and racial representation in Phase 1, 2, and 3 studies will improve but may not completely remedy this situation. Even under the best of circumstances, studies that are conducted on a small sample are limited in their ability to determine side effects and optimal dosages in the larger population. Information about adverse drug reactions and the full range of dosing regimens are sometimes only learned after a drug is made available for prescribing[29,30]; yet, the dosing recommendations in the *PDR* that are based almost entirely on data from Phase 1, 2, and 3 studies do not incorporate information obtained during Phase 4 (after drug release) unless a manufacturer applies to the FDA to change the package insert.

Clinically Relevant Low-Dose Information Amid Lengthy Write-ups in the *PDR*

The *PDR* sometimes offers efficacy and toxicity data associated with lower drug dosages, but these data can be difficult to find or recognize. In the description of cimetidine (Tagamet), one reads: "800 mg h.s. [at bedtime] is the dose of choice for most [acute duodenal ulcer] patients . . . "[31(p2403)]; yet, who these "most patients" are is not precisely defined. Elsewhere in the write-up, one finds results of a study in which cimetidine (400 mg at bedtime) healed 66% of patients with duodenal ulcers after 4 weeks of treatment; other data indicate that treatment with 800 and 1600 mg of cimetidine given at bedtime healed 75% and 81% of patients, respectively. Thus, most patients healed in response to 400 mg of cimetidine that was taken at bedtime, but the recommendation ignores these results. A more prominent mention of the effectiveness of the lower dose in the dosage guidelines for cimetidine would offer physicians an alternative for use with patients who are prone to side effects.

Ondansetron hydrochloride (Zofran) provides another example. If one reviews a detailed table that is published in the *PDR* and that summarizes the efficacy of the recommended dosage (8 mg 3 times daily) of ondansetron hydrochloride, one is likely to miss the effectiveness of another dosage (4 mg 3 times daily), unless one reads a footnote to the table.[31(p862)] In addition, the effectiveness of a dosage of 1 mg 3 times daily[32-34] in some subjects is not mentioned at all.

With ranitidine hydrochloride, the *PDR* acknowledges the effectiveness of treating a duodenal ulcer with a dosage of 100 mg twice daily, which is 33% lower than the recommended dosage of 150 mg twice daily[31(p1110)]; yet, a preparation is not marketed for treatment with the lower dosage.

Absence of Dosing Adjustments for Elderly Patients in Drug Descriptions

Many drugs demonstrate altered pharmacokinetics in elderly patients, owing sometimes to hepatic, but more commonly, to decreased renal excretion as a consequence of a decreased glomerular filtration rate and renal blood flow. As a result, elderly patients should receive lower doses of certain drugs than do other adult subjects to achieve equivalent efficacy and to prevent unnecessary toxic effects. Lower doses may be safer, too, because the responses of older patients to drugs can be more unpredictable than for other patient populations.[35] This unpredictability, coupled with a higher drug use than in other age groups, has resulted in a higher incidence of side effects in the elderly compared with that in the younger adult population.[30,36,37]

Until recently, the FDA did not require package inserts to include dosage adjustments for elderly patients. In 1989, for 425 drugs that are often used by elderly patients, only about half had information in the *PDR* about use in this population.[38] Thus, information in the *PDR* may be misleading with regard to the safety of "standard adult" dosages in elderly patients. Given the growing number of elderly patients in the United States, and the possibility that interindividual variation in these patients may be even broader than among the general population, the *PDR* should provide dosage guidelines for elderly patients for all drugs that are used in this population.

Omission of Specific Dosages for Specific Diagnoses

Drug manufacturers are not required to study every possible use of a new drug. Approval by the FDA requires proof of effectiveness in the treatment of 1 definable disorder. Yet, once a drug is approved, physicians can (and often do) use it for any condition that they choose. In some cases, these "new" uses prove to be helpful to patients; thus, medical practice is not necessarily reflected by what is contained in the *PDR*. For a manufacturer to add a new indication to the *PDR* would require the filing of a New Drug Application with the FDA. As a result, guidelines for use and dosage in the *PDR* may not be accurate for certain conditions. Examples include drugs such as diclofenac for pain or tendinitis,[39-42] propranolol hydrochloride (Inderal) for mitral valve prolapse syndrome,[43] trazodone hydrochloride (Desyrel) for insomnia,[44-46] and topical tretinoin (Retin-A).[47]

This may be a particular problem for certain classes of therapeutic agents. One example relates to antidepressant drugs, for which most dosage guidelines in the *PDR* make no reference to specific diagnoses. Although fluoxetine, paroxetine hydrochloride (Paxil), sertraline hydrochloride (Zoloft), venlafaxine hydrochloride (Effexor), amitriptyline hydrochloride (Elavil), imipramine hydrochloride (Tofranil), and other antidepressants were initially approved for treating major depression, the guidelines do not indicate that the recommended dosages are specific for this condition. This is important because these drugs are commonly utilized in treating milder conditions (ie, dysthymic panic, and obsessive-compulsive disorders, pain

and premenstrual syndromes, insomnia, and other types of depression) that may respond to lower dosages than those recommended for major depression. The result is that physicians tend to prescribe the *PDR*-recommended dosages that befit major depression to patients with milder conditions; this practice may play a role in the high incidence of side effects that are seen with antidepressant drugs.

Unfocused, Inaccurate, and Inadequately Updated Data for Side Effects in the *PDR*

The range and rate of side effects listed in the *PDR* are derived from findings from both preclinical and clinical studies, which are, by necessity, limited in the number of subjects and duration of treatment. Thus, previously unrecognized side effects and varying incidences of already recognized side effects may be discovered during Phase 4,[48] as drugs are administered to a larger number of patients with a wide variety of diseases and conditions and for longer terms than when those drugs were used in Phase 2 and 3 trials.[3] Typically, though, a package insert (*PDR* description) for a new drug is written before the drug is able to be prescribed. The result is that the *PDR* tends to present potentially inaccurate, imprecise, and incomplete data with regard to side effects.

Moreover, a review of the profile of side effects of a given drug in the *PDR* can often be so extensive that clinically important side effects may be difficult for the physician to discern from those that are less frequent and less severe. This is particularly the case with older medications, for which the frequency of side effects is generally not provided in the *PDR*. Because this information is lacking in the *PDR*, physicians may not appropriately warn patients of side effects that are most serious and most likely to occur, and when a side effect occurs, physicians may overlook the drug as the culprit.[30]

For example, since 1990, the *PDR* has listed the rate of fluoxetine-induced sexual impairments (reduced libido, impaired ability for ejaculation, or orgasm) at about 2% each,[31(p946)] whereas studies have reported the combined incidences as high as 34%.[49] Physicians who have prescribed fluoxetine may not have been aware of these facts, in part because the *PDR* was not updated to reflect this information. Interestingly, because the manufacturer sought FDA approval for this drug in treating obsessive-compulsive disorders, a new side-effect table offers rates of 11% for decreased libido plus 7% for abnormal ejaculation in males; the lower incidences listed in the table regarding use in depression remain the same.

Outdated Information in the *PDR*

Even though a new edition of the *PDR* is published annually, the information contained therein is not necessarily up-to-date. If one compares the drug descriptions in the 1995 *PDR* with versions published a decade (or, in some cases, 2 decades) earlier, many of the descriptions are virtually identical in the 2 versions. Examples include the descriptions of Benadryl (diphenhydramine hydrochloride), Esidrix (hydrochlorthiazide), Dalmane (flurazepam hydrochloride), and Elavil (amitriptyline).

With most medications, postmarketing studies and clinical experience reveal unanticipated changes in uses and dosing patterns. These discoveries are reported in journals and some textbooks, but physicians may not consult these sources as often as they consult the *PDR*. Consequently, the *PDR* does not keep physicians informed about new uses and new concerns. This issue is related to the general lack of incorporation of information obtained from postmarketing (Phase 4) studies into the *PDR*.

AN INHERENT CONFLICT OF INTEREST?

The poor prescribing habits of physicians and the relationship between these habits and iatrogenic illness have been documented.[30,48] We believe that such habits in part relate to the information on which physicians base therapeutic decisions. Where do physicians turn for this information? Ideally, this information would be objective and would derive from medical school course work, textbooks, journals, postgraduate training, and continuing education courses. The reality, though, is that a substantial portion derives from the *PDR*. In essence, the industry that develops medications is a principal source of information for physicians who prescribe and choose among these products, thus presenting a problematic conflict of interest.

Although it is expected that physicians should play an independent role in the evaluation and utilization of the medications that they prescribe, reliance on the *PDR* (and other pharmaceutical company–derived sources of information) will almost certainly compromise independent judgments. In addition, as a company-derived collection of package inserts, the *PDR* provides neither adequate comparative analyses among drugs in similar or different classes nor information about cost, which is an issue of immense importance in the current era of health care provision.

THE ROLE OF THE FDA IN THE CONTENT OF THE *PDR*

Although the information contained in the *PDR* is generated by the pharmaceutical manufacturers, the individual drug descriptions must be approved by the FDA. Generally, the approval process is negotiated by representatives of the manufacturers and by FDA officials, often with input from external advisers to the FDA. This helps to provide a consensus for what is included in the package insert, but it may limit the information that manufacturers can include in their drug descriptions. For example, FDA regulations that require manufacturers to establish the safety and efficacy of a given drug and dosage may preclude a manufacturer's ability to include information about lower doses that have been shown to be effective in premarketing studies but have not been shown conclusively enough or in enough subjects to meet FDA standards. Similarly, requirements by the FDA may make it difficult for manu-

facturers to add information about previously unproved uses for their drugs despite findings during Phase 4 studies. Thus, procedural features and statutory rules probably contribute to shortcomings in the *PDR*.

ASSURANCE OF A RELIABLE SOURCE OF DRUG INFORMATION FOR PHYSICIANS

The ultimate responsibility for therapeutic decisions lies with the medical community, but physicians rely on the data that are made available to them. Without the *PDR* or a similar equivalent, where would physicians derive drug information, and would it be an improvement?

One possibility for ensuring a more objective source of drug information might be the dissemination to all physicians on an annual basis of 1 or more monograph, that would provide such information. The principal impediment to the dissemination of this type of monograph to all practicing physicians is financial, since the cost and preparation of an annual mailing would be large. Although the advent of computer-based technology should allow development of online, readily updated, objective, and inexpensive guides for the prescribing of drugs that include comparative information about the pharmacology and cost of different drugs, it is not clear that an interest group is committed to the development of such a guide. Nevertheless, this alternative deserves further consideration. We believe that a more feasible alternative is to improve the *PDR*, thereby maintaining the benefit of its already established system of annual dissemination and its long history of acceptance by physicians. Improvement of the *PDR* could be accomplished by having it meet well-defined medical and pharmacologic standards including (1) regular updating of drug descriptions to incorporate new data, in particular, data obtained in Phase 4 studies with regard to clinical uses, side effects, and doses; (2) recommendations about adjustments in dosing required for both younger adult and elderly patients and, to the extent possible, for pediatric patients as well; (3) highlighted sections to illustrate changes in annual editions; (4) more precise information with regard to the frequency of side effects and results of studies with lower than "standard" doses; and (5) the current wholesale cost of a drug.

Are these changes realistic? Could pharmaceutical manufacturers, the medical profession, and the FDA work cooperatively to fashion such a *PDR*? In fact, this potential has already been met in isolated cases. For example, the pharmacokinetic data on desipramine hydrochloride (Norpramin) mentions that a 36-fold difference in plasma levels has been seen in individuals who take identical oral doses of this drug, thus alerting physicians to the wide range of clinical responses that may occur.

The oral anticoagulant warfarin sodium (Coumadin) demonstrates that dosage guidelines can be updated. For 2 decades, warfarin has sometimes been prescribed in unnecessarily high dosages, as reflected by a high incidence of side effects.[50,51] In response to this problem, in 1990, the manufacturer updated the dosage recommendations for this drug. The new dosages are lower, the range is wider, and the recommendations include the need to individualize dosages, in particular with lower dosages for elderly and debilitated patients.[31(pp950-951)]

The *PDR* dosage recommendations can be changed when it has been deemed worthwhile or necessary. For example, triazolam (Halcion) and temazepam (Restoril) have had a lowering of dosages recommended in the *PDR*.

Indeed, if the potential of a "new" *PDR* is to be maximized, a reevaluation of the role of the FDA must also be part of the process. A requirement of more information about clinical responses at different dosing levels for different diseases, an assessment of drugs so as to define appropriate dosages for geriatric patients, and a regular updating of dosage guidelines and of prevalence rates of side effects would seem to be appropriate stipulations. In addition, a revision of regulations by the FDA so that manufacturers would add newly discovered uses and results of efficacy and toxicity in postmarketing studies. By requiring that manufacturers add dates to all drug descriptions, the FDA would alert readers to the timeliness of the data in the *PDR*.

CONCLUSIONS

The *PDR* is a mainstay of drug information for American physicians and probably the profession's leading source of drug data and prescribing guidelines. Despite this key role as a source of drug information, we believe that a number of aspects of the *PDR* require reappraisal in light of the evolving demography of the American population, pharmacokinetic and pharmacodynamic discoveries, clinical experiences with marketed drugs, and the reality of cost containment in medicine today.

Because physicians, as well as informed patients, need a source of drug information in 1 form or another, there is a role for a "*PDR*"—an objective, comprehensive, carefully conceived collection of descriptions of available drugs that can provide guidance about prescribing and utilizing medications. Although ultimately we believe that computer-based, online sources will become the standard for drug information to physicians (and, indeed, one of these sources may well be the *PDR*), at the present time we propose that appropriate revisions of what is in part an imprecise and outdated *PDR* could prove to be beneficial to the prescribing of drugs and, thus, to patient care.

Accepted for publication January 9, 1996.

We thank J. Edward Jackson, MD, for useful comments.

Corresponding author: Paul A. Insel, MD, Departments of Pharmacology and Medicine, University of California, San Diego, School of Medicine, Box 0636, La Jolla, CA 92093.

REFERENCES

1. *Physicians' Desk Reference*. 1st-49th eds. Montvale, NJ: Medical Economics Data Production Co; 1947-1995.
2. Connelly DP, Rich EC, Curley SP, Kelly JT. Knowledge resource preferences of family physicians. *J Fam Pract*. 1990;30:353-359.
3. American Medical Association. *Drug Evalua-*

tions, Annual 1993. Chicago, Ill: American Medical Association; 1993.
4. Greenblatt DJ. Basic pharmacokinetic principles and their application to psychotropic drugs. *J Clin Psychiatry.* 1993;54(suppl):8-13.
5. Dawling S. Monitoring of tricyclic antidepressant therapy. *Clin Biochem.* 1982;15:56-61.
6. Woolsey RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *JAMA.* 1993;269:1532-1536.
7. McEvoy GK, ed. *American Hospital Formulary Service, Drug Information 1993.* Bethesda, Md: American Society of Hospital Pharmacists; 1994.
8. Brandon ML, Weiner M. Clinical investigation of terfenadine: a non-sedating antihistamine. *Ann Allergy.* 1980;44:71-75.
9. Brandon ML, Weiner M. Clinical studies of terfenadine (Seldane) in seasonal allergic rhinitis. *Arzneimittelforschung.* 1982;32:1204-1205.
10. Jick H. Evaluation of drug efficacy by a preference technic. *N Engl J Med.* 1966;275:1399-1403.
11. Jick H. Comparative studies with a new hypnotic under current investigation. *Curr Ther Res.* 1967;9:355-357.
12. Merlotti L, Roehrs T, Koshorek G, Zorick F, Lamphere J, Roth T. The dose effects of zolpidem on the sleep of healthy normals. *J Clin Psychopharmacol.* 1989;9:9-14.
13. Koshorek G, Roehrs T, Sicklesteel J, Merlotti L, Russo L, Roth T. Dose effects of zolpidem on transient insomnia. *Sleep Res.* 1988;17:47.
14. Vogel G, Thurmond A, MacIntosh M, Clifton T. The effects of zolpidem (Ambien) on transient insomnia. *Sleep Res. 1998;17:67.*
15. Thompson M, Bell D. Further experience with ibuprofen in the treatment of arthritis. *Rheumatol Phys Med.* 1970;10(suppl 10):100-103.
16. Chalmers TM. Clinical experience with ibuprofen in the treatment of rheumatoid arthritis. *Ann Rheum Dis.* 1969;28:513-517.
17. Mutru O, Penttila M, Pesonen J, Salmela P, Suhonen O, Sonck T. Diclofenac sodium (Voltaren) and indomethacin in the ambulatory treatment of rheumatoid arthritis: a double-blind multicentre study. *Scand J Rheumatol.* 1978;22(suppl): 51-56.
18. Ciccolunghi SN, Chaudri HA, Schubiger BI, Reddrop R. Report on a long-term tolerability study of up to two years with diclofenac sodium (Voltaren). *Scand J Rheumatol.* 1978;22(suppl): 86-96.
19. Kantor TG. Use of diclofenac in analgesia. *Am J Med.* 1986;suppl 4B:64-69.
20. Siegmeth W, Placheta P. Long-term comparative study: diclofenac (Voltaren) and naproxen (Proxen) in arthritis. *J Suisse Med.* 1978;108: 349-353.
21. Wernicke JF, Dunlop SR, Dornseif BE, Bosomworth JC, Humbert M. Low-dose fluoxetine therapy for depression. *Psychopharmacol Bull.* 1988;24: 183-188.
22. Altamura AC, Montgomery SA, Wernicke JF. The evidence for 20 mg a day of fluoxetine as the optimal dose in the treatment of depression. *Br J Psychiatry.* 1988;153(suppl 3):109-112.
23. Langman MJ, Henry DA, Ogilvie A. Ranitidine and cimetidine for duodenal ulcer. *Scand J Gastroenterol.* 1981;69(suppl):115-117.
24. Dobrilla G, de Pretis G, Felder M, Chilovi F. Endoscopic double-blind controlled trial of ranitidine vs placebo in the short-term treatment of duodenal ulcer. *Hepatogastroenterology.* 1981; 28:49-52.
25. Berstad A, Kett K, Aadland E, et al. Treatment of duodenal ulcer with ranitidine, a new histamine H2-receptor antagonist. *Scand J Gastroenterol.* 1980;15:637-639.
26. Lauritsen K, Andersen BN, Havelund T, et al. Effect of 10 mg and 20 mg omeprazole daily on duodenal ulcer: double-blind comparative trial. *Aliment Pharmacol Ther.* 1989;3:59-67.
27. Kessler DA, Rose JL, Temple RJ, Schapiro R. Griffin JP. Therapeutic-class wars—drug promotion in a competitive marketplace. *N Engl J Med.* 1994;331:1350-1353.
28. Cain JW. Poor response to fluoxetine: underlying depression, serotonergic overstimulation, or a 'therapeutic window'? *J Clin Psychiatry.* 1992; 53:272-277.
29. Clark WG, Brater DC, Johnson AR. *Goth's Medical Pharmacology.* 12th ed. St Louis, Mo: Mosby–Year Book; 1992.
30. Melmon KL, Morrelli HF, Hoffman BB, Nierenberg DW. *Melmon and Morrelli's Clinical Pharmacology: Basic Principles in Therapeutics.* 3rd ed. New York, NY: McGraw-Hill International Book Co; 1993.
31. *Physicians' Desk Reference.* 49th ed. Montvale, NJ: Medical Economics Data Production Co; 1995.
32. Beck TM, Ciociola AA, Jones SE, et al. Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. *Ann Intern Med.* 1993; 118:407-413.
33. Beck TM. Efficacy of ondansetron tablets in the management of chemotherapy-induced emesis: review of clinical trials. *Semin Oncol.* 1992;19 (suppl 15):20-25.
34. Cubeddu LX, Pendergrass K, Ryan T, et al. Efficacy of oral ondansetron, a selective antagonist of 5-HT3 receptors, in the treatment of nausea and vomiting associated with cyclophosphamide-based chemotherapies. *Am J Clin Oncol.* 1994; 17:137-146.
35. Oh VM. Multiple medication: problems of the elderly patient. *Int Dent J.* 1991;41:348-358.
36. Brawn LA, Castleden CM. Adverse drug reactions: an overview of special considerations in the management of the elderly patient. *Drug Saf.* 1990;5:421-435.
37. Recchia AG, Shear NH. Organization and function of an adverse drug reaction clinic. *J Clin Psychiatry.* 1994;34:68-79.
38. Office of the Inspector General, Health and Human Services. *Medical Drug Utilization Review.* April 1989.
39. Minotti V, Patoia L, Roila F, et al. Double-blind evaluation of analgesic efficacy of orally administered diclofenac, nefopam, and acetylsalicylic acid (ASA) plus codeine in chronic cancer pain. *Pain.* 1989;36:177-183.
40. Nuutinen LS, Wuolijoki E, Pentikainen IT. Diclofenac and oxycodone in treatment of postoperative pain: a double-blind trial. *Acta Anaesthesiol Scand.* 1986;30:620-624.
41. Machtey I. Diclofenac in the treatment of painful joints and traumatic tendinitis (including strains and sprains): a brief review. *Semin Arthritis Rheum.* 1985;15(suppl 1):87-92.
42. Zuinen C. Diclofenac/misoprostol vs diclofenac/placebo in treating acute episodes of tendinitis/bursitis of the shoulder. *Drugs.* 1993;45(suppl 1):17-23.
43. Johnson MS. Response of ventricular arrhythmias to propranolol in mitral valve prolapse. *Ala Med.* 1988;58:14-16.
44. Nierenberg AA, Keck PE Jr. Management of monoamine oxidase inhibitor-associated insomnia with trazodone. *J Clin Psychopharmacol.* 1989;9:42-45.
45. Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant-associated insomnia. *Am J Psychiatry.* 1994; 151:1069-1072.
46. Metz A, Shader RI. Adverse interactions encountered when using trazodone to treat insomnia associated with fluoxetine. *Int Clin Psychopharmacol.* 1990;5:191-194.
47. Stern RS. Drug promotion for a unlabeled indication—the case of topical tretinoin. *N Engl J Med.* 1994;331:1348-1349.
48. Gilman AG, Rall TW, Nies AS, Taylor P. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* Elmsford, NY: Pergamon Press Inc; 1990.
49. Jacobsen FM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. *J Clin Psychiatry.* 1992;53:119-122.
50. Eckman MH, Levine HJ, Pauker SG. Effect of laboratory variation in the prothrombin-time ratio on the results of oral anticoagulant therapy. *N Engl J Med.*1993;329:696-670.
51. Hull R, Hirsh J, Jay R, et al. Different intensities of anticoagulation in the long-term treatment of proximal venous thrombosis. *N Engl J Med.* 1982; 307:1676-1681.

Published in final edited form as:
J Couns Psychol. 2016 October ; 63(5): 509–519. doi:10.1037/cou0000143.

Discriminatory experiences associated with posttraumatic stress disorder symptoms among transgender adults

Sari L. Reisner, ScD[1,2,3], **Jaclyn M. White Hughto, MPH**[3,4], **Kristi E. Gamarel, PhD**[5], **Alex S. Keuroghlian, MD, MSc**[3,6], **Lauren Mizock, PhD**[7], and **John Pachankis, PhD**[4]

Jaclyn M. White Hughto: jwhite@fenwayhealth.org; Kristi E. Gamarel: kristi_gamarel@brown.edu; Alex S. Keuroghlian: akeuroghlian@partners.org; Lauren Mizock: lauren.mizock@gmail.com; John Pachankis: john.pachankis@yale.edu

[1]Division of General Pediatrics, Boston Children's Hospital/Harvard Medical School, Boston, MA

[2]Dept of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[3]The Fenway Institute, Fenway Health, Boston, MA

[4]Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT

[5]Dept of Psychiatry & Human Behavior, Alpert Medical School of Brown University, Providence, RI

[6]Dept of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Boston, MA

[7]Psychology, Worcester State University, Worcester, MA

Abstract

Discrimination has been shown to disproportionately burden transgender people; however, there has been a lack of clinical attention to the mental health sequelae of discrimination, including posttraumatic stress disorder (PTSD) symptoms. Additionally, few studies contextualize discrimination alongside other traumatic stressors in predicting PTSD symptomatology. The current study sought to fill these gaps. A community-based sample of 412 transgender adults (mean age 33, SD=13; 63% female-to-male spectrum; 19% people of color; 88% sampled online) completed a cross-sectional self-report survey of everyday discrimination experiences and PTSD symptoms. Multivariable linear regression models examined the association between self-reported everyday discrimination experiences, number of attributed domains of discrimination, and PTSD symptoms, adjusting for prior trauma, sociodemographics, and psychosocial co-morbidity. The mean number of discrimination attributions endorsed was 4.8 (SD=2.4) and the five most frequently reported reasons for discrimination were: gender identity and/or expression (83%), masculine and feminine appearance (79%), sexual orientation (68%), sex (57%), and age (44%). Higher everyday discrimination scores (β=0.25; 95% CL=0.21–0.30) and greater number of attributed reasons for discrimination experiences (β=0.05; 95% CL=0.01–0.10) were independently associated with PTSD symptoms, even after adjusting for prior trauma experiences. Everyday discrimination experiences from multiple sources necessitate clinical consideration in treatment for PTSD symptoms in transgender people.

Corresponding Author: Sari L. Reisner, ScD, 300 Longwood Avenue, Mailstop BCH 320, Boston, MA 02115, sari.reisner@childrens.harvard.edu, Phone: 617-927-6017; Fax: 617-267-0764.

The authors do not have any conflicts of interest.

Keywords

PTSD; discrimination; stigma; transgender

Transgender people, who have a gender identity that differs from their assigned sex at birth, experience high levels of prejudice, discrimination, and violence (Bockting, Miner, Romine, Hamilton, & Coleman, 2013; Grant, 2011; Lombardi, Wilchins, Priesing, & Malouf, 2002; Mizock & Lewis, 2008; Shipherd, Maguen, Skidmore, & Abramovitz, 2011). A national study of more than 6,000 U.S. transgender respondents found that 63% reported an emotionally- or life-impairing experience of discrimination (Grant, 2011). Discrimination toward transgender people occurs across settings (e.g., employment, healthcare) and can be both chronic (e.g., interpersonal rejection) and acute (e.g., victimization) (Lombardi, 2009; Mizock & Lewis, 2008; Mizock & Mueser, 2014). Physical violence and sexual assault due to transgender identity are also highly prevalent across the life course (Clements-Nolle, Marx, & Katz, 2006; Grant, 2011; Stotzer, 2009). Consistent with minority stress theory (Hendricks & Testa, 2012; Meyer, 2003b), both violent and non-violent forms of discrimination are associated with adverse mental health outcomes in transgender people, including depression, anxiety, psychological distress, and substance abuse (Grant, 2011; Lombardi, et al., 2002).

Posttraumatic stress disorder (PTSD), a stress-sensitive disorder associated with significant morbidity and impairment (Kessler, 2000), represents one of the most common mental health conditions to arise from direct or vicarious exposure to life-threatening events, serious injury, or sexual assault (APA, 2013). PTSD is characterized by four key symptoms: (1) persistent intrusive thoughts or re-experiencing of the event; (2) avoidance of stimuli associated with the event; (3) negative cognitions and mood such as emotional numbing and detachment from others; and (4) changes in arousal or reactivity such as hypervigilance, irritability, exaggerated startle response, or self-destructive reckless behavior (APA, 2013). While PTSD affects an estimated 6.8% of the U.S. general adult population (Kessler et al., 2005), prevalence estimates in transgender samples range from 18 to 61% (Rowe, Santos, McFarland, & Wilson, 2015; Shipherd, et al., 2011; Valera, Sawyer, & Schiraldi, 2001; Wharton, 2007) and greater severity and frequency of emotional numbing, behavioral avoidance, and physiological arousal relative to non-transgender people have been reported (Wilson, 2013).

Despite the high prevalence of discrimination and PTSD in transgender people, the relationship between these phenomena remains understudied. A possible explanation for the dearth of research in this area is that exposure to non-violent forms of discrimination may not meet *DSM* criteria for a traumatic event (e.g., Criterion A). However, like acute traumatic stress, chronic and persistent threats to one's identity in the form of everyday discrimination threaten a person's core human needs for trust, understanding, control and belonging, with harmful mental health effects (Swim & Thomas, 2006). Further, trauma and discrimination, whether acute or chronic, produce similar stress responses, including avoidance of stimuli associated with the traumatic or discriminatory event (Bockting, et al., 2013; Carter & Forsyth, 2010; Meyer, 2003b; Pascoe & Richman, 2009) and hypervigilance

(e.g., anticipatory stress) about the possibility of future trauma or discrimination (Bockting, et al., 2013; Carter & Forsyth, 2010; Meyer, 2013; Pachankis, Goldfried, & Ramrattan, 2008), as well as similar physiological responses in reaction to acute laboratory-based stressors (Hatzenbuehler & McLaughlin, 2014). Despite evidence that traumatic stress exposure and stigma-related stress operate through similar minority stress processes (Meyer, 2003b), no studies have explored the relationship between discrimination and PTSD symptoms in transgender people, a highly stigmatized and underserved group.

In addition to known traumatic stressors such as childhood physical and/or sexual abuse and intimate partner violence, which increase probability of PTSD symptoms (Brewin, Andrews, & Valentine, 2000; Golding, 1999), a potential source of additional traumatic stress responses for transgender people is exposure to acts of discrimination based on gender identity or gender presentation. In addition, qualitative studies have illustrated that transgender individuals experience discrimination and oppression based on their gender identity and intersecting stigmatized identities (e.g., race/ethnicity, age, social class, and citizenship status) (Daley, Solomon, Newman, & Mishna, 2008; de Vries, 2014; Gamarel, Walker, Rivera, & Golub, 2014; Sevelius, 2013).

While research indicates that individuals with multiple identities often incorporate these identities into a single unified sense of self (McAdams, 1997; Meyer, 2010; Singer, 2004), multiple identities can provoke different forms of discrimination in diverse contexts. Indeed, multiple minority statuses can lead to greater discrimination exposure and result in greater erosion of core needs, as well as hypervigilance, avoidance, and physiological stress responses (e.g. Pascoe & Richman, 2009). For example, a study of 873 Latino and Black adults in New York City found that participants who experienced multiple domains of discrimination related to age, race, gender, weight, income, religion, mental or physical illness, immigration status, or sexual orientation, had a greater probability of reporting poor mental health than those who experienced no discrimination or discrimination in only one domain (Stuber, Galea, Ahern, Blaney, & Fuller, 2003). Similarly, a national study of 1,052 youth found that multiply disadvantaged youth faced greater exposure to multiple forms of discrimination than their more advantaged counterparts, and experiencing numerous forms of discrimination was more strongly associated with adverse mental and physical health outcomes than experiencing only one form of disadvantage (Grollman, 2012). Given that many transgender people may possess multiple stigmatized identities or characteristics (e.g., minority race/ethnicity, older age, low SES) and report discrimination and distress (Bockting, et al., 2013; Daley, et al., 2008; de Vries, 2014; Gamarel, Walker, et al., 2014; Golub & Gamarel, 2013; Reisner, Bailey, & Sevelius, 2014; Sevelius, 2013; Witten, 2009), the additive stress associated with experiencing discrimination based on multiple minority stigmas represents an important area for research.

Appearance-related stigma represents a possible mechanism through which transgender people experience discrimination. Appearance-related stigma refers to the extent to which one's appearance produces a negative reaction in others (Jones, Farina, Hastorf, & French, 1984). Transgender individuals who do not conform to the socially sanctioned expression of their assigned sex at birth often experience mistreatment by others who view their self-expression as non-normative (Bockting, et al., 2013). Conversely, transgender individuals

with high visual conformity are said to have "passing privilege" in that their stigma (i.e., being transgender) is concealable (Jones, et al., 1984) and they are therefore able to hide their transgender status and avoid mistreatment (Sevelius, 2013; Xavier, 1999). Social (i.e., living full-time in one's gender) and medical gender affirmation (i.e., hormones/surgery to masculinize/feminize) processes may impact the extent to which a transgender person appears more or less visually gender nonconforming, in turn impacting exposure to experiences of discrimination; however, the relationship between gender affirmation processes and experiences of discrimination are understudied.

Despite accumulating evidence that transgender people evince high prevalence of discrimination and PTSD symptoms, critical questions remain unanswered as to whether experiencing discrimination, as well as discrimination based on multiple stigmatized identities, is associated with PTSD symptoms. The purpose of this study was to: (1) examine discrimination experiences in a sample of transgender adults and explore reasons attributed to discrimination; (2) explore whether endorsing a higher number of attributed reasons for discrimination is associated with more PTSD symptoms; (3) identify whether gender affirmation processes are associated with discrimination experiences, including whether higher visible gender nonconformity is a risk factor and whether social transition or medical gender affirmation are protective factors for PTSD symptoms; and (4) evaluate whether discrimination experiences and the number of attributed domains are independently associated with elevated PTSD symptoms, after adjustment for some known traumatic stressors (e.g., childhood abuse and intimate partner violence).

Method

Participants and Procedures

A community-based sample of 452 transgender and gender nonconforming Massachusetts residents, ages 18 to 75 years, were purposively sampled from August-December 2013 for Project VOICE (Voicing Our Individual and Community Experiences), a study designed to examine the association between social stress and health. Participants were recruited via transgender-specific online and in-person venues. The majority (88%) were sampled online (via transgender electronic listservs, emails, web postings at local community-based websites, and social networking sites); 12% were sampled in-person (completed the survey via electronic tablets provided by the research team onsite at transgender community events, local social programming, and other gatherings). Eligible respondents were ages 18 years or older, self-identified as transgender or gender nonconforming, lived in Massachusetts for at least 3 months in the last year, and had the ability to read/write in either English or Spanish. Participants completed a one-time survey assessing demographics, experiences of discrimination and victimization, and health. Participants provided informed consent before beginning the survey. Using community-based participatory research principles (Leung, Yen, & Minkler, 2004), between March–July 2013 a team of community-based advocates, transgender leaders, researchers, and LGBT policy experts, working with gender minority people in the Commonwealth, together created the survey instrument and data collection plan. Whenever possible, validated questions or survey items adapted from prior transgender health research were utilized to ensure comparability of findings, including those from such

sources as the U.S. National Transgender Discrimination Survey (Reisner, Conron, Scout, et al., 2014) and Behavioral Risk Factor Surveillance System (BRFSS) (CDC, 2012). The survey was designed for a 5th grade reading level. Participants could opt to be entered into a community raffle for two tablet computers. We followed best practices for Internet research with transgender people, including initial usability and pilot testing, quality management processes to ensure unduplicated responses and valid study respondents (Miner, Bockting, Romine, & Raman, 2011) to ensure the integrity and validity of online data collected (Reisner et al., 2015). Two versions of the Project VOICE survey were fielded. The short version did not ask participants about discrimination experiences; thus, only participants who completed the long survey were included in the analytic sample (n=412). The survey was translated and back translated into Spanish, with input from transgender community members to ensure cultural relevance and appropriate translation. Four respondents completed surveys in Spanish. All study activities were IRB-approved.

Measures

Posttraumatic Stress Disorder (PTSD) Symptoms—PTSD symptoms were assessed with a 4-item scale designed for primary care settings (Ouimette, Wade, Prins, & Schohn, 2008; Prins et al., 2003) recommended by the U.S. Department of Veteran's Affairs (U.S. Department of Veteran's Affairs, 2014). Participants were asked: "In your life, have you ever had any experience that was so frightening, horrible, or upsetting that, in the past month you: (1) Have had nightmares about it or thought about it when you did not want to? (2) Tried hard not to think about it or went out of your way to avoid situations that reminded you of it? (3) Were constantly on guard, watchful, or easily startled? (4) Felt numb or detached from others, activities, or your surroundings?" Participants responded to each item using binary (yes/no) responses. The PC-PTSD has a test-retest Pearson's correlation coefficient of 0.83 ($p<0.001$), correlates highly with the Clinician-Administered PTSD Scale (Blake et al., 1995) 0.83 ($p<0.001$), and has an overall diagnostic accuracy of 85% (Prins, et al., 2003; Prins et al., 2004). The scale has also demonstrated good internal consistency in non-transgender samples (Cronbach's alpha ranges from 0.79–0.93) (Maguen et al., 2010; Mason, Mennis, & Schmidt, 2011; Sayer et al., 2011). This study represent the first time this measure has been used in a sample of transgender individuals. A factor analysis supported a single factor solution in the current study data (Eigenvalue=2.9; proportion of variance explained (PVE)=71.9%). Items were summed and scores ranged from 0–4; higher scores reflected more traumatic stress symptoms (α=0.87 in the current study).

Discrimination Experiences—Participants completed the Everyday Discrimination Scale, which consists of 11 items assessing the frequency of participants' experiences of everyday discrimination in the past 12 months on a Likert scale ranging from 0="*never*" to 4="*very often*." Sample items: "You have been treated with less courtesy than other people;" "People have acted as if they think you are not smart" (Krieger, Smith, Naishadham, Hartman, & Barbeau, 2005; Williams, Yan, Jackson, & Anderson, 1997). The Everyday Discrimination Scale has demonstrated good reliability and validity (Taylor, Kamarck, & Shiffman, 2004; Williams et al., 2012; Williams, Neighbors, & Jackson, 2003). In sample of LGBT participants, Cronbach's alpha for the discrimination scale was 0.94, and discrimination scores were correlated positively with depressive symptoms, anxiety, and

substance use (Gamarel, Reisner, Laurenceau, Nemoto, & Operario, 2014; Gamarel, Reisner, Parsons, & Golub, 2012; Gordon & Meyer, 2008; S. L. Reisner, White, Bradford, & Mimiaga, 2014). A factor analysis confirmed a single factor solution in the current dataset (Eigenvalue=6.9; PVE=62.9%). Items were summed and scores ranged from 0–44, with higher scores indicating higher levels of everyday discrimination experiences (α=0.94 in current dataset).

Reasons Attributed to Discrimination—Fourteen items assessed participants' attributed reasons for everyday discrimination using binary (yes/no) responses. Domains included those from prior research (Gordon & Meyer, 2008; Williams, et al., 1997) and theoretically relevant to this study: age, sex, race, ethnicity, nationality, religion, sexual orientation, disability, education or income level, weight, gender expression, masculine/feminine appearance, other aspect of appearance, and other reason. The number of attributed domains was summed; scores ranged from 0–14 with higher scores indicating higher number of domains of discrimination endorsed.

Other forms of trauma—Participants completed brief measures of childhood abuse and intimate partner violence used in prior research (Reisner, Falb, Wagenen, Grasso, & Bradford, 2013). Childhood abuse was queried by asking: "Were you ever physically or sexually abused as a child under age 15 years-old?" Participants who indicated "yes" were compared to those who indicated "no." Similarly, intimate partner violence was assessed with the item: "Have you ever been slapped, punched, kicked, beaten up, or otherwise physically or sexually hurt by your spouse (or former spouse), a boyfriend/girlfriend, or some other intimate partner?" These items are similar to other screening instruments commonly used to assess childhood abuse and IPV in clinical settings (Basile, Hertz, & Back, 2007; Hulme, 2004; McFarlane, Parker, Soeken, & Bullock, 1992). Previous use of the scale with LGBT populations have found associations with adverse mental health outcomes (S.L. Reisner, et al., 2013).

Sociodemographics—Age in years was assessed continuously. Gender was assessed using a two-step method (S.L. Reisner, Conron, Tardiff, et al., 2014) asking: (1) assigned sex at birth (*female, male*) and (2) current gender identity (*man, woman, female-to-male (FTM)/trans man, male-to-female (MTF)/trans woman, genderqueer, gender variant, gender nonconforming, other*). The two items were cross-tabulated to categorize participants as being on the female-to-male (FTM) trans masculine or male-to-female (MTF) trans feminine spectrum according to their natal sex. Participants assigned female at birth with a current nonbinary gender identity were categorized as FTM trans masculine; those assigned male at birth with a current nonbinary gender identity were characterized as MTF trans feminine. An indicator of non-binary gender was created to compare respondents with non-binary gender identities (gender variant, genderqueer, androgynous, gender nonconforming) to those with binary gender identities (man, woman, FTM, MTF). We note that intersex is not an assigned sex at birth; all infants, including those who are intersex, are assigned either a male or female sex at birth on their birth certificate. Social gender transition was assessed by asking participants if they lived full-time in their felt gender identity (yes/no). Medical gender affirmation was operationalized as being on cross-sex hormone therapy and/or having had

gender-related reassignment surgery (yes/no). High visual gender nonconformity was coded as those who "most of the time" or "always" endorsed the statement: "People can tell I'm transgender even if I don't tell them" and were compared to those who endorsed "never," "occasionally," or "sometimes." Race/ethnicity captured whether participants were white (non-Hispanic), Black (non-Hispanic), Latino/Hispanic, Other race/ethnicity, and Multiracial. Participants were categorized as people of color (POC) or non-Hispanic white. Perceived income ranged from 0="*no income*" to 3="*high income/upper class.*" Educational attainment was queried and ranged from 1="high school or less" to 4="graduate school." Unstable housing was operationalized as "rarely," "sometimes," or "often" having trouble "finding a safe place to hang out or sleep (housing)" in the past 12 months and compared to stable housing (i.e., "never" having such trouble). Sexual orientation was assessed by asking respondents how they identify with response options as "heterosexual/straight," "lesbian/gay," "bisexual," "queer," or "another sexual orientation." Sexual minority (i.e., lesbian, gay, bisexual, queer, another sexual orientation) respondents were compared to non-sexual minority (i.e., heterosexual, straight) respondents. Survey mode (online or in-person) was included as a covariate.

Depressive symptoms—Participants completed the 10-item Center of Epidemiologic Studies Depression Scale (CES-D-10) (Radloff, 1977) to assess past-week depressive symptoms. In the current dataset, Cronbach's α=0.88; a two factor solution was supported (cumulative PVE=60.7%) for negative affect (factor 1, Eigenvalue=4.9) and positive affect (factor 2, Eigenvalue=1.1), consistent with previous validation studies (Bradley, Bagnell, & Brannen, 2010; Zhang et al., 2012). Scores were summed such that higher scores indicated higher depressive symptoms. A score of 10 or more was operationalized to indicate a positive screen for clinically significant depression as recommended in prior research (Andresen, Malmgren, Carter, & Patrick, 1994). The CES-D-10 has been shown to correlate highly with the 20-item CES-D (Carpenter et al., 1998), which is sensitive in detecting clinical diagnoses of major depressive disorder. Furthermore, Cronbach's alpha for the CES-D scale was 0.88 in a sample of transgender adults (Reisner, et al., 2014).

Substance use—Participants were asked if they had used marijuana, cocaine, crack, club drug, methamphetamine, heroin, poppers, hallucinogens, downers, painkillers, or any other drug in the past 12-months (Yes/No). Past-12 month polydrug drug use was assessed by summing the number of drugs participants reported in the last 12 months. Participants using two or more drugs were compared to those reporting none or one drug.

Data Analysis

Statistical analyses were performed in SAS v9.4.1. Distributions of individual items were assessed, including missingness. Because missingness violated the missing completely at random assumption required for valid statistical inferences using listwise deletion (Allison, 2003), data were multiply imputed. A fully conditional specification imputation method was used shown to perform well in many different scenarios of missingness (Lee & Carlin, 2010; van Buuren, 2007; van Buuren, Brand, Groothuis-Oudshoorn, & Rubin, 2006). All subsequent analyses were conducted using the imputed data.

Univariate statistics were used to summarize the distribution of variables (mean, standard deviation [SD], frequencies, proportion). Two-sided tests were conducted with statistical significance at alpha=0.05. Tests for normality were conducted to ensure statistical assumptions for linear regression models were tenable. Analyses then examined whether any sociodemographic, depressive symptoms or substance use factors were associated with everyday experiences of discrimination to identify those groups who reported higher discrimination experiences. A linear multivariable regression model was fit (Model 1), regressing everyday discrimination scores on: number of reasons attributed to discrimination experiences (continuous), other traumatic experiences (binary) [childhood abuse, intimate partner violence], and sociodemographics [age, income, education (each continuous); FTM spectrum, non-binary gender identity, live full-time, medical gender affirmation, high visual gender nonconformity, POC, unstably housed, sexual minority, online survey mode, past-week depression, polydrug use (each binary)]. Next, analyses examined whether everyday experiences of discrimination were statistically associated with PTSD symptom scores (Model 2), adjusting for all variables described in Model 1. Multicollinearity diagnostics were computed for all regression models using variance inflation factor (VIF) values. All VIF values were less than 10, indicating no detection of multicollinearity (Jou, Huang, & Cho, 2014).

Age, everyday discrimination experiences scale scores, number of reasons attributed to discrimination, and PTSD symptoms were transformed to z-scores (mean=0, SD=1) to facilitate interpretation. The regression of a standardized variable (e.g., PTSD symptoms) on a standardized predictor (e.g., everyday discrimination experiences) generates standardized slopes that range from −1.0 and 1.0 (beta weights). For a binary predictor (e.g., childhood abuse yes/no), the standardized slope represents the difference between the means of the two groups on the outcome. Because the outcome variable is standardized (z-scored), the mean differences are in SD. The slope (beta) or difference between the means equals Cohen's *d* (effect size estimates). A Cohen's *d* of 0.20 (i.e., a fifth of a standard deviation) is a small effect, 0.50 (i.e., half a SD) a medium effect, and 0.80 a large effect (Cohen, 1988). Beta coefficients can therefore be interpreted in terms of SD unit changes in the statistical predictor relative to the outcome.

Results

Sample Characteristics

Table 1 presents characteristics of study sample. Participants had a mean age of 32.7 (SD=12.8); 62.6% were FTM spectrum; 59.7% identified their gender as binary; 19.2% were POC (2.9% Black, 9.0% Latino/Hispanic, 2.9% Other race, 4.4% Multiracial). There was high prevalence of childhood abuse age <15 years (46.6%), intimate partner violence (33.3%), depression (26.5%), polydrug use (18.5%), and unstable housing (25.5%). PTSD symptom scores ranged from 0 to 4 (M=1.95, SD=1.71). Overall, 44.4% of the sample met criteria for probable PTSD (PTSD symptom score 3+) (Prins, et al., 2003). The mean everyday discrimination score was 19.9 (SD=9.6). The mean number of discrimination attributions was 4.8 (SD=2.4). The five most frequently reported reasons attributed to discrimination were: gender identity and/or expression (83.2%), how masculine/feminine

you appear (78.6%), sexual orientation (68.0%), sex (assigned sex at birth) (56.8%), and age (43.5%) (Table 2). Linear models adjusted for survey mode (online vs in-person) are presented in Table 3 showing the statistically significant associations of PTSD symptoms, everyday discrimination experiences, and number of attributed domains of discrimination.

Everyday Discrimination Experiences (Table 4)

As shown in Model 1, FTM spectrum, POC, high visual gender nonconformity, greater number of reasons attributed to discrimination, childhood abuse age <15 years, past-week depression, and unstable housing were each independently and significantly associated with increased everyday discrimination scores. In this same model, sexual minority status, higher income, non-binary gender, and online sampling were each protective and associated with lower everyday discrimination scores.

PTSD Symptoms (Table 4)

In Model 2, higher everyday discrimination scores, greater number of attributed reasons for discrimination, childhood abuse age <15 years, intimate partner violence, social gender transition (living full-time in one's identified gender–distinct from medical gender affirmation), high visual gender nonconformity, unstable housing, past-week depression, and past-12 month polydrug use were each independently and significantly associated with higher PTSD scores. On the contrary, younger age, FTM spectrum gender, medical gender affirmation, and online sampling were each independently and significantly associated with lower PTSD scores.

Discussion

In this community-based sample of transgender adults, associations were found between discrimination experiences and PTSD symptoms. The present findings are consistent with a burgeoning body of evidence documenting elevated risk for mental health problems among individuals who experience discrimination (Diaz, Ayala, Bein, Henne, & Marin, 2001; Landrine & Klonoff, 1996; Williams, et al., 2003), including transgender people (Shipherd, et al., 2011). Notably, the prevalence of PTSD symptoms reported here is much higher than national studies of the general population (Kessler, et al., 2005).

Many participants experienced known sources of trauma including childhood abuse and intimate partner violence, but the association between discrimination experiences and PTSD symptoms existed after statistically adjusting for these. Further, the magnitude of the association between discrimination and PTSD symptoms (β=0.25) was comparable to the magnitude of association between childhood abuse and PTSD symptoms (β=0.29), and exceeded the magnitude of association between intimate partner violence and PTSD symptoms (β=0.18). In other words, discrimination experiences were associated with PTSD symptoms regardless of reporting of other known traumatic experiences. These findings point to the importance of identifying mechanisms that explain associations between discrimination and PTSD symptoms, including both interpersonal and intrapersonal pathways (Hatzenbuehler, Nolen-Hoeksema, & Dovidio, 2009). For example, prior evidence suggests that emotion dysregulation (i.e., difficulty monitoring, evaluating, and modifying

emotional reactions) mediates associations between daily experiences of discrimination and subsequent daily depressive symptoms (Hatzenbuehler, et al., 2009) and explains evaluated PTSD symptoms in several samples (Bowleg et al., 2014).

In addition, a greater number of domains attributed to discrimination was independently associated with higher levels of PTSD symptoms in the present study, suggesting that co-occurrence of stigmatized minority statuses may be associated with greater exposure to discrimination, as well as more PTSD symptoms. Findings are consistent with the view that an individual's health cannot be fully understood by examining isolated systems of social oppression (Crenshaw, 1991). Individuals hold multiple co-existing identities, typically experienced as a unified self (Crenshaw, 1991; Hembree et al., 2009); however possessing multiple stigmatized identities might increase the chances of experiencing discrimination toward any one of those identities (Stuber et al., 2003). Thus, individuals who experience multiple forms of discrimination may be at high risk of poor mental health as a result of their disproportionate exposure to social oppressions, which can diminish coping resources and may exacerbate PTSD symptoms (Cole, 2009; Mizock & Mueser, 2014). These results are particularly important in light of research that suggests coping with cumulative stressors is associated with wear and tear on biological systems, termed "allostatic load" (Geronimus, 1992; McEwen & Stellar, 1993). These findings highlight the importance of examining multiple forms of discrimination, rather than a singular stressor, in the mental health of transgender people.

Gender affirmation—an interpersonal process through which a person's gender identity is socially recognized—has been theorized as a key determinant of health for transgender people of color (Sevelius, 2013). This study found that gender affirmation processes are important to consider in understanding PTSD symptoms in transgender people more broadly. Consistent with prior research (Bockting, et al., 2013; Grant, 2011), visibly gender nonconforming participants in the present study had significantly higher discrimination scores. No similar differences in discrimination were found for either social transition (i.e., living full-time) or medical gender affirmation (i.e., hormones and/or surgery). However, high visual gender nonconformity and social transition were each associated with increased PTSD symptoms. Medical gender affirmation was significantly protective and associated with significantly decreased PTSD symptoms, which is consistent with prior research showing that medical gender affirmation is associated with positive mental health outcomes in transgender people (Colizzi, Costa, & Todarello, 2014; Gómez-Gil et al., 2012; Keo-Meier et al., 2014; E. C. Wilson, Chen, Arayasirikul, Wenzel, & Raymond, 2015).

Of note, other known social determinants of health were also associated with PTSD symptoms in this sample, including younger age (Chiu, deRoon-Cassini, & Brasel, 2011). An interesting gender difference emerged: MTFs had significantly higher PTSD scores than FTMs. This difference is consistent with U.S. general population data showing approximately two-fold increased risk for PTSD in females than males (e.g., Tolin & Foa, 2006); however, conflation of sex and gender in much epidemiologic research (Krieger, 2003) makes the sex- and gender-linked pathways shaping differences in psychiatric conditions difficult to interpret (Tolin & Foa, 2006). Unstable housing was associated with elevated PTSD symptoms, supporting low socioeconomic status as a risk factor (Bender,

Ferguson, Thompson, Komlo, & Pollio, 2010). Additionally, childhood abuse, intimate partner violence, depression, and polydrug use statistically predicted PTSD symptoms in this sample, supporting known PTSD-specific psychosocial risk factors in the U.S. general population for transgender people (Balan et al., 2013; O'Donnell, Creamer, & Pattison, 2014; Ullman, Relyea, Peter-Hagene, & Vasquez, 2013).

Several limitations must be noted. As a cross-sectional study, findings demonstrate associations only; causality cannot be inferred. The presence of "Criterion A" or the "stressor criterion" (Breslau & Kessler, 2001) was not necessary for inclusion in this study, nor a prerequisite for assessment of PTSD symptoms. Given that 90% or more of the general population will experience a traumatic event in their lifetime (Breslau & Kessler, 2001; Breslau et al., 1998), assessment of traumatic exposure was excluded from the screening items (Prins, et al., 2003). The brief screening assessment for PTSD symptoms used in this study was designed for primary care settings, not for research purposes. Discrimination and PTSD symptoms were both self-reported subjective measures. Future research utilizing objective measures (e.g., clinician-assessed PTSD diagnosis) is needed to circumvent the possibility that self-reported discrimination experiences are confounded with mental health status (Meyer, 2003a). In addition, future mixed-methods research to explore the attributed reasons (e.g., sex, gender, race) for discrimination would make a valuable contribution. For example, the most frequent reason attributed to discrimination experiences was gender identity and/or expression; however, more than half of the sample reported experiencing discrimination due to sex. A more in-depth understanding of transgender experiences and perceptions regarding sex- and gender-based discrimination is warranted. There is substantial heterogeneity of trauma responses (Bonanno & Mancini, 2012), which the current study was not designed to assess. Future studies would benefit from considering transgender identity formation alongside gender affirmation (Devor, 2004). Children or adolescents may be abused because of discrimination related to their gender nonconforming presentation (Grossman & Howell, 2005); similarly, intimate partner violence may occur due to discrimination related to a partner's transgender status (Ard & Makadon, 2011; Brennan et al., 2012; Stotzer, 2009). Thus, childhood abuse and intimate partner violence can be driven by discrimination and may therefore not be necessarily distinct from it. Although the items for childhood abuse and intimate partner violence have been used in prior research (Reisner, et al., 2013), their brief single-item nature could be improved in future research by utilizing screeners with established psychometric properties.

Despite the limitations, our findings have implications for treatment interventions. (Maguen, Shipherd, & Harris, 2005). Considering everyday experiences of multiple forms of discrimination in PTSD treatment represents a critical aspect of clinical care for traumatized transgender people. Integrating evidenced-based treatments for PTSD, such as cognitive behavioral interventions (Forneris et al., 2013; Kar, 2011; Maguen, et al., 2005; Resick, Nishith, Weaver, Astin, & Feuer, 2002), with gender minority stress models (Hendricks & Testa, 2012) will ensure cultural responsiveness of interventions to meet the unique needs of transgender communities. Coping resources can act as a buffer against discrimination (Thoits, 1991); thus, skills-focused coping may represent an important component of clinical intervention. Given that only a minority of individuals who experience traumatic stressors develop PTSD symptomatology (Yehuda & McFarlane, 1995) and that the majority of

transgender individuals demonstrate resilience in a context of pervasive societal oppressions (Mizock & Lewis, 2008), uncovering the biopsychosocial mechanisms underlying vulnerability to and protection against PTSD represents a key future research direction with this population. Given that online respondents had statistically significantly lower discrimination and PTSD symptom scores relative to those completing the survey in-person, community efforts that engage transgender people "face-to-face" represent an important way of transgender people at-risk social stress and PTSD symptomatology.

Acknowledgments

Acknowledgements and Credits: We wish to thank our participants, outreach consultants (Lorelei Erisis, Maria Roman), and community partners: Massachusetts Transgender Political Coalition (MTPC) (Jesse Begenyi, Mason Dunn, Gunner Scott, Devyn Shea); Boston Medical Center Health Care for the Homeless (Pam Klein, Rebecca Thal); Network/La Red (Tre'Andre Valentine); AIDS Project Worcester (Jesse Pack); Boston Glass (Tharyn Grant); Fenway staff (Emilia Dunham, Julia Coffey-Esquivel, Amaya Perez-Brumer, Angela Robertson, Nelisa Rash, Layla Stamper, Dana Pardee, Justice Williams, Anum Awan).

Funding: This project was partly supported with funding from the Miller Foundation and Fenway. Dr. Reisner is partly supported by grant NIMH R01MH094323; Ms. White by NIMH T32MH020031 and P30MH062294; Dr. Gamarel by NIMH T32MH078788; Dr. Keuroghlian by the Kraft Family National Center for Leadership & Training in Community Health. Funding sources had no role in study design, collection, data analysis and interpretation, article writing, or decision to submit for publication.

References

Allison PD. Missing data techniques for structural equation modeling. Journal of Abnormal Psychology. 2003; 112(4):545–557. [PubMed: 14674868]

Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D. American Journal of Preventive Medicine. 1994; 10(2):77–84. [PubMed: 8037935]

APA. Diagnostic and Statistical Manual of Mental Misorders, (DSM-5®). Washington, DC: American Psychiatric Publishing; 2013.

Ard KL, Makadon HJ. Addressing intimate partner violence in lesbian, gay, bisexual, and transgender patients. Journal of General Internal Medicine. 2011; 26(8):930–933. [PubMed: 21448753]

Balan S, Widner G, Shroff M, van den Berk-Clark C, Scherrer J, Price RK. Drug use disorders and post-traumatic stress disorder over 25 adult years: Role of psychopathology in relational networks. Drug and Alcohol Dependence. 2013; 133(1):228–234. [PubMed: 23726975]

Basile, K.; Hertz, M.; Back, S. Intimate partner violence and sexual violence victimization assessment instruments for use in healthcare settings: version 1. 2007. Retrieved October 18, 2015, from http://www.cdc.gov/violenceprevention/pdf/ipv/ipvandsvscreening.pdf

Bender K, Ferguson K, Thompson S, Komlo C, Pollio D. Factors associated with trauma and posttraumatic stress disorder among homeless youth in three US cities: The importance of transience. Journal of Traumatic Stress. 2010; 23(1):161–168. [PubMed: 20146399]

Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. Journal of Traumatic Stress. 1995; 8(1):75–90. [PubMed: 7712061]

Bockting WO, Miner MH, Romine RE, Hamilton A, Coleman E. Stigma, mental health, and resilience in an online sample of the US transgender population. American Journal of Public Health. 2013; 103(5):943–951. [PubMed: 23488522]

Bonanno GA, Mancini AD. Beyond resilience and PTSD: Mapping the heterogeneity of responses to potential trauma. Journal of Psychological Trauma. 2012; 4(1):74–83.

Bowleg L, Fitz CC, Burkholder GJ, Massie JS, Wahome R, Teti M, Tschann JM. Racial discrimination and posttraumatic stress symptoms as pathways to sexual HIV risk behaviors among urban Black heterosexual men. AIDS care. 2014; 26(8):1050–1057. [PubMed: 24797317]

Bradley KL, Bagnell AL, Brannen CL. Factor validity of the Center for Epidemiological Stuies Depression 10 in adolescents. Issues Ment Health Nurs. 2010; 31(6):408–412. [PubMed: 20450343]

Brennan J, Kuhns LM, Johnson AK, Belzer M, Wilson EC, Garofalo R. Syndemic theory and HIV-related risk among young transgender women: the role of multiple, co-occurring health problems and social marginalization. American Journal of Public Health. 2012; 102(9):1751–1757. [PubMed: 22873480]

Breslau N, Kessler RC. The stressor criterion in DSM-IV posttraumatic stress disorder: an empirical investigation. Biological Psychiatry. 2001; 50(9):699–704. [PubMed: 11704077]

Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. Archives of General Psychiatry. 1998; 55(7):626–632. [PubMed: 9672053]

Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. Journal of Consulting and Clinical Psychology. 2000; 68(5):748. [PubMed: 11068961]

Carpenter J, Andrykopwski M, Wilson J, Hall LA, Rayens MK, Sachs B, Cunningham L. Psychometrics for two short forms of the Centre for Epidemiological Studies-Depression Scale. Issues in Mental Health Nursing. 1998; 19:481–494. [PubMed: 9782864]

Carter RT, Forsyth J. Reactions to racial discrimination: Emotional stress and help-seeking behaviors. Journal of Psychological Trauma. 2010; 2(3):183.

CDC. Behavioral Risk Factor Surveillance System Survey Questionnaire. Atlanta, GA: Centers for Disease Control and Prevention; 2012.

Chiu KB, deRoon-Cassini TA, Brasel KJ. Factors identifying risk for psychological distress in the civilian trauma population. Academic Emergency Medicine. 2011; 18(11):1156–1160. [PubMed: 22044521]

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. Journal of Homosexuality. 2006; 51(3):53–69. [PubMed: 17135115]

Cohen, J. Statistical Power Analysis for the Behavioral Sciences, 2nd Edition. 2. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc; 1988.

Cole ER. Intersectionality and research in psychology. American Psychologist. 2009; 64(3):170. [PubMed: 19348518]

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: Results from a longitudinal study. Psychoneuroendocrinology. 2014; 39:65–73. [PubMed: 24275005]

Crenshaw K. Mapping the margins: Intersectionality, identity politics, and violence against women of color. Stan L Rev. 1991:1241–1299.

Daley A, Solomon S, Newman PA, Mishna F. Traversing the margins: Intersectionalities in the bullying of lesbian, gay, bisexual, and transgender youth. Gay and Lesbian Social Services. 2008; 19(3–4)

de Vries KM. Intersectional identities and conceptions of the self: The experiences of transgender people. Symbolic Interaction. 2014; 35(1):49–67.

Devor AH. Witnessing and mirroring: A fourteen stage model of transsexual identity formation. Journal of Gay & Lesbian Mental Health. 2004; 8:41–67.

Diaz RM, Ayala G, Bein E, Henne J, Marin BV. The impact of homophobia, poverty, and racism on the mental health of gay and bisexual Latino men: Findings from 3 US cities. American Journal of Public Health. 2001; 91(6):927. [PubMed: 11392936]

Forneris CA, Gartlehner G, Brownley KA, Gaynes BN, Sonis J, Coker-Schwimmer E, Woodell CL. Interventions to prevent post-traumatic stress disorder: a systematic review. American Journal of Preventive Medicine. 2013; 44(6):635–650. [PubMed: 23683982]

Gamarel KE, Reisner SL, Laurenceau JP, Nemoto T, OPerario D. Gender minority stress, mental heath, and relationship quality: A dyadic investigation of transgener women and their cisgender male partners. Journal of Family Psychology. 2014; 28(4):437–447. [PubMed: 24932942]

Gamarel KE, Reisner SL, Parsons JT, Golub SA. Association between socioeconomic position discrimination and psychological distress: Findngs from a community-based sample of gay and bisexual men in New York City. American Journal of Public Health. 2012; 102(11):2094–2101. [PubMed: 22994188]

Gamarel KE, Walker JJ, Rivera L, Golub SA. Identity safety and relational health in youth spaces: A needs assessment with LGBTQ youth of color. LGBT Youth. 2014; 11(3):289–314.

Geronimus AT. The weathering hypothesis and the health of African-American women and infants: evidence and speculations. Ethn Dis. 1992; 2(3):207–221. [PubMed: 1467758]

Golding JM. Intimate partner violence as a risk factor for mental disorders: A meta-analysis. Journal of Family Violence. 1999; 14(2):99–132.

Golub SA, Gamarel KE. The impact of anticipated HIV stigma on delays in HIV testing behaviors: Findings from a community-based sample of men who have sex with men and transgender women in New York City. AIDS Patient Care and STDs. 2013; 27(11):621–627. [PubMed: 24138486]

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Almaraz MC, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012; 37(5):662–670. [PubMed: 21937168]

Gordon AR, Meyer IH. Gender nonconformity as a target of prejudice, discrimination, and violence against LGB individuals. Journal of LGBT Health Research. 2008; 3(3):55–71. [PubMed: 19042905]

Grant, JM.; Mottet, Lisa A.; Tanis, Justin; Harrison, Jack; Herman, Jody L.; Keisling, Mara. Injustice at Every Turn: A Report of the National Transgender Discrimination Survey. Washington, DC: National Center for Transgender Equality and National Gay and Lesbian Task Force; 2011.

Grollman EA. Multiple forms of perceived discrimination and health among adolescents and young adults. Journal of Health and Social Behavior. 2012; 53(2):199–214. [PubMed: 22588219]

Grossman AH, Howell TJ. Parents' Reactions to Transgender Youths' Gender Nonconfonning Expression and Identity. Journal of Gay & Lesbian Social Services. 2005; 18:1.

Hatzenbuehler ML, McLaughlin KA. Structural Stigma and Hypothalamic–Pituitary–Adrenocortical Axis Reactivity in Lesbian, Gay, and Bisexual Young Adults. Annals of Behavioral Medicine. 2014; 47(1):39–47. DOI: 10.1007/s12160-013-9556-9 [PubMed: 24154988]

Hatzenbuehler ML, Nolen-Hoeksema S, Dovidio J. How does stigma "get under the skin"? The mediating role of emotion regulation. Psychological Science. 2009; 20(10):1282–1289. [PubMed: 19765237]

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Montori VM. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2009; 94(9):3132–3154. [PubMed: 19509099]

Hendricks ML, Testa RJ. A conceptual framework for clinical work with transgender and gender nonconforming clients: An adaptation of the Minority Stress Model. Professional Psychology Research and Practice. 2012; 43(5):460.

Hulme PA. Retrospective measurement of childhood sexual abuse: A review of instruments. Child Maltreatment. 2004; 9(2):201–217. [PubMed: 15104889]

Jones, EE.; Farina, A.; Hastorf, AH.; French, RdS. Social Stigma: The Psychology of Marked Relationships. New York, NY: WH Freeman; 1984.

Jou YJ, Huang CCL, Cho HJ. A VIF-based optimization model to alleviate collinearity problems in multiple linear regression. Computational Statistics. 2014; 29(6):1515–1541.

Kar N. Cognitive behavioral therapy for the treatment of post-traumatic stress disorder: a review. Journal of Neuropsychiatric Disease and Treatment. 2011; 7:167. [PubMed: 21552319]

Keo-Meier CL, Herman LI, Reisner SL, Pardo ST, Sharp C, Babcock JC. Testosterone Treatment and MMPI–2 Improvement in Transgender Men: A Prospective Controlled Study. Journal of Consulting and Clinical Psychology. 2014; 83(1):43.

Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry. 2000; 61(Suppl 5):4–12. discussion 13–14. [PubMed: 10761674]

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry. 2005; 62(6):593–602. [PubMed: 15939837]

Krieger N. Genders, sexes, and health: what are the connections—and why does it matter? International Journal of Epidemiology. 2003; 32(4):652–657. [PubMed: 12913047]

Krieger N, Smith K, Naishadham D, Hartman C, Barbeau EM. Experiences of discrimination: validity and reliability of a self-report measure for population health research on racism and health. Social Science and Medicine. 2005; 61(7):1576–1596. DOI: 10.1016/j.socscimed.2005.03.006 [PubMed: 16005789]

Landrine H, Klonoff EA. The schedule of racist events: A measure of racial discrimination and a study of its negative physical and mental health consequences. Journal of Black Psychology. 1996; 22(2):144–168.

Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. American Journal of Epidemiology. 2010; 171(5):624–632. [PubMed: 20106935]

Leung MW, Yen IH, Minkler M. Community based participatory research: a promising approach for increasing epidemiology's relevance in the 21st century. International Journal of Epidemiology. 2004; 33(3):499–506. [PubMed: 15155709]

Lombardi EL. Varieties of transgender/transsexual lives and their relationship with transphobia. Journal of Homosexuality. 2009; 56(8):977–992. [PubMed: 19882422]

Lombardi EL, Wilchins RA, Priesing D, Malouf D. Gender violence: Transgender experiences with violence and discrimination. Journal of Homosexuality. 2002; 42(1):89–101. [PubMed: 11991568]

Maguen S, Lucenko BA, Reger MA, Gahm GA, Litz BT, Seal KH, Marmar CR. The impact of reported direct and indirect killing on mental health symptoms in Iraq war veterans. Journal of Traumatic Stress. 2010; 23(1):86–90. [PubMed: 20104592]

Maguen S, Shipherd JC, Harris HN. Providing culturally sensitive care for transgender patients. Cognitive and Behavioral Practice. 2005; 12:479–490.

Mason MJ, Mennis J, Schmidt CD. A social operational model of urban adolescents' tobacco and substance use: A mediational analysis. Journal of Adolescence. 2011; 34(5):1055–1063. [PubMed: 21144577]

McAdams DP. The case for unity in the (post) modern self. Self and Identity: Fundamental Issues. 1997; 1:46–78.

McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. Archives of Internal Medicine. 1993; 153(18):2093–2101. [PubMed: 8379800]

McFarlane J, Parker B, Soeken K, Bullock L. Assessing for abuse during pregnancy: severity and frequency of injuries and associated entry into prenatal care. JAMA. 1992; 267(23):3176–3178. [PubMed: 1593739]

Meyer IH. Prejudice as stress: conceptual and measurement problems. American Journal of Public Health. 2003a; 93(2):262–265. [PubMed: 12554580]

Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychological Bulletin. 2003b; 129(5):674. [PubMed: 12956539]

Meyer IH. Identity, stress, and resilience in lesbians, gay men, and bisexuals of color. The Counseling Psychologist. 2010; 38(3):442–454.

Meyer IH. Prejudice, Social Stress, and Mental Health in Lesbian, Gay, and Bisexual Populations. Psychology of Sexual Orientation and Gender Diversity. 2013; 1:3–26.

Miner MH, Bockting WO, Romine RS, Raman S. Conducting Internet research with the transgender population: Reaching broad samples and collecting valid data. Social Science Computer Review. 2011; 30(2):202. [PubMed: 24031157]

Mizock L, Lewis TK. Trauma in transgender populations: Risk, resilience, and clinical care. Journal of Emotional Abuse. 2008; 8(3):335–354.

Mizock L, Mueser K. Employment, mental health, internalized stigma, and coping with transphobia among transgender individuals. Psychology of Sexual Orientation and Gender Diversity. 2014; 1(2):146–158.

O'Donnell ML, Creamer M, Pattison P. Posttraumatic stress disorder and depression following trauma: understanding comorbidity. American Journal of Psychiatry. 2014; 161(8):1390. [PubMed: 15285964]

Ouimette P, Wade M, Prins A, Schohn M. Identifying PTSD in primary care: comparison of the Primary Care-PTSD screen (PC-PTSD) and the General Health Questionnaire-12 (GHQ). Journal of Anxiety Disorders. 2008; 22(2):337–343. [PubMed: 17383853]

Pachankis JE, Goldfried MR, Ramrattan ME. Extension of the rejection sensitivity construct to the interpersonal functioning of gay men. Journal of Consulting and Clinical Psychology. 2008; 76(2): 306. [PubMed: 18377126]

Pascoe EA, Richman LS. Perceived Discrimination and Health: A Meta-Analytic Review. Psychological Bulletin. 2009; 135(4):531–554. DOI: 10.1037/a0016059 [PubMed: 19586161]

Prins A, Ouimette P, Kimerling R, Cameron RP, Hugelshofer DS, Shaw-Hegwer J, Sheikh JI. The primary care PTSD screen (PC-PTSD): Development and operating characteristics. Primary Care Psychiatry. 2003; 9(1):9–14.

Prins A, Ouimette P, Kimerling R, Cameron RP, Hugelshofer DS, Shaw-Hegwer J, Sheikh JI. The primary care PTSD screen (PC-PTSD): Corrigendum. Primary Care Psychiatry. 2004; 9:151.

Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psych Meas. 1977; 1:385–401.

Reisner SL, Bailey Z, Sevelius J. Racial/ethnic disparities in history of incarceration, experiences of victimization, and associated health indicators among transgender women in the US. Women & Health. 2014; 54(8):75.

Reisner SL, Conron K, Scout N, Mimiaga MJ, Haneuse S, Austin SB. Comparing in-person and online survey respondents in the US National Transgender Discrimination Survey: implications for transgender health research. LGBT Health. 2014; 1(2):98–106. [PubMed: 26789619]

Reisner SL, Conron KJ, Tardiff LA, Jarvi S, Gordon AR, Austin SB. Monitoring the health of transgender and other gender minority populations: Validity of natal sex and gender identity survey items in a U.S. national cohort of young adults. BMC Public Health. 2014; 14:1224. [PubMed: 25427573]

Reisner SL, Falb KL, Wagenen AV, Grasso C, Bradford J. Sexual orientation disparities in substance misuse: the role of childhood abuse and intimate partner violence among patients in care at an urban community health center. Subst Use Misuse. 2013; 48(3):274–289. [PubMed: 23368669]

Reisner SL, Hughto JM, Dunham EE, Heflin KJ, Begenyi JB, Coffey-Esquivel J, Cahill S. Legal Protections in Public Accommodations Settings: A Critical Public Health Issue for Transgender and Gender-Nonconforming People. Milbank Quarterly. 2015; 93(3):484–515. [PubMed: 26219197]

Reisner SL, White JM, Bradford JB, Mimiaga MJ. Transgender Health Disparities: Comparing Full Cohort and Nested Matched-Pair Study Designs in a Community Health Center. LGBT Health. 2014; 1(3):177–184. [PubMed: 25379511]

Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA. A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. Journal of Consulting and Clinical Psychology. 2002; 70(4):867. [PubMed: 12182270]

Rowe C, Santos GM, McFarland W, Wilson EC. Prevalence and correlates of substance use among trans* female youth ages 16–24 years in the San Francisco Bay Area. Drug and Alcohol Dependence. 2015; 147:160–166. [PubMed: 25548025]

Sayer NA, Frazier P, Orazem RJ, Murdoch M, Gravely A, Carlson KF, Noorbaloochi S. Military to civilian questionnaire: a measure of postdeployment community reintegration difficulty among veterans using Department of Veterans Affairs medical care. Journal of Traumatic Stress. 2011; 24(6):660–670. [PubMed: 22162082]

Sevelius JM. Gender Affirmation: A Framework for Conceptualizing Risk Behavior among Transgender Women of Color. Sex Roles. 2013; 68(11–12):675–689. [PubMed: 23729971]

Shipherd JC, Maguen S, Skidmore WC, Abramovitz SM. Potentially traumatic events in a transgender sample: Frequency and associated symptoms. Traumatology. 2011; 17(2):56–67.

Singer JA. Narrative identity and meaning making across the adult lifespan: An introduction. Journal of Personality. 2004; 72(3):437–460. [PubMed: 15102034]

Stotzer RL. Violence against transgender people: A review of United States data. Aggression and Violent Behavior. 2009; 14(3):170–179.

Stuber J, Galea S, Ahern J, Blaney S, Fuller C. The Association between Multiple Domains of Discrimination and Self-assessed Health: A Multilevel Analysis of Latinos and Blacks in Four Low-Income New York City Neighborhoods. Health Services Research. 2003; 38(6 Pt 2):1735–1760. [PubMed: 14727795]

Swim, JK.; Thomas, MA. Responding to everyday discrimination: A synthesis of research on goal-directed, self-regulatory coping behaviors. In: Levin, S.; Laar, CV., editors. Stigma and Group Inequality. Mahwah, NJ: Erlbaum; 2006. p. 105-128.

Taylor TR, Kamarck TW, Shiffman S. Validation of the Detroit Area Study Discrimination Scale in a community sample of older African American adults: the Pittsburgh healthy heart project. Int J Behav Med. 2004; 11(2):88–94. [PubMed: 15456677]

Thoits, PA. The Social Context of Coping. New York, NY: Springer; 1991. Gender differences in coping with emotional distress; p. 107-138.

Tolin DF, Foa EB. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. Psychological Bulletin. 2006; 132(6):959. [PubMed: 17073529]

U.S. Department of Veteran's Affairs. PTSD: National Center for PTSD, Primary Care PTSD Screen (PC-PTSD). 2014. Retrieved October 6, 2014, from http://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp

Ullman SE, Relyea M, Peter-Hagene L, Vasquez AL. Trauma histories, substance use coping, PTSD, and problem substance use among sexual assault victims. Addictive Behaviors. 2013; 38(6):2219–2223. [PubMed: 23501138]

Valera RJ, Sawyer RG, Schiraldi GR. Perceived health needs of inner-city street prostitutes: A preliminary study. American Journal of Health Behavior. 2001; 25(1):50–59. [PubMed: 11289729]

van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Medical Res. 2007; 16(3):219–242.

van Buuren S, Brand JP, Groothuis-Oudshoorn C, Rubin DB. Fully conditional specification in multivariate imputation. J Stat Computation Simulation. 2006; 76(12):1049–1064.

Wharton, VW. Gender variance and mental health: A national survey of transgender trauma history, posttraumatic stress, and disclosure in therapy. Smith College; 2007.

Williams DR, Dolly JA, Oyserman D, Sonnega J, Mohammed SA, Jackson JS. Research on discrimination and health: An exloratory study of unresolved conceptual and meausrement issues. American Journal of Public Health. 2012; 102(5):975–978. [PubMed: 22420798]

Williams DR, Neighbors HW, Jackson JS. Racial/ethnic discrimination and health: Findings from community studies. American Journal of Public Health. 2003; 93(2):200–208. [PubMed: 12554570]

Williams DR, Yan Y, Jackson JS, Anderson NB. Racial Differences in Physical and Mental Health: Socio-economic Status, Stress and Discrimination. Journal of Health Psychology. 1997; 2(3): 335–351. DOI: 10.1177/135910539700200305 [PubMed: 22013026]

Wilson EC, Chen YH, Arayasirikul S, Wenzel C, Raymond HF. Connecting the Dots: Examining Transgender Women's Utilization of Transition-Related Medical Care and Associations with Mental Health, Substance Use, and HIV. Journal of Urban Health. 2015; 92(1):182–192. [PubMed: 25476958]

Wilson, MS. Violence and Mental Health in the Transgender Community. Ohio University; 2013.

Witten TM. Graceful exits: Intersection of aging, transgender identities, and the family/community. Journal of GLBT Family Studies. 2009; 5(1–2):35–61.

Xavier J. Passing as privilege. Part Two of a Series on Transfeminism. 1999

Yehuda R, McFarlane AC. Conflict between current knowledge about posttraumatic stress disorder and its original conceptual basis. American Journal of Psychiatry. 1995; 152(12):1705–1713. [PubMed: 8526234]

Zhang W, O'Brien N, Forrest JI, Salters KA, Patterson TL, Montaner JSG, Lima VD. Validating a shortened depression scale (10 item CES-) among HIV-positive people in British Columbia, Canada. PLoS ONE. 2012; 7(7):e40793. [PubMed: 22829885]

Table 1

Descriptive Statistics of Transgender Adults in Massachusetts (n=412)

	Mean (SD)	%	n
Outcome			
PTSD Symptom Scores (range 0–4)[+]			
Mean (SD)	1.95 (1.71)	--	412
Median (IQR)	2.00 (4.00)	--	412
Independent Variables			
Everyday Discrimination Scores (range 0–44)			
Mean (SD)	19.88 (9.58)	--	412
Median (IQR)	19.00 (13.00)	--	412
Number of Attributed Reasons for Discrimination Experiences			
Mean (SD) (range 0–14)	4.84 (2.39)	--	412
Median (IQR)	5.00 (3.00)	--	412
Covariates			
Childhood Abuse Age < 15 Years		46.6	192
Intimate Partner Violence		33.3	137
Depression (CESD Score 10+)		26.5	109
Substance Use, Past 12 Months (2 or More)		18.5	336
Age – Mean (SD) (range 18–72)	32.74 (12.79)	--	412
FTM Spectrum		62.6	258
Binary Gender Identity		59.7	246
Social Gender Transition (Live Full-Time)		76.9	317
Medical Gender Affirmation (Hormones and/or Surgery)		58.7	242
High Visual Nonconforming Gender Expression		21.6	89
People of Color (POC)		19.2	79
Socioeconomic Status			
Income (0–3)	1.39 (0.73)	--	412
Educational Attainment (1–4)	2.65 (0.97)	--	412
Unstably Housed		25.5	105
Sexual Minority (Lesbian/Gay/Bisexual/Queer/Other)		87.1	359
Online Survey Mode		87.9	362

[+]Note: 44.4% of the sample (n=183) met criteria for probable PTSD (score 3+)

Table 2

Reasons Attributed for Discrimination (14 Attributions) (n=412)

	%	n
Age	43.5	170
Sex	56.8	234
Race	11.9	49
Ethnicity	11.4	47
Nationality	5.8	24
Religion	13.4	55
Sexual Orientation	68.0	280
Disability	17.7	73
Education and/or Income	23.1	95
Weight	29.9	123
Gender Identity and/or Expression	83.2	343
How Masculine or Feminine You Appear	78.6	324
Other Appearance	30.1	124
Other Reason	10.6	44

Table 3

Linear Models Adjusted for Survey Mode Showing Associations Between PTSD Symptoms, Everyday Experiences of Discrimination, and Number of Reasons for Discrimination Among Transgender Adults in Massachusetts (n=412).

	PTSD Symptoms	Everyday Experiences of Discrimination	Number of Attributed Reasons for Discrimination
PTSD Symptoms	1.00		
Everyday Experiences of Discrimination	0.41 ***	1.00	
Number of Attributed Reasons for Discrimination	0.23 ***	0.38 ***	1.00

*** $p<0.0001$

Table 4

Multivariable Linear Models[+] Examining Everyday Experiences of Discrimination (Model 1) and PTSD Symptoms (Model 2) Among Transgender Adults in Massachusetts (n=412)

	Multivariable Model: Everyday Experiences of Discrimination		Multivariable Model: PTSD Symptoms	
	Beta (95% CL)	p-value	Beta (95% CL)	p-value
Independent Variables:				
Everyday Experiences of Discrimination	–	–	**0.25 (0.21, 0.30)**	**<0.0001**
Number of Attributed Reasons for Discrimination	**0.29 (0.25, 0.33)**	**<0.0001**	**0.05 (0.01, 0.10)**	**0.015**
Covariates:				
Physical and/or Sexual Abuse Age < 15 Years vs None	**0.31 (0.23, 0.39)**	**<0.0001**	**0.29 (0.21, 0.37)**	**<0.0001**
Intimate Partner Violence vs None	0.06 (−0.02, 0.14)	0.113	**0.18 (0.10, 0.26)**	**<0.0001**
Depression, Last 7 Days vs None	**0.44 (0.35, 0.53)**	**<0.0001**	**0.23 (0.14, 0.32)**	**<0.0001**
Polydrug Use, Last 12 Months (2+ Substances) vs 0/1 Substance	0.05 (−0.05, 0.15)	0.302	**0.13 (0.03, 0.23)**	**0.009**
Age (Continuous in Years)	0.01 (−0.03, 0.06)	0.521	**−0.17 (−0.21, −0.12)**	**<0.0001**
FTM Spectrum vs MTF Spectrum	**0.16 (0.06, 0.25)**	**0.001**	**−0.21 (−0.30, −0.11)**	**<0.0001**
Non-Binary Gender Identity vs Gender Binary Identity	**−0.14 (−0.23, −0.05)**	**0.003**	−0.03 (−0.13, 0.06)	0.493
Social Gender Transition (Live Full-Time) vs Not	0.07 (−0.03, 0.17)	0.167	**0.13 (0.03, 0.23)**	**0.014**
Medical Gender Affirmation (Hormones/Surgery) vs Not	0.03 (−0.06, 0.13)	0.459	**−0.10 (−0.19, −0.01)**	**0.043**
High Visual Gender Nonconformity vs Low/Moderate	**0.25 (0.16, 0.34)**	**<0.0001**	**0.17 (0.08, 0.27)**	**0.0003**
People of Color vs Non-White (Non-Hispanic)	**0.12 (0.02, 0.22)**	**0.016**	−0.05 (−0.15, 0.05)	0.312
Income (Continuous 0–3)	**−0.11 (−0.14, −0.07)**	**<0.0001**	−0.03 (−0.07, 0.01)	0.106
Educational Attainment (Continuous 1–4)	0.03 (−0.01, 0.07)	0.183	−0.02 (−0.07, 0.02)	0.262
Unstably Housed vs Stably Housed	**0.39 (0.30, 0.48)**	**<0.0001**	**0.24 (0.15, 0.33)**	**<0.0001**
Sexual Minority vs Heterosexual/Straight	**−0.12 (−0.23, −0.01)**	**0.034**	0.04 (−0.08, 0.15)	0.533
Online vs In-Person Survey Mode	**−0.30 (−0.43, −0.18)**	**<0.0001**	**−0.47 (−0.60, −0.34)**	**<0.0001**
R-Squared:	**0.323**		**0.296**	
F-Value:	**57.28**	**<0.0001**	**47.74**	**<0.0001**

[+]Z-scored variables: Everyday Discrimination Scale Scores, Number of Attributed Domains of Discrimination, PTSD Symptoms, Age.

UNITED STATES DISTRICT COURT

DISTRICT OF MARYLAND

JENNIFER ELLER, *Plaintiff*, v. PRINCE GEORGE'S COUNTY PUBLIC SCHOOLS, et al., *Defendants*.	Case Number: 18-cv-03649-TDC

[PROPOSED] ORDER GRANTING PLAINTIFF'S MOTION *IN LIMINE* TO EXCLUDE EXPERT TESTIMONY OF DR. MARCELLUS R. CEPHAS

Upon consideration of Plaintiff Jennifer Eller's motion *in limine* for an order to exclude expert testimony of Dr. Marcellus R. Cephas, it is hereby ORDERED:

1. That Plaintiff's motion *in limine* is GRANTED.

2. Dr. Marcellus R. Cephas's testimony is excluded.

_____
Date

_____
THEODORE D. CHUANG
United States District Judge