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Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 14 October 2020. See [summaries of product characteristics](#) (SPCs), [British National Formulary](#) (BNF) or the [Medicines and Healthcare products Regulatory Agency](#) (MHRA) or [NICE](#) websites for up-to-date information.

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1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria. The review follows the NHS England Specialised Commissioning process and template and is based on the criteria outlined in the PICO framework (see [appendix A](#)). This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people.

Gender dysphoria in children, also known as gender identity disorder or gender incongruence of childhood ([World Health Organisation 2020](#)), refers to discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves¹ regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics ([Diagnostic and Statistical Manual of Mental Disorders 2013](#)).

GnRH analogues suppress puberty by delaying the development of secondary sexual characteristics. The intention is to alleviate the distress associated with the development of secondary sex characteristics, thereby providing a time for on-going discussion and exploration of gender identity before deciding whether to take less reversible steps. In England, the GnRH analogue triptorelin (a synthetic decapeptide analogue of natural GnRH, which has marketing authorisations for the treatment of prostate cancer, endometriosis and precocious puberty [onset before 8 years in girls and 10 years in boys]) is used for this purpose. The use of triptorelin for children and adolescents with gender dysphoria is [off-label](#).

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual, and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, support young people and their families in managing the uncertainties inherent in gender identity development and provide on-going opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of GnRH analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex ([NHS England 2013](#)).

2. Executive summary of the review

Nine observational studies were included in the evidence review. Five studies were retrospective observational studies ([Brik et al. 2020](#), [Joseph et al. 2019](#), [Khatchadourian et al. 2014](#), [Klink et al. 2015](#), [Vlot et al. 2017](#)), 3 studies were prospective longitudinal observational studies ([Costa et al. 2015](#), [de Vries et al. 2011](#), [Schagen et al. 2016](#)) and 1 study was a cross-sectional study ([Staphorsius et al. 2015](#)). Two studies (Costa et al. 2015

¹ Gender refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men ([World Health Organisation, Health Topics: Gender](#)).

and Staphorsius et al. 2015) provided comparative evidence and the remaining 7 studies used within-person, before and after comparisons.

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Critical outcomes

The critical outcomes for decision making are the impact on gender dysphoria, mental health and quality of life. The quality of evidence for these outcomes was assessed as very low certainty using modified GRADE.

Impact on gender dysphoria

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect gender dysphoria (measured using the Utrecht Gender Dysphoria Scale [UGDS]). The mean (\pm SD) gender dysphoria (UGDS) score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [\pm 7.91] versus 53.9 [\pm 17.42], p=0.333).

Impact on mental health

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may reduce depression (measured using the Beck Depression Inventory-II [BDI-II]). The mean (\pm SD) BDI score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [\pm 7.12] versus 4.95 [\pm 6.72], p=0.004).

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anger (measured using the Trait Anger Scale [TPI]). The mean (\pm SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [\pm 5.54] versus 17.88 [\pm 5.24], p=0.503).

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anxiety (measured using the Trait Anxiety Scale [STAI]). The mean (\pm SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [\pm 10.07] versus 37.95 [\pm 9.38], p=0.276).

Impact on quality of life

No evidence was identified.

Important outcomes

The important outcomes for decision making are impact on body image, psychosocial impact, engagement with health care services, impact on extent of and satisfaction with surgery and stopping treatment. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on body image

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect body image (measured using the Body Image Scale [BIS]). The mean [\pm SD] body image (BIS) scores were not statistically significantly different from baseline compared with follow-up for primary sexual characteristics (n=57, 4.10 [\pm 0.56] versus 3.98 [\pm 0.71], p=0.145), secondary sexual characteristics (n=57, 2.74 [\pm 0.65] versus 2.82 [\pm 0.68], p=0.569) or neutral body characteristics (n=57, 2.41 [\pm 0.63] versus 2.47 [\pm 0.56], p=0.620).

Psychosocial impact

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may improve psychosocial impact over time (measured using the Children's Global Assessment Scale [CGAS]). The mean [\pm SD] CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [\pm 10.12] versus 73.90 [\pm 9.63], p=0.005).

This study also found that psychosocial functioning may improve over time (measured using the Child Behaviour Checklist [CBCL] and the self-administered Youth Self-Report [YSR]). The mean [\pm SD] CBCL scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 60.70 [\pm 12.76] versus 54.46 [\pm 11.23], p<0.001), internalising T score (n=54, 61.00 [\pm 12.21] versus 52.17 [\pm 9.81], p<0.001) and externalising T score (n=54, 58.04 [\pm 12.99] versus 53.81 [\pm 11.86], p=0.001). The mean [\pm SD] YSR scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 55.46 [\pm 11.56] versus 50.00 [\pm 10.56], p<0.001), internalising T score (n=54, 56.04 [\pm 12.49] versus 49.78 [\pm 11.63], p<0.001) and externalising T score (n=54, 53.30 [\pm 11.87] versus 49.98 [\pm 9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017).

The study by [Costa et al. 2015](#) in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that during treatment with GnRH analogues psychosocial impact in terms of global functioning may improve over time (measured using the CGAS). In the group receiving GnRH analogues, the mean [\pm SD] CGAS score was statistically significantly higher (improved) after 6 months (n=60, 64.70 [\pm 13.34]) and 12 months (n=35, 67.40 [\pm 13.39]) compared with baseline (n=101, 58.72 [\pm 11.38], p=0.003 and p<0.001, respectively). However, there was no statistically significant difference in global functioning (CGAS scores) between the group receiving GnRH analogues plus psychological support and the group receiving psychological support only at any time point.

The study by [Staphorsius et al. 2015](#) in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) gave mean [\pm SD] CBCL scores for each group, but statistical analysis is unclear (transfemales receiving GnRH analogues 57.4 [\pm 9.8], transfemales not receiving GnRH analogues 58.2 [\pm 9.3], transmales receiving GnRH analogues 57.5 [\pm 9.4], transmales not receiving GnRH analogues 63.9 [\pm 10.5]).

Engagement with health care services

The study by [Brik et al. 2018](#) in 143 children and adolescents with gender dysphoria receiving GnRH analogues found that 9 adolescents in the original sampling frame (9/214, 4.2%) were excluded from the study because they stopped attending appointments.

The study by [Costa et al. 2015](#) in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only had a large loss to follow-up over time. The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after 12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.

Impact on extent of and satisfaction with surgery

No evidence was identified.

Stopping treatment

The study by [Brik et al. 2018](#) in 143 children and adolescents with gender dysphoria receiving GnRH analogues reported the reasons for stopping GnRH analogues. During the follow-up period 6.2% (9/143) of adolescents had stopped GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability), although they wanted to continue treatments for gender dysphoria.

The study by [Khatchadourian et al. 2014](#) in 27 adolescents with gender dysphoria who started GnRH analogues reported the reasons for stopping them. Eleven out of 26 where data was available (42%) stopped GnRH analogues during follow up.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Evidence was available for bone density, cognitive development or functioning, and other safety outcomes. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Bone density

The study by [Joseph et al. 2019](#) in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density (measured with the z-score). However, the z-scores were largely within 1 standard deviation of normal,

and actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up:

- The mean z-score [\pm SD] for lumbar bone mineral apparent density (BMAD) was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [\pm 0.154], 1 year -0.228 [\pm 1.027], $p=0.000$) and transmales (baseline -0.186 [\pm 1.230], 1 year -0.541 [\pm 1.396], $p=0.006$).
- The mean z-score [\pm SD] for lumbar BMAD was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.486 [\pm 0.809], 2 years -0.279 [\pm 0.930], $p=0.000$) and transmales (baseline -0.361 [\pm 1.439], 2 years -0.913 [\pm 1.318], $p=0.001$).
- The mean z-score [\pm SD] for femoral neck bone mineral density (BMD) was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.0450 [\pm 0.781], 2 years -0.600 [\pm 1.059], $p=0.002$) and transmales (baseline -1.075 [\pm 1.145], 2 years -1.779 [\pm 0.816], $p=0.001$).

The study by [Klink et al. 2015](#) in 34 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar (transmales only), but not femoral bone density. However, the z-scores are largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from BMD measurements in transmales):

- The mean z-score [\pm SD] for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower when starting gender-affirming hormones in transmales (GnRH analogues 0.28 [\pm 0.90], gender-affirming hormones -0.50 [\pm 0.81], $p=0.004$).

The study by [Vlot et al. 2017](#) in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density. However, the z-scores were largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from in transmales with a bone age ≥ 14 years). This study reported change in bone density from starting GnRH analogues to starting gender-affirming hormones by bone age:

- The median z-score [range] for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues -0.20 [-1.82 to 1.18], gender-affirming hormones -1.52 [-2.36 to 0.42], $p=0.001$) but was not statistically significantly different in transfemales with a bone age ≥ 15 years.
- The median z-score [range] for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues -0.05 [-0.78 to 2.94], gender-affirming hormones -0.84 [-2.20 to 0.87], $p=0.003$) and in transmales with a bone age ≥ 14 years (GnRH analogues 0.27 [-1.60 to 1.80], gender-affirming hormones -0.29 [-2.28 to 0.90], $p\leq 0.0001$).

- The median z-score [range] for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues -0.71 [-3.35 to 0.37], gender-affirming hormones -1.32 [-3.39 to 0.21], $p \leq 0.1$) or in transfemales with a bone age ≥ 15 years (GnRH analogues -0.44 [-1.37 to 0.93], gender-affirming hormones -0.36 [-1.50 to 0.46]).
- The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues -0.01 [-1.30 to 0.91], gender-affirming hormone -0.37 [-2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥ 14 years (GnRH analogues 0.27 [-1.39 to 1.32], gender-affirming hormones -0.27 [-1.91 to 1.29], $p=0.002$).

Cognitive development or functioning

The study by [Staphorsius et al. 2015](#) in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) measured cognitive development or functioning (using an IQ test, and reaction time and accuracy measured using the Tower of London task):

- The mean (\pm SD) IQ in transfemales receiving GnRH analogues was 94.0 (\pm 10.3) and 109.4 (\pm 21.2) in the control group. In transmales receiving GnRH analogues the mean (\pm SD) IQ was 95.8 (\pm 15.6) and 98.5 (\pm 15.9) in the control group.
- The mean (\pm SD) reaction time in transfemales receiving GnRH analogues was 10.9 (\pm 4.1) and 9.9 (\pm 3.1) in the control group. In transmales receiving GnRH analogue it was 9.9 (\pm 3.1) and 10.0 (\pm 2.0) in the control group.
- The mean (\pm SD) accuracy score in transfemales receiving GnRH analogues was 73.9 (\pm 9.1) and 83.4 (\pm 9.5) in the control group. In transmales receiving GnRH analogues it was 85.7 (\pm 10.5) and 88.8 (\pm 9.7) in the control group.

No statistical analyses or interpretation of the results was reported.

Other safety outcomes

The study by [Schagen et al. 2016](#) in 116 adolescents with gender dysphoria found that GnRH analogues do not affect renal or liver function:

- There was no statistically significant difference between baseline and 1 year results for serum creatinine in transfemales, but there was a statistically significant decrease between baseline and 1 year in transmales ($p=0.01$).
- Glutamyl transferase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels did not significantly change from baseline to 12 months of treatment.

The study by [Khatchadourian et al. 2014](#) in 27 adolescents with gender dysphoria who started GnRH analogues narratively reported adverse effects from GnRH analogues in 26 adolescents:

- 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated
- 1 transmale developed leg pains and headaches, which eventually resolved
- 1 participant gained 19 kg within 9 months of starting GnRH analogues.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

No cost-effectiveness evidence was found for GnRH analogues in children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Some studies reported data separately for the following subgroups of children and adolescents with gender dysphoria: sex assigned at birth males (transfemales) and sex assigned at birth females (transmales). This included some direct comparisons of these subgroups, and differences were largely seen at baseline as well as follow up. No evidence was found for other specified subgroups.

Sex assigned at birth males (transfemales)

Impact on gender dysphoria

The study by [Costa et al. 2015](#) in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females. Sex assigned at birth males had a statistically significantly lower (improved) mean [\pm SD] UGDS score of 51.6 [\pm 9.7] compared with sex assigned at birth females (56.1 [\pm 4.3], $p < 0.001$), but it was not reported if this was at baseline or follow-up.

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females at baseline and follow up. The mean [\pm SD] UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean UGDS score: 47.95 [\pm 9.70] versus 56.57 [\pm 3.89]) and follow up (n=not reported, 49.67 [\pm 9.47] versus 56.62 [\pm 4.00]); between sex difference $p < 0.001$).

Impact on mental health

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males compared with sex assigned at birth females. Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression, but sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at baseline and follow up.

- The mean [\pm SD] depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BDI score [\pm SD]: 5.71 [\pm 4.31] versus 10.34 [\pm 8.24]) and follow-up (n=not reported, 3.50 [\pm 4.58] versus 6.09 [\pm 7.93]), between sex difference $p = 0.057$
- The mean [\pm SD] anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean TPI score [\pm SD]: 5.22 [\pm 2.76] versus 6.43 [\pm 2.78]) and follow-

up (n=not reported, 5.00 [\pm 3.07] versus 6.39 [\pm 2.59]), between sex difference $p=0.022$

- The mean [\pm SD] anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean STAI score [\pm SD]: 4.33 [\pm 2.68] versus 7.00 [\pm 2.36]) and follow-up (n=not reported, 4.39 [\pm 2.64] versus 6.17 [\pm 2.69]), between sex difference $p<0.001$.

Impact on body image

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that the impact on body image may be different in sex assigned at birth males compared with sex assigned at birth females. Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

- The mean [\pm SD] BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [\pm SD]: 4.02 [\pm 0.61] versus 4.16 [\pm 0.52]) and follow up (n=not reported, 3.74 [\pm 0.78] versus 4.17 [\pm 0.58]) between sex difference $p=0.047$.
- The mean [\pm SD] BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [\pm SD]: 2.66 [\pm 0.50] versus 2.81 [\pm 0.76]) and follow up (n=not reported, 2.39 [\pm 0.69] versus 3.18 [\pm 0.42]), between sex difference $p=0.001$.
- The mean [\pm SD] BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, 2.60 [\pm 0.58] versus 2.24 [\pm 0.62]), between sex difference $p=0.777$.

Psychosocial impact

The study by [Costa et al. 2015](#) in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that sex assigned at birth males had statistically significant lower mean [\pm SD] CGAS scores at baseline compared with sex assigned at birth females (n=201, 55.4 [\pm 12.7] versus 59.2 [\pm 11.8], $p=0.03$), but no conclusions could be drawn.

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth males compared with sex assigned at birth females, but no conclusions could be drawn.

- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females (at baseline or follow up) for the CBCL Total T score, the CBCL internalising T score, the YSR Total T score or the YSR internalising T score.

- Sex assigned at birth males had statistically higher mean [\pm SD] CGAS scores compared with sex assigned at birth females at baseline (n=54, 73.10 [\pm 8.44] versus 67.25 [\pm 11.06]) and follow up (n=54, 77.33 [\pm 8.69] versus 70.30 [\pm 9.44]), between sex difference p=0.021.
- Sex assigned at birth males had statistically lower mean [\pm SD] CBCL externalising T scores compared with sex assigned at birth females at baseline (n=54, 54.71 [\pm 12.91] versus 60.70 [\pm 12.64]) and follow up (n=54, 48.75 [\pm 10.22] versus 57.87 [\pm 11.66]), between sex difference p=0.015.
- Sex assigned at birth males had statistically lower mean [\pm SD] YSR externalising T scores compared with sex assigned at birth females at both baseline (n=54, 48.72 [\pm 11.38] versus 57.24 [\pm 10.59]) and follow up (n=54, 46.52 [\pm 9.23] versus 52.97 [\pm 8.51]), between sex difference p=0.004.

Bone density

The studies by [Joseph et al. 2019](#), [Klink et al. 2015](#) and [Vlot et al. 2017](#) provided evidence on bone density in sex assigned at birth males (see above for details).

Cognitive development or functioning

The study by [Staphorsius et al. 2015](#) provided evidence on cognitive development or functioning in sex assigned at birth males (see above for details).

Other safety outcomes

The study by [Schagen et al. 2016](#) provided evidence on renal function in sex assigned at birth males (see above).

Sex assigned at birth females (transmales)

Impact on gender dysphoria

The studies by [de Vries et al. 2011](#) and [Costa et al. 2015](#) found that gender dysphoria (measured using the UGDS) in sex assigned at birth females is higher than in sex assigned at birth males at baseline and follow up (see above for details).

Impact on mental health

The study by [de Vries et al. 2011](#) found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females compared with sex assigned at birth males. Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression, but sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at both baseline and follow up (see above for details).

Impact on body image

The study by [de Vries et al. 2011](#) found that the impact on body image may be different in sex assigned at birth females compared with sex assigned at birth males. Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different (see above for details).

Psychosocial impact

The studies by [de Vries et al. 2011](#) and [Costa et al. 2015](#) found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth females compared with sex assigned at birth males, but no conclusions could be drawn (see above for details).

Bone density

The studies by [Joseph et al. 2019](#), [Klink et al. 2015](#) and [Vlot et al. 2017](#) provided evidence on bone density in sex assigned at birth females (see above for details).

Cognitive development or functioning

The study by [Staphorsius et al. 2015](#) provided evidence on cognitive development or functioning in sex assigned at birth females (see above for details).

Other safety outcomes

The study by [Schagen et al. 2016](#) provided evidence on renal function in sex assigned at birth females (see above for details).

From the evidence selected:

- (a) **what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?**
- (b) **what were the ages at which participants commenced treatment with GnRH analogues?**
- (c) **what was the duration of treatment with GnRH analogues?**

All studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria that was in use at the time. In 5 studies ([Costa et al. 2015](#), [Klink et al. 2015](#), [Schagen et al. 2016](#), [Staphorsius et al. 2015](#) and [Vlot et al. 2017](#)) the DSM-fourth edition, text revision (IV-TR) criteria were used. The study by [Brik et al. 2020](#) used DSM-V criteria. It was not reported how gender dysphoria was defined in the remaining 3 studies.

The studies show variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.

Most studies did not report the duration of treatment with GnRH analogues ([Joseph et al. 2019](#), [Khatchadourian et al. 2014](#), [Vlot et al. 2017](#), [Costa et al. 2015](#), [de Vries et al. 2011](#), [Schagen et al. 2016](#)), but where this was reported ([Brik et al. 2020](#), [Klink et al. 2015](#), [Staphorsius et al. 2015](#)) there was a wide variation ranging from a few months to about 5 years.

Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using modified GRADE. They all reported physical and mental health comorbidities and concomitant treatments very poorly. All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

Many of the studies did not report statistical significance or confidence intervals. Changes in outcome scores for clinical effectiveness and bone density were assessed with regards to statistical significance. However, there is relatively little interpretation of whether the changes in outcomes are clinically meaningful.

In the observational, retrospective studies providing evidence on bone density, participants acted as their own controls and change in bone density was determined between starting GnRH analogues and follow up. Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time.

Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. The study by [de Vries et al. 2011](#) reported statistically significant reductions in the Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) scores from baseline to follow up, which include measures of distress. As the aim of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics, this may be an important finding. However, as the studies all lack appropriate controls who were not receiving GnRH analogues, any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the expected increase in bone density (which is expected during puberty). However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after they are stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
 - a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
 - b) what were the ages at which participants commenced treatment with GnRH analogues?
 - c) what was the duration of treatment with GnRH analogues?

See [appendix A](#) for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 23 July 2020.

See [appendix B](#) for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially

relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See [appendix C](#) for evidence selection details and [appendix D](#) for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See appendices [E](#) and [F](#) for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See [appendix G](#) for GRADE Profiles.

4. Summary of included studies

Nine observational studies were identified for inclusion. Five studies were retrospective observational studies ([Brik et al. 2020](#), [Joseph et al. 2019](#), [Khatchadourian et al. 2014](#), [Klink et al. 2015](#), [Vlot et al. 2017](#)), 3 studies were prospective longitudinal observational studies ([Costa et al. 2015](#), [de Vries et al. 2011](#), [Schagen et al. 2016](#)) and 1 study was a cross-sectional study ([Staphorsius et al. 2015](#)).

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase ‘people’s assigned sex at birth’ rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than ‘puberty blockers’ and gender-affirming hormones rather than ‘cross sex hormones’. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of these included studies and full details are given in [appendix E](#).

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Brik et al. 2020 Retrospective observational single-centre study Netherlands	The study was conducted at the Curium-Leiden University Medical Centre gender clinic in Leiden, the Netherlands and involved adolescents with gender dysphoria. The sample size was 143 adolescents (median age at start of treatment was 15.0 years, range 11.1 to 18.6 years in transfemales; 16.1 years, range 10.1 to 17.9 years in transmales) from a sampling frame of 269 children and adolescents registered at the clinic between November 2010 and January 2018.	Intervention 143 children and adolescents receiving GnRH analogues (no specific treatment, dose, route or frequency of administration reported). The median duration was 2.1 years (range 1.6–2.8 years). Comparison No comparator.	Critical Outcomes <ul style="list-style-type: none"> No critical outcomes reported Important outcomes <ul style="list-style-type: none"> Stopping treatment

Study	Population	Intervention and comparison	Outcomes reported
	<p>Participants were included in the study if they were diagnosed with gender dysphoria according to the DSM-5 criteria, registered at the clinic, were prepubertal and within the appropriate age range, and had started GnRH analogues. No concomitant treatments were reported.</p>		
<p>Costa et al. 2015</p> <p>Prospective longitudinal observational single centre cohort study</p> <p>United Kingdom</p>	<p>The study was conducted at the Gender Identity Development Service in London and involved adolescents with gender dysphoria. The sample size was 201 adolescents (mean [±SD] age 15.52±1.41 years, range 12 to 17 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean [±SD] age at the start of GnRH analogues was 16.48 [±1.26] years, range 13 to 17 years.</p> <p>Participants were invited to participate following a 6-month diagnostic process using DSM-IV-TR criteria. No concomitant treatments were reported.</p>	<p>Intervention</p> <p>101 adolescents assessed as being immediately eligible for GnRH analogues (no specific treatment, dose or route of administration reported) plus psychological support. The average duration of treatment was approximately 12 months (no exact figure given).</p> <p>Comparison</p> <p>100 adolescents assessed as not immediately eligible for GnRH analogues (more time needed to make the decision to start GnRH analogues) who had psychological support only. None received GnRH analogues throughout the study.</p>	<p>Critical Outcomes</p> <ul style="list-style-type: none"> • No critical outcomes reported <p>Important outcomes</p> <ul style="list-style-type: none"> • Psychosocial impact
<p>de Vries et al. 2011</p> <p>Prospective longitudinal observational single centre before and after study</p> <p>Netherlands</p>	<p>The study was conducted at the Amsterdam gender identity clinic of the VU University Medical Centre and involved adolescents who were defined as “transsexual”. The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008.</p> <p>Participants were invited to participate if they subsequently started gender-affirming hormones between 2003 and 2009. No diagnostic criteria or concomitant treatments were reported.</p>	<p>Intervention</p> <p>70 individuals assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported).</p> <p>Comparison</p> <p>No comparator.</p>	<p>Critical Outcomes</p> <ul style="list-style-type: none"> • Gender dysphoria • Mental health (depression, anger and anxiety) <p>Important outcomes</p> <ul style="list-style-type: none"> • Body image • Psychosocial impact

Study	Population	Intervention and comparison	Outcomes reported
<p>Joseph et al. 2019</p> <p>Retrospective longitudinal observational single centre study</p> <p>United Kingdom</p>	<p>This study was conducted at the Early intervention clinic at University College London Hospital (all participants had been seen at the Gender Identity Development Service in London) and involved adolescents with gender dysphoria. The sample size was 70 adolescents with gender dysphoria (no diagnostic criteria described) all offered GnRH analogues. The mean age at the start of treatment was 13.2 years (SD ± 1.4) for transfemales and 12.6 years (SD ± 1.0) for transmales. Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported. No concomitant treatments were reported.</p>	<p>Intervention GnRH analogues. No specific treatment, duration, dose or route of administration reported.</p> <p>Comparison No comparator.</p>	<p>Critical Outcomes</p> <ul style="list-style-type: none"> No critical outcomes reported <p>Important outcomes</p> <ul style="list-style-type: none"> Safety: bone density
<p>Khatchadourian et al. 2014</p> <p>Retrospective observational chart review single centre study</p> <p>Canada</p>	<p>This study was conducted at the Endocrinology and Diabetes Unit at British Columbia Children's Hospital, Canada and involved youths with gender dysphoria. The sample size was 27 young people with gender dysphoria who started GnRH analogues (at mean age 14.7 [SD ± 1.9] years) out of 84 young people seen at the unit between 1998 and 2011. Diagnostic criteria and concomitant treatments were not reported.</p>	<p>Intervention 84 young people with gender dysphoria. For GnRH analogues no specific treatment, duration, dose or route of administration reported.</p> <p>Comparison No comparator.</p>	<p>Critical Outcomes</p> <ul style="list-style-type: none"> No critical outcomes reported <p>Important outcomes</p> <ul style="list-style-type: none"> Stopping treatment Safety: adverse effects
<p>Klink et al. 2015</p> <p>Retrospective longitudinal observational single centre study</p> <p>Netherlands</p>	<p>This study was conducted in the Netherlands at a tertiary referral centre. It is unclear which centre this was. The sample size was 34 adolescents (mean age 14.9 [SD ± 1.9] years for transfemales and 15.0 [SD ± 2.0] years for transmales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.</p>	<p>Intervention The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones with discontinuation of GnRH analogues after gonadectomy. Duration of GnRH analogues was 1.3 years (range 0.5 to 3.8 years) in transfemales and 1.5 years (0.25 to 5.2 years) in transmales.</p> <p>Comparison No comparator.</p>	<p>Critical Outcomes</p> <ul style="list-style-type: none"> No critical outcomes reported <p>Important outcomes</p> <ul style="list-style-type: none"> Safety: bone density

Study	Population	Intervention and comparison	Outcomes reported
<p>Schagen et al. 2016</p> <p>Prospective longitudinal study</p> <p>Netherlands</p>	<p>This study was conducted at the Centre of Expertise on Gender Dysphoria at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 116 adolescents (median age [range] 13.6 years [11.6 to 17.9] in transfemales and 14.2 years [11.1 to 18.6] in transmales during first year of GnRH analogues) out of 128 adolescents who started GnRH analogues.</p> <p>Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were reported.</p>	<p>Intervention</p> <p>The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg at 0, 2 and 4 weeks followed by intramuscular injections every 4 weeks, for at least 3 months).</p> <p>Comparison</p> <p>No comparator.</p>	<p>Critical Outcomes</p> <ul style="list-style-type: none"> No critical outcomes reported <p>Important outcomes</p> <ul style="list-style-type: none"> Safety: liver and renal function.
<p>Staphorsius et al. 2015</p> <p>Cross-sectional (single time point) assessment single centre study</p> <p>Netherlands</p>	<p>This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 85, of whom 40 were adolescents with gender dysphoria (20 of whom were being treated with GnRH analogues) and 45 were controls without gender dysphoria (not further reported here). Mean (\pmSD) age 15.1 (\pm2.4) years in transfemales and 15.8 (\pm1.9) years in transmales. Details of the sampling frame are not reported.</p> <p>Participants were included if they were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with measurable oestradiol and testosterone levels in girls and boys, respectively. No concomitant treatments were reported.</p>	<p>Intervention</p> <p>The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously or intramuscularly). The mean duration of treatment was 1.6 years (SD \pm1.0).</p> <p>Comparison</p> <p>Adolescents with gender dysphoria not treated with GnRH analogues.</p>	<p>Critical Outcomes</p> <ul style="list-style-type: none"> No critical outcomes reported <p>Important outcomes</p> <ul style="list-style-type: none"> Psychosocial impact Safety: cognitive functioning
<p>Vlot et al. 2017</p> <p>Retrospective observational data analysis study</p> <p>Netherlands</p>	<p>This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 70 adolescents (median age [range] 15.1 years [11.7 to 18.6] for transmales and 13.5 years [11.5 to</p>	<p>Intervention</p> <p>The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously).</p> <p>Comparison</p> <p>No comparator.</p>	<p>Critical Outcomes</p> <ul style="list-style-type: none"> No critical outcomes reported <p>Important outcomes</p>

Study	Population	Intervention and comparison	Outcomes reported
	18.3] for transfemales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were receiving GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported.		<ul style="list-style-type: none"> Safety: bone density
Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; GnRH, Gonadotrophin releasing hormone; SD, Standard deviation.			

5. Results

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
<p>Impact on gender dysphoria</p> <p>Certainty of evidence: very low</p>	<p>This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning.</p> <p>One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on gender dysphoria in adolescents, measured using the Utrecht Gender Dysphoria Scale (UGDS). The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria.</p> <p>The study measured the impact on gender dysphoria at 2 time points:</p> <ul style="list-style-type: none"> before starting a GnRH analogue (mean [\pmSD] age: 14.75 [\pm1.92] years), and shortly before starting gender-affirming hormones (mean [\pmSD] age: 16.64 [\pm1.90] years). <p>The mean (\pmSD) UGDS score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [\pm7.91] versus 53.9 [\pm17.42], p=0.333) (VERY LOW).</p> <p>This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect gender dysphoria.</p>

<p>Impact on mental health: depression</p> <p>Certainty of evidence: very low</p>	<p>This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person.</p> <p>One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria. Depression was measured using the Beck Depression Inventory-II (BDI-II). The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.</p> <p>The study provided evidence for depression measured at 2 time points:</p> <ul style="list-style-type: none"> • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). <p>The mean (±SD) depression (BDI) score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [±6.72], p=0.004) (VERY LOW).</p> <p>This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, may reduce depression.</p>
<p>Impact on mental health: anger</p> <p>Certainty of evidence: very low</p>	<p>This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person.</p> <p>One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anger in children and adolescents with gender dysphoria. Anger was measured using the Trait Anger Scale of the State-Trait Personality Inventory (TPI). This is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger.</p> <p>The study provided evidence for anger measured at 2 time points:</p> <ul style="list-style-type: none"> • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). <p>The mean (±SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503) (VERY LOW).</p> <p>This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect anger.</p>
<p>Impact on mental health: anxiety</p>	<p>This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person.</p>