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Evidence Check

Evidence for effective interventions for children and young people with gender dysphoria

An Evidence Check rapid review brokered by the Sax Institute for the NSW Ministry of Health—September 2020.

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This report was prepared by: Cathy Watson, Sandra Davidson, Siobhan Bourke, Louise Bourchier, Meredith Temple-Smith and Lena Sanci.

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Contents

List of abbreviations

ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BC	bicalutamide
BMAD	bone mineral apparent density
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CA	cyproterone acetate
CASP	Critical Appraisal Skills Program
CGAS	Children's Global Assessment Scale
CSHT	cross-sex hormone treatment
DXA	dual-energy X-ray absorptiometry
ED	eating disorder
FA	fractional anisotropy
FN	femoral neck
FP	fertility preservation
FSH	follicle-stimulating hormone
GAHT	gender-affirming hormone therapy
GD	gender dysphoria
GICT	gender identity conversion therapy [GICT],
GID	gender identity disorder
GnRH	gonadotropin-releasing hormone
GnRHa	gonadotropin-releasing hormone agonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRS	gender reassignment surgery
Hb	haemoglobin
HbA1c	haemoglobin A1c
Hct	haematocrit
HDL	high-density lipoprotein

K+	potassium
L	lynestrenol
LDL	low-density lipoprotein
LH	luteinising hormone
LS	lumbar spine
MPA	medroxyprogesterone acetate
NOS	not otherwise specified
RCHGS	Royal Children's Hospital Gender Service
OC	oral contraceptive pill
SSC	spermatogonial stem cell
TAYAs	transgender adolescents and young adults
TE	testosterone esters
TG	transgender
TGD	trans and gender diverse
TSH	thyroid-stimulating hormone
TTC	testicular tissue cryopreservation
TVQ	Transsexual Voice Questionnaire
UGDS	Utrecht GD Scale
WM	white matter
WPATH	World Professional Association for Transgender Health

Executive summary

Background

Transgender is a term used to describe people whose gender identity is incongruent with the sex they were assigned at birth. Gender dysphoria refers to clinically significant distress arising from the incongruence between birth-assigned sex and gender identity. Children and young people who have gender dysphoria or who are trans and gender diverse (TGD) are an especially vulnerable group. They are at high risk of harm from discrimination, bullying, social exclusion and physical assault.[1] They also have a high prevalence of mental health comorbidities, including depression, anxiety, self-harm, eating disorders and suicidality.[2] Gender dysphoria is a term applied by mental health assessment according to DSM V.[3] Not all trans and gender diverse people have gender dysphoria.

People experiencing gender dysphoria or who are trans and gender diverse are seeking out gender-related treatment in increasing numbers. This may be because of increased awareness of services, as well as a rise in people seeking care. There is a growing demand in NSW for expert clinical care specific to children and young people.[1,4] Patient expectations for services and participation in clinical care choices are also changing.[4] As an evolving sector, treatment approaches, guidelines and safety information for TGD children and young people are continuing to develop.

The aim of this Evidence Check is to provide an overview of current evidence for the clinical care of children and young people who are trans or gender diverse or who have gender dysphoria in Australia and other comparable settings. The review was commissioned by the NSW Ministry of Health to identify the benefits and risks of treatment for TGD children and young people up to, but not including, the age of 18. The review's findings will be used to inform decisions regarding the provision of state-wide clinical services for this vulnerable population.

Evidence Check questions

The Evidence Check aimed to address the following questions:

Question 1: What are effective clinical medical interventions for TGD children and young people and those with gender dysphoria?

Question 2: What are the effective psychosocial interventions for TGD children and young people and those with gender dysphoria?

Summary of methods

The Evidence Check was undertaken in January 2020 using the Cochrane Library, Joanna Briggs Institute, MEDLINE, Embase, PsycINFO, CINAHL and Scopus databases. An additional search was undertaken in August 2020 to identify recent publications and additional texts that included long-term follow-up (Appendix 1). Both quantitative and qualitative studies were included where they met the criteria. Inclusion criteria were: (1) studies on children and young people (including prepubertal) under 18; (2) peer-reviewed research; (3) published since and including 2005; (4) geographically located in Australia, New Zealand, Canada, the US, the UK, Western Europe and Scandinavia; (5) research related to fertility preservation; (6) studies that included discussion of costs; and (7) studies of adults where treatment was received when the individuals were under the age of 18 years.

We included peer-reviewed studies where gender dysphoria was treated in adolescents and studies that included an intervention (puberty suppression, gender-affirming hormone therapy, sometimes referred to as cross-sex hormone therapy, 'top' surgery and psychosocial interventions). Appendix 2 contains a list of included studies.

Evidence grading

We used the NHMRC levels of evidence to assess the quality of included studies (see Table 1a, Appendix 3).[5] Systematic reviews with meta-analysis were considered the highest quality, followed by graded practice guidelines. Randomised controlled trials (RCTs) were not available in this area. Comparative studies with controls were followed by comparative studies without controls. We also included case studies and expert opinion as reference, but these were considered lower quality. We assessed studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group approach.[6]

Because of the heterogeneity in the design of the included studies, Critical Appraisal Skills Program (CASP)[7] was used to inform quality assessment of the systematic reviews, qualitative papers and cohort studies.

The NHMRC matrix was used to summarise the evidence base (Table 1b, Appendix 3).

Key findings

Forty-six papers met the eligibility criteria for inclusion in this Evidence Check. Most evidence identified was graded NHMRC levels of evidence III-2 or III-3. It is unlikely, given the nature of this area, that randomised controlled trials and systematic reviews of randomised controlled trials (NHMRC levels I and II) will enhance the evidence base for interventions in the future. The overall quality of evidence available, using the NHMRC matrix, was mostly satisfactory or uncertain (levels C–D), but 16 studies were assessed to be of good applicability to the NSW context.

Of the empirical studies, 14 were prospective cohort studies[8,9,12–22], 14 were retrospective cohort[23-36], three were case studies with a single subject[37–39], two were qualitative studies[40,41] and one was a case-control study.[42]

The remainder of included papers were reviews with no meta-analyses[4, 24,43–46], standards of care or clinical practice guidelines[1,47,48], or expert consensus position statements.[29,49,50]

None of the prospective studies we identified were RCTs and few had controls. Where controls were used, they were usually age-matched peers who did not have gender dysphoria, which made comparison with outcome measures difficult. The lack of RCTs in the evidence base can be explained by the ethically problematic nature of withholding treatment for a control group of TGD adolescents with gender dysphoria.

Relying on case notes is subject to a high degree of bias as researchers cannot control either the exposure or outcome assessments and must rely on previous medical record input, which is subjective and may be inaccurate or contain inconsistent outcome measures. Retrospective studies in general are considered a weaker form of evidence because they rely on previously collected data that was not designed to answer the question being examined.

Because of the low number and quality of included studies for each question, we considered it important to include guidelines and position statements from experts in this area. Additionally, to inform practice in emerging fields of research such as TGD adolescent health, it was necessary to include expert consensus in the form of expert opinions, committee statements and clinical guidelines where quality of evidence is lacking.

Many papers reference the Tanner stages[1] to identify the most appropriate time to initiate a particular therapy. The Tanner stages of breast and male external genitalia development are found in Appendix 4.

Question 1: What are effective clinical medical interventions for TGD children and young people and those with gender dysphoria?

Question 1a: What are the most effective medical interventions for children and young people with gender dysphoria?

Puberty suppression

1. A gonadotropin-releasing hormone agonist (GnRHa) is the most effective treatment for puberty suppression.
2. Puberty suppression for TGD adolescents appears to be effective, safe, well tolerated and reversible, thus allowing the adolescent to explore their gender identity before embarking on irreversible, or partially irreversible, treatment[10–12,23,24,26,28,37](NHMRC levels III-2–IV).
3. Puberty suppression reduces emotional and behavioural problems associated with gender dysphoria.[22] A key psychological benefit associated with puberty suppression is the prevention of

future psychological distress that TGD adolescents may experience when they develop the secondary sexual characteristics of the sex they were assigned at birth.[29] However, it is also possible that puberty suppression may increase social isolation for adolescents, who remain in a prepubertal state and thus out of sync with their peers.[47]

4. In terms of achieving the appearance of the desired sex, the outcomes of gender-affirming hormone therapy (GAHT) and surgery are better among individuals for whom puberty was suppressed compared with those who initiated physical transition after puberty had been completed[9] (NHMRC level III-2).

Gender-affirming hormone therapy (GAHT)

1. Gender-affirming hormone therapy (GAHT) promotes changes in body composition in ways that align with the desired gender.
2. GAHT is associated with improved body image, decreased body dissatisfaction, reduced gender dysphoria and improved psychological wellbeing[14,23,29,30,40] (NHMRC levels III-2–IV and below; includes one qualitative study).
3. A key benefit of GAHT is that it appears to increase bone density following the negative impact of puberty suppression on bone density[9,15,17] (NHMRC levels III-2–III-3). Where GnRH has not been used for puberty suppression in trans girls, anti-androgen medications such as cyproterone acetate or spironolactone may be used in addition to GAHT to also relieve gender dysphoria[23] (NHMRC level III-2)

Gender-affirming surgery

1. Few studies have examined gender-affirming surgery in children and adolescents, and clinical guidelines rely heavily on expert opinion. We identified only three studies[29,34,40] all focusing on chest surgery in trans boys. The paucity of studies is to be expected given the age restrictions on gender-affirming surgery and the inclusion criteria of this Evidence Check for studies of young people where treatment was undertaken under the age of 18 years. The evidence for the effectiveness of this chest surgery is very weak (NHMRC level IV) and should be considered preliminary.
2. Keeping in mind the preliminary nature of the evidence, existing studies suggest trans boys have a high level of satisfaction with chest surgery and that chest surgery is associated with a reduction in gender dysphoria.
3. It has been suggested that clinical protocols for gender-affirming treatments need adjustment to meet the specific needs of non-binary adolescents[40] (NHMRC ungraded: qualitative).

Question 1b: What are the risks or potential harms from medical interventions for children and young people with gender dysphoria?

Puberty suppression

1. GnRHa is the most effective treatment for puberty suppression; however, it is also the most expensive.

2. For young people with needle phobia, GnRHa may not be acceptable as it is delivered via injection.
3. Some adolescents experience a loss of bone density mineralisation from a lack of oestrogen or testosterone, which is a concern as it increases the risk of osteoporosis and bone fractures in the future. More research is needed to understand whether the bone density mineralisation changes are fully reversible, and why only some adolescents experience this adverse side effect[8,9,15,17] (NHMRC levels III-2–IV).
4. Other side effects such as hot flushes, weight gain, acne and mood changes are common but are generally well tolerated.
5. Fertility may be compromised in individuals who start puberty suppression treatment at a young age because the treatment impairs the development of sperm cells (spermatogenesis) and egg formation in the ovary (oocyte maturation).[51] Fertility preservation options should be discussed with the young person and their caregivers before starting GnRHa. We found no empirical evidence for fertility compromise in adolescents in any empirical studies but recommendations regarding discussing fertility preservation prior to medical intervention for TGD children and adolescents were given in guidelines, reviews without meta-analyses and position statements.[1,24,47,48,50,51]
6. There is a theoretical potential for increased social isolation for TGD adolescents as they undergo treatment, as the timing of their puberty may be out of sync with their peers[47] (NHMRC level ungraded: clinical practice guideline).

GAHT

1. Side effects such as acne, weight gain, mood swings and hot flushes are common with GAHT but rarely lead to cessation of therapy. Scalp hair loss may also occur in trans boys[12,28,30] (NHMRC level of evidence III-2).
2. Rarely, other serious adverse outcomes, including breast and ovarian cancer among trans boys receiving androgen therapy, have been reported in the literature. However, there are too few cases to suggest a causative link between GAHT and gynaecological malignancy[49] (NHMRC level ungraded: committee opinion).
3. GAHT is only partially reversible. Voice deepening, facial hair growth and reduction in scalp hair growth may be irreversible for trans boys. Reversing the effects of breast development in trans girls may require surgery[49,48] (NHMRC level of evidence ungraded: clinical guideline and committee opinion).
4. Because GAHT may affect future fertility, recommendations to discuss fertility preservation before medical intervention for TGD children and adolescents were given in guidelines, reviews without meta-analyses and position statements.[1,24,47,48,50,51]

Top surgery

1. Top surgery (mastectomy for trans boys and breast contouring for trans girls) is considered to be irreversible[1,47,48,51] (NHMRC ungraded: position statement, standard of care and guidelines).

2. While the majority of young people who had top surgery experienced high levels of satisfaction, varying degrees of satisfaction with the outcome have been reported[2,30] (NHMRC level of evidence IV).

Question 1c: What is the variation in the effectiveness and risks associated with medical interventions for children and young people with gender dysphoria

Puberty suppression

1. There is no minimum age to start puberty suppression; rather, the pubertal stage is used to determine what is most appropriate for each child or adolescent. The recommendation is for trans boys to start at Tanner stage 2 and trans girls at Tanner stage 2–3[1,47,51], depending on individual circumstances (NHMRC level of evidence ungraded: standards of care and clinical practice guidelines). For example, a trans girl who has already gained their desired height may wish to begin GnRH earlier than a trans girl who has not gained their desired height, as long as they have reached Tanner stage 2.
2. Careful monitoring is required regarding bone density. Where loss of bone density is evident, it is recommended considering shorter use of GnRHa or earlier start of GAHT[4,43,47] (NHMRC level of evidence ungraded: clinical practice guideline and reviews without meta-analyses).

GAHT

3. Historically, GAHT has rarely been started before 16 years of age. However, recent studies and expert consensus suggest the most appropriate stage at which to begin treatment should not be decided on age alone. Comorbidities such as mental health issues and medical conditions should be taken into account when considering medical interventions, as well as psychosocial factors such as parental support and the readiness of the adolescent for informed consent[48] (NHMRC level of evidence: ungraded; clinical practice guideline).
4. A multidisciplinary team may include a paediatrician, adolescent physician, endocrinologist, general practitioner, fertility counsellors, nurse, counsellors, speech pathologists, family workers, psychiatrists and psychologists[1,4,48,50,51] (NHMRC level of evidence ungraded: reviews without meta-analyses and clinical practice guidelines).

Top surgery

Top surgery is not generally performed before 18 years of age due to irreversibility of these procedures[1,47,48, 50,51] (NHMRC level of evidence ungraded: clinical practice guidelines, standards of care and position statements).

Long-term benefits, risks and safety profile of puberty suppression and gender-affirming hormone therapy

A summary of studies concerning long-term outcomes is found in Table 6. In eligible studies that include outcomes of interventions, the benefits and risks of puberty suppression are well established. Puberty suppression results in favourable mental health outcomes[18,23,30] and less suicidal ideation[52,53] (level B–D). No adverse cardiovascular risk factors were identified and no adverse biochemical

profiles. The major adverse outcome is loss of bone mineral density,[8,9,47] which is partially resolved with subsequent gender-affirming hormone therapy (level B–D).

Gender-affirming therapy appears to be safe in long-term studies identified. Previous bone mineral density loss is at least partially reversed, although in some studies, previous levels are not attained[8,9,14,17] (level B–C). It is possible that some TGD individuals do not attain their height potential following puberty suppression, although this may be a desired outcome.[17] There are conflicting studies regarding biochemical profile and cardiovascular risk.[8,14] There may be increased prevalence of obesity in TGD with GAHT.[35] Most authors concur there is no clinical significance to altered biochemistry including lipid profile but recommend reducing other risk factors for cardiovascular risk while taking GAHT.

Question 2: What are the effective psychosocial interventions for TGD children and young people and those with gender dysphoria?

Evidence for the effectiveness of psychosocial interventions for TGD adolescents is lacking. We identified only three studies[18,38,41], all of which were low quality. It is unclear why so few studies have investigated the effect of psychosocial interventions for TGD children and young people and it is particularly surprising given the high prevalence of psychological distress in this population.[54]

While each of the three studies reported positive findings, the small self-selected samples, non-standardised interventions, absence of control groups, lack of validated pre and post measures and failure to account for confounders means it is not possible to isolate the effect of the psychosocial intervention from other factors.

Question 2a: What have been shown to be the most effective psychosocial interventions for treating children and young people with gender dysphoria?

1. There is a lack of evidence from which to draw any conclusions regarding the effectiveness of psychosocial interventions for treating children and young people with gender dysphoria.
2. Only one paper empirically examined the effect of psychological support for a cohort of transgender adolescents (level D).[18] This study compared the effect of psychological support and GnRHa with psychological support alone. It found all participants reported an improvement in psychological functioning at six months. However, only participants who received both GnRHa and psychological support continued to improve over the next 12 months. Another paper[41] described a pilot program of group work for parents and carers of transgender adolescents (level C–D) and one paper[38] reported a single subject case study in which a trans girl in a youth justice facility received intensive voice feminisation therapy (level D).

Question 2b: What have been shown to be the risks or potential harms from psychosocial interventions for treating children and young people with gender dysphoria?

There was no evidence of risk or potential harms from the psychosocial interventions identified in this Evidence Check. Of note, we did not identify any studies that met inclusion criteria whose aim was to change an individual's gender identity.

Question 2c: Is there variation in the effectiveness or risks associated with psychosocial interventions for treating children and young people with gender dysphoria?

There was no evidence of effectiveness or risks associated with psychosocial interventions identified in this Evidence Check.

Gaps in the evidence

Although the preliminary evidence suggests gender-affirming treatments are associated with mental health benefits there are large gaps in the evidence base regarding the benefits and potential harms of both medical and psychosocial interventions for TGD children and young people. Evidence gaps are a common characteristic of new and emerging fields of research and, therefore, are not unexpected. We anticipate that research over the next decade will address many of the outstanding questions regarding the impact of treatment for TGD children and young people.

Key gaps in the evidence base are:

- Understanding variations in characteristics of TGD and non-binary youth and the variation in their medical and psychosocial intervention needs
- Timing of gender-affirming medical interventions
- The role of pubertal suppression and GAHT on the outcomes of surgery, and whether young people are less likely to request surgery
- Understanding variation in bone density loss among adolescents receiving puberty suppressing treatment
- The effect of exercise and diet on bone density
- Long-term impact of medical intervention in childhood/adolescence on mental health, social and physical health outcomes in adulthood
- Use of validated instruments to measure a wide range of outcomes
- The independent effect of medical interventions on psychological outcomes
- The effect of psychosocial interventions, both in the absence of and in conjunction with treatments.

Applicability

The applicability to NSW of many of the included papers was unclear because of small sample sizes, measurement tools adapted for a particular country and results that relied on retrospective design using case notes. There was also a lack of large well-designed studies that had control groups.

Some of the larger studies that reported on aspects such as efficacy, safety and side effects of interventions are highly applicable. The Australian Standards of Care and Treatment Guidelines for Transgender and Gender Diverse Children and Adolescents[1] inform the local context and reference other important guidelines such as the World Professional Association for Transgender Health (WPATH) guidelines.[48] Other key Australian papers inform the results of this Evidence Check and are particularly applicable to the NSW context.[4,43,45]

Summary and conclusion

Children and young people who are trans and gender diverse (TGD) or have gender dysphoria are a vulnerable population as a result of stigma and marginalisation. Because of this and minority stress, they experience high rates of mental health and behavioural problems as well as social, educational and economic disadvantage. NSW, like other states and territories, is experiencing an increase in demand for expert clinical care for this population. As such, the NSW Ministry of Health has commissioned this Evidence Check to collate and evaluate evidence regarding the benefits and risks of treatment for TGD children and young people. The brief for this review was to examine the evidence regarding the impact of treatment in children and young people up to, but not including, the age of 18 years. We identified 46 papers, which included 34 empirical studies, six reviews and six guidelines or consensus statements.

Overall, the available evidence of the benefits and harms of treatment for this age group is of low quality. The empirical studies we identified are characterised by: (1) small, convenience samples, which limits the degree to which the findings can be generalised to the broader population of TGD children and young people; (2) an absence of randomised controlled trials (RCTs), which compare the outcomes for those who received treatment with those who did not; (3) a narrow range of outcome measures, which impedes a broad understanding of the impact of the treatment; (4) a lack of standardised measures, which makes it difficult to compare findings across studies; and (5) a failure to control for obvious potential confounders (i.e. variables that are likely to have influenced the observed outcome). The absence of RCTs in the evidence base stems from the ethical concerns about withholding treatment for young people with gender dysphoria, and this is unlikely to change in the future.

Keeping in mind the limitations of the evidence, we identified a range of clinical interventions for TGD children and young people for puberty suppression and gender-affirming hormone therapy (GAHT). The evidence for puberty suppression indicates that it is safe and, although it is commonly associated with minor side effects (e.g. hot flushes, acne, weight gain, mood swings), is well tolerated. Key benefits of puberty suppression treatment are that it is reversible and allows the young person to explore their gender identity before embarking on irreversible, or partially irreversible, treatment. Puberty suppression also prevents the distress some individuals would experience as they develop secondary sexual characteristics contrary to their affirmed gender. An important concern about

puberty suppression treatment is its potential impact on bone mineral density (BMD). At this stage the evidence about BMD is inconclusive. It appears some young people experience a loss of BMD and some do not. The factors underlying this variability are unclear. Another concern raised in several guidelines is the potential adverse impact of puberty suppression on fertility; we did not identify any empirical studies exploring this outcome, however.

There is good evidence that GAHT effectively changes body composition in line with the desired gender and some evidence that these changes are associated with an improvement in measures of psychological wellbeing. There is moderate evidence that an important benefit of GAHT is that it reverses the bone density loss observed during puberty suppression. Common side effects of this treatment include acne, hot flushes, mood swings, weight gain and, in trans boys, male pattern baldness. These side effects were generally well tolerated. Several studies identified a potential risk associated with testosterone therapy in relation to haematological and metabolic changes that may increase future cardiovascular risk; the evidence is conflicting, however. Some effects of GAHT are irreversible or only partially reversible. Although quality evidence is lacking, available evidence suggests fertility is compromised by GAHT.

To date, there is very little evidence for either the benefits or the risks of gender-affirming surgery in TGD young people up until, but not including, the age of 18.

Similarly, there is a lack of evidence regarding the potential benefits and harms of psychosocial interventions for TGD children and young people and those with gender dysphoria. We did not identify any studies that attempted to change an individual's gender identity, which is not surprising given that conversion therapies have long been discredited by medical and psychological bodies across Australia and internationally. However, we also did not identify any studies that examined the outcomes of supportive psychological therapies, either neutrally or affirmatively framed.

Overall, there is considerable scope for improvement in the quality of evidence of treatments for TGD children and young people. There is a need for better reporting of the characteristics of the study sample combined with a better understanding of the characteristics and needs of TGD youth more broadly. This information will enable decision makers to better estimate the degree to which findings from individual studies can be applied to the young people presenting for specific services. Future studies should be designed to measure outcomes across multiple domains using validated and standardised measures that enable findings from different studies to be compared. Although it may not be possible to conduct RCTs on this population, appropriate consideration and treatment of potential confounders in the study's analysis will provide more insight into the causal relationship between the treatment and the observed outcomes.

Background

Transgender is a general term used to describe people whose gender identity is incongruent with the sex they were assigned at birth. Gender dysphoria refers to clinically significant distress that is experienced as a result of the incongruence between birth-assigned sex and gender identity.[3] Many children who question their gender at a young age will not go on to identify as trans and gender diverse, and will come to feel that their gender is congruent with the sex they were assigned at birth.[43] While the exact proportion of children who desist or de-transition is unclear, estimates range from 73% to 98%.[56] Those individuals who remain trans or experience persistent gender dysphoria are a uniquely vulnerable group who are at significantly increased risk of harm from discrimination, bullying, social exclusion and physical assault.[1] They also have a high prevalence of mental health comorbidities, including depression, anxiety, self-harm, eating disorders and suicidality.[2] A recent Australian study of 859 TGD youth aged between 14 and 25 found 80% reported ever self-harming and 48% reported ever attempting suicide.[57]

In Australia and elsewhere, more people experiencing gender dysphoria or who are trans and gender diverse are self-identifying and seeking out gender-related clinical care.[1,4] Patient expectations for services and participation in clinical care choices are also changing.[4] These changes are reflected in an increasing demand for expert clinical care to meet the needs of TGD children and young people.[1,55] As an evolving sector, treatment approaches, guidelines and safety information for TGD children and young people are moving rapidly.

Naturally, the needs and vulnerabilities of children and young people are different from those of older patients and age-specific approaches are essential. Most studies of gender transition focus on an adult population, however, with comparatively few addressing the needs of young people. There is also a paucity of longitudinal studies from which to draw, meaning the long-term outcomes of some aspects of medical transition are not yet well understood. When considering the risks and benefits of medical treatments (including puberty suppression, cross-sex hormones and gender-affirming surgeries) the risks of intervention need to be weighed against the risks of non-intervention.

The aim of this Evidence Check is to provide an overview of current evidence for the clinical care of children and young people who are trans or gender diverse or who have gender dysphoria in Australia and comparable settings. The review was commissioned by the NSW Ministry of Health to identify the benefits and risks of treatment for TGD children and young people up to, but not including, the age of 18. Findings from the Evidence Check will be used to inform decisions regarding the provision of state-wide clinical services for this vulnerable population.

Methods

Peer-reviewed literature

The literature search was conducted in January 2020 using the Cochrane Library, Joanna Briggs Institute, MEDLINE, Embase, PsycINFO, CINAHL and Scopus databases.

The search terms used were:

- (Transgender OR "gender dysphoria" OR trans or "gender diverse" OR "trans or gender diverse" OR TGD OR "gender incongruent" OR "gender identity" OR "gender identity disorders") AND (Treatment OR management OR interventions OR "hormone blocker*" OR hormone therapy" OR "puberty suppression" OR "puberty blocker*" OR "pubertal suppression" OR anti-androgen OR oestradiol OR "gender-affirming hormone dose" OR "gonadotropin releasing hormone agonist" OR "gender reassignment") AND (Adolesc* OR youth OR "young per*" OR teen* OR "young adult" OR pediatric OR paediatric OR child*) AND (Safety OR benefits OR Side-effect* OR risk* OR harm* OR "significant adverse drug reaction*" OR ADRs).

Two reviewers completed the literature search (LB and CW). Two reviewers (CW and SD) independently screened and reviewed the abstracts and full texts of articles in Covidence.[58] Reference lists of reviews of the literature that did not fulfil the inclusion criteria were used to identify studies that had been missed in our search. An additional search using the above criteria was also conducted in August 2020 to identify papers investigating long-term follow-up, and to identify recently published papers (CW and SB).

A flow chart of the literature selection process is included as Appendix 1a and Appendix 1b.

Inclusion criteria

Both quantitative and qualitative studies were included where they met the criteria. Inclusion criteria were (1) studies on children and young people (including prepubertal) under 18; (2) peer reviewed research; (3) published since and including 2005; (4) geographically located in Australia, New Zealand, Canada, the US, the UK, Western Europe and Scandinavia; (5) research related to fertility preservation; (6) studies that included discussion of costs; and (7) studies of adults where treatment was received when adults were under the age of 18 years (this criterion was applied for the additional search conducted in August 2020).

We included peer-reviewed studies where gender dysphoria was treated in adolescents and studies that included an intervention (puberty suppression, gender-affirming hormone therapy, 'top' surgery and psychosocial interventions).

Further clarification was applied to the age criteria. Where participant follow-up was reported beyond 18 years, we included studies in which the intervention was commenced at 17 years or younger. We also included studies reporting on interventions for transgender adolescents up to the age of 25 where the mean age was 17 years or younger and mean age was reported in the study, or if more than 50% of the sample was 17 years or younger.

As there were multiple updates found for guidelines, standards and position statements, we included the most recent published from each organisation, and those published from 2015.

We included studies from Australia, New Zealand, Canada, the US, the UK, Portugal, Spain, France, Belgium, the Netherlands, Ireland, Luxembourg, Liechtenstein, Monaco, Vatican City, Italy, Switzerland, Germany, Greece, Austria and Scandinavia.

Exclusion criteria

Studies were excluded if they: (1) were published before 2005 (or guidelines / standards published before 2015); (2) were not in English; (3) focused on 'bottom' surgery; (4) dealt primarily with the ethical and legal dimensions of gender transition for young people, including consent; (5) focused on stakeholder and community views; and (6) did not clearly separate adolescents from an adult sample when examining administered treatments.

We also excluded empirical studies that contained no intervention, reviews where no search strategies were reported, study protocols, and comments / analyses of guidelines and standards.

Evidence grading

We used the NHMRC levels of evidence to assess the quality of included studies (see Table 1a).[5]

Systematic reviews with meta-analysis were considered the highest quality, followed by graded practice guidelines. Randomised controlled trials were not available in this area. Comparative studies with controls were followed by comparative studies without controls. We also included case studies and expert opinion as reference, but these were considered lower quality. We assessed studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group approach.[6]

Because of the heterogeneity of the designs of the included studies, we used the Critical Appraisal Skills Program (CASP)[7] to inform quality assessment of systematic reviews, qualitative papers and cohort studies.

The NHMRC matrix was used to summarise the evidence base (see Table 1b).

Included studies

Forty-six papers met the eligibility criteria for inclusion in the Evidence Check. The overall quality of the studies was low, with most evidence falling within the NHMRC levels of evidence III-2 or III-3. The

evidence base was rated as C (satisfactory), with most papers graded as level III, studies with a moderate to high risk of bias. Consistency was rated B–C (good to satisfactory). Most studies were consistent, with discrepancies in some studies that could be attributed to low sample size or study design flaws. The clinical impact was moderate. Generalisability was graded as B–C (good to satisfactory), with several of the studies arising from the Amsterdam cohort[59], but it is clinically appropriate to apply this evidence to the NSW target group as they have similar healthcare systems and health practices. Applicability overall was rated as C (satisfactory), with evidence likely to be applicable to the Australian context with some caveats.

A summary table of the included studies is attached as Appendix 2.

Findings

Question 1: What are effective clinical medical interventions for TGD children and young people and those with gender dysphoria?

Question 1a: What have been shown to be the most effective medical interventions for children and young people with gender dysphoria?

Medical intervention 1: Puberty suppression

Included studies

The World Professional Association for Transgender Health (WPATH)[48] and the Endocrine Society[47] recommend suppressing puberty with gonadotropin-releasing hormone agonists for individuals with a longstanding history of gender dysphoria and related distress that has worsened with the onset of puberty.

We identified 28 papers that addressed the effectiveness of puberty suppression for transgender children and adolescents that met our eligibility criteria (Table 2). Of these, 18 were empirical,[8-12,15,22-31,37,42] six were guidelines[1,31,47-49,51] and four were reviews.[4,43,44,45]

The quality of the empirical studies was low, with 16 rated NHMRC level of evidence Grade III-2[8-13,22-27,30] or below and two unable to be graded (qualitative / single case study).[37,40] Overall, the evidence was rated as C–D (satisfactory / poor).

Some studies examined puberty suppression in isolation, while for others it was combined with gender-affirming hormone therapy (GAHT). Gonadotropin-releasing hormone agonist (GnRHa) is a type of medication that affects gonadotropins and sex hormones and is used to effectively suppress puberty[1,43] (levels B–C). GnRHa included leuprolide injection, histrelin implant and triptorelin injection. GnRHa medications can be an expensive means of achieving puberty suppression.

Anti-androgens (or androgen blockers), which do not supress puberty, can be useful for trans girls before they start their oestrogen therapy and may be used subsequently as part of the GAHT regime. These drugs partially block the peripheral effects of endogenous testosterone. Androgen blockers include spironolactone, cyproterone acetate and bicalutamide. Cyproterone acetate was found to be effective for puberty suppression and could offer a safe and valuable alternative for GnRHa, especially for older trans girls[12] (level C). Authors cautioned, however, that high doses of cyproterone acetate, as used in androgen deprivation therapy, had been associated with severe liver dysfunction

and recommended periodic monitoring of liver function during treatment. In another study, medroxyprogesterone acetate (MPA) effectively suppressed puberty in most trans girls, but not in all[28] (level D). In this study, depot medroxyprogesterone was also used for trans boys to suppress menstruation as an alternative to GnRHa.

Bicalutamide, although not considered equivalent to the 'gold standard' of GnRHa for puberty suppression, has the added benefit for trans girls of inducing breast development[24] (level C–D). It is worth noting this treatment is 'off-label' in Australia, as it is registered for metastatic carcinoma of the prostate.

An oral progestin, lynestrenol (not currently available in Australia), is also used in trans boys prior to GAHT. Although there is no evidence that it suppresses puberty, in one study luteinising hormone decreased and free testosterone increased[27] (level C). It appears that most progestogen alternatives to GnRHa are well tolerated and less expensive, but they are also less effective.

Gender dysphoria

Key organisations WPATH[48] and the Endocrine Society[47] recommend puberty suppression for TGD youth based on available empirical evidence for a positive effect of puberty suppression. The only quantitative study that measured gender dysphoria and body satisfaction before and after initiating GnRHa found no change on the Utrecht Gender Dysphoria Scale and the Body Image Scale[13] (level C–D). Anecdotal reports in one chart review indicated trans girls who received bicalutamide for puberty suppression were very satisfied with the ensuing breast development[24] (level C–D). Breast development is a secondary effect of puberty suppression treatment with bicalumatide and is not observed when GnRHa is used.

Physical changes

Effects noted in participants treated with pro-androgenic and anti-androgenic progestins (lynestranol and cyproterone acetate) for puberty suppression included halting or reducing undesired sex characteristics (e.g. facial hair, menstruation) and developing some sex characteristics in line with their affirmed gender (e.g. breast development, reduced facial hair growth). The bodily changes included loss of lean mass, gains of fat mass and decreased grip strength for trans girls, and increased lean mass and total body mass and decreased body fat for trans boys.[8] These bodily changes all occurred within 12 months of starting puberty suppression therapy[8] (level C). The largest study, which included 192 participants, found higher levels of satisfaction in body shape in trans girls than trans boys[26] (level C). These authors propose that setting realistic expectations will assist with eventual body satisfaction. A major limitation with this study was the presence of possible confounders such as exercise and diet. The retrospective study design also made it difficult to separate the impact of puberty suppression treatment from the impact of GAHT.

Cyproterone acetate (CA) has been recommended for trans boys to induce amenorrhoea and reduce dysphoria about menstruation[1] (level B–C). Being oral, it is cheaper and more easily administered than injectable GnRHa and may also relieve dysphoria in trans female adolescents by keeping testosterone levels below the prepubertal range and supressing male pubertal changes.

One recent paper reported that most adolescents who use puberty suppressing treatment proceed with GAHT[60] (level C).

Mental health and wellbeing

Most studies found pubertal suppression for TGD adolescents who requested this treatment was associated with favourable mental health outcomes. Improved mental wellbeing was reported in three studies[10,13,40] (level C–D). In one paper, puberty suppression was associated with a reduction in disordered eating behaviour and an increase in a sense of progress, relief and optimism[40] (level D). In a large cross-sectional study, rates of suicidal ideation were lower among those who received puberty suppression compared with those who did not[36] (level B). Some authors reported that puberty suppression treatment was associated with decreases in behavioural, emotional and depressive symptoms but no change was found for anxiety, anger, gender dysphoria and body satisfaction[13] (level C–D). Improved social outcomes for one participant was reported in a single subject case study[37] (level D). Reductions in eating disorders during puberty suppression were reported in one study that was well designed and used validated measurements[10] (level C–D). One study compared 178 TGD adolescents receiving puberty suppression with 272 TGD adolescents who had not commenced puberty suppression and found those who underwent puberty suppression had fewer emotional and behavioural problems than their untreated TGD peers, and had similar or fewer problems than their same-age cisgender peers on the Youth Self-Report domains[22], including 'internalising', 'externalising', 'peer relations' and 'suicidality'.

Biochemistry

In a prospective study with 116 participants, sex steroids and liver function were monitored at three-to-six-month intervals during GnRHa (triptorelin) treatment[11] (level B–C). Gonadotropins and sex steroid levels were successfully suppressed within three months. All subjects sufficiently suppressed without additional adjustment of medication. No sustained abnormalities of liver enzymes or creatinine were recorded, although alkaline phosphatase decreased. The authors surmised that this decrease was probably related to a change in growth velocity and lower bone mineral accrual, which are related to alkaline phosphatase levels.

Fertility

Compromised future fertility is a known concern for young TGD people who take puberty suppressing medication. Fertility may be compromised if puberty suppression treatment is started at a young age because the treatment impairs spermatogenesis and oocyte maturation. Two guidelines[47,51] (level B–C) and one systematic review[24] (level B–C) addressed this concern, indicating that the potential effects of puberty suppression on fertility should be discussed with the patient and family and sperm/egg extraction offered before commencing puberty suppression.

Quality of evidence

Overall, the quality of evidence for puberty suppression was satisfactory to poor, mainly due to small sample sizes. Other limitations included missing data, lack of control groups and inconsistent reporting (especially in retrospective studies using chart review).

Medical intervention 2: Gender-affirming hormone therapy (GAHT)

Effectiveness of gender-affirming hormone therapy for trans girls

Included studies

We identified 23 papers addressing the effectiveness of gender-affirming hormone therapy for trans girls that met our eligibility criteria. Of these, 13 were empirical[8-12,14,23,25,26,29,30,32,33], six were guidelines or position statements[1,47-51] and four were reviews[4,43–45] (see Table 3).

The quality of the empirical studies was low, with seven rated NHMRC level of evidence grade III-2 or grade III-3[9,10,12,14,23,32,33] and four rated level IV.[25,26.29,30] Overall, the evidence was rated as C–D (satisfactory/poor).

There was little homogeneity among the studies regarding the type of oestrogen used, and whether it was used in combination with another therapy. Of the 23 papers, nine reported use of oestrogen alone1, [9,23,25,26,29,32,33,47], six in the form of estradiol[9,23,25,26,29,47] and the remainder did not specify the type of oestrogen used.10, 13, 30, [32,33. 44, 48, 50, 51] GnRHa use before oestrogen therapy was associated with a significantly lower average dose of oral estradiol.[23]

Feminising bodily changes

Feminising treatment with oestrogens and anti-androgens results in desired changes such as increased breast growth, reduced facial and bodily hair growth and female pattern fat distribution[46] (level C–D). In a relatively large (N=116) multi-site study, GAHT resulted in physiologic hormone levels of the affirmed gender reached after six months[33] (level D). Body composition changes towards the gender-affirmed sex were reported in a large cohort (N=192)[26] (level C). Increases in hip circumference were evident in one small study (N=80, level C), along with breast development in 83% of subjects within three months.[14] Combined oestrogen and cyproterone acetate resulted in 67% of subjects reaching Tanner stage B3 after six months in one study[45] (level B).

Bone density restoration

The loss of bone density from the use of puberty suppressing agents has been a concern.[15,61] Once gender-affirming hormone therapy has begun for females, a return towards normal values has been observed[9] (level C). One study followed 34 trans girls and trans boys who started GnRH until the age of 22. Although trans boys showed a non-significant trend towards loss of bone density, trans girls at the age of 22 demonstrated a significantly lower lumber bone mineral density z score, a score which reflects how an individual's score differs from the mean score for the population[15] (level B). One study followed 22 trans girls at three time points: at the start of puberty suppression, at the start of GAHT and 24 months after starting GAHT. Following bone density mass decrease during puberty suppression, the addition of GAHT resulted in bone mineral apparent density returning towards normal levels[9] (level C).

Improvement in mental health outcomes

Mental health comorbidities are highly prevalent in transgender youth. Psychiatric comorbidities, particularly mood disorders, tend to decrease in intensity after medical hormone intervention[43] (level B–C). GAHT is likely to reduce the incidence of mental health issues in transgender youth by inducing the onset of secondary sexual characteristics consistent with affirmed gender[1,4] (level B–C).

Resolution of gender dysphoria offers psychological outcomes similar to, or better than, non-transgender age-matched young adults[51] (level B–C).

One prevalence study found that in its cohort of 298 transgender women aged 16–29, 41.5% had one or more mental health or substance dependence diagnoses.[62] Gender-affirming hormone therapy improved mental health outcomes in one study[29] (level C), where suicide attempts fell from 13% pre-treatment to 7% post-treatment. This study had inherent limitations, having a small sample size (N=27) and a limited design (retrospective chart review). Donaldson[25], in a small (N=5) study, reported improved body satisfaction with oestradiol, and low suicidal ideation and self-injurious behaviour (level D).

However, an expert opinion statement reiterated the positive effect of GAHT, stating that it has been shown to decrease depression and increase self-esteem among transgender patients[49] (level C).

Effectiveness of gender-affirming hormone therapy for trans boys

Included studies

We identified 20 papers that met our eligibility criteria that addressed the effectiveness of gender-affirming hormone therapy for trans boys. Of these, 11 were empirical[8,9,16,23,26,29,30,32,33,40,42], six were guidelines or position statements[1,47-49,50,51] and three were reviews.[4,43,45]

Compared with studies of trans girls, there was even greater heterogeneity in studies of trans boys regarding the type of hormone used and whether it was used in combination with another therapy. Testosterone (without specifying the type used) was reported in 10 papers.[4,30,32,33,40,44,47,48,49,51] The description of testosterone esters was reported in two studies[9,17], while the other eight reported testosterone cypionate with ethinylestradiol[63], testosterone enanthate and / or cypionate[29], testosterone cypionate and differing doses of GnRHa[23], testosterone ester or testosterone undecanoate[16], testosterone enanthate[1], lynestrenol and testosterone esters[27], and testosterone and lynestrenol.[45]

Concurrent use of GnRHa correlated with lower doses of subcutaneous testosterone cypionate use than with those using testosterone alone.[23]

Masculinising effects

Benefits of GAHT for trans boys include masculinising the appearance by inducing the onset of secondary sexual characteristics of the desired gender[1,48] (level B–C). Benefits of GAHT for trans boys included increased hair growth in extremities, face, abdomen and chest[17,40] (level C–D), with most occurring by 12–15 months, as well as voice deepening[17,27] (level C–D), enlarged clitoris (clitoromegaly) and cessation of menses[27,48] (level C).

Body image and mental health

Many trans boys reported feeling happier, less anxious or less gender dysphoric, having higher self-esteem, and described positive body changes after commencing GAHT[40,49] (level C–D). In their prospective study, de Vries et al.[30] found trans boys were more satisfied after GAHT than following GnRHa, and reduced anger and anxiety was reported for trans boys (level D). None of their cohort (N=55) expressed regret following GAHT (as measured 12 months post-surgery), a view that was echoed in another study in which the time that had elapsed following surgery was not reported[40] (level

D). In their position statement, Lopez et al.[51] claimed complete resolution of gender dysphoria alongside psychological outcomes similar or better than non-transgender, age-matched young adults (level B–C).

In one retrospective chart review investigating the response to GnRHa and GAHT over a 13-year period, 12% of the cohort had attempted suicide prior to GAHT treatment, but this proportion dropped to 5% after treatment, with the authors concluding that once puberty blockers or GAHT were started, there was a reduction of anxiety / depression and suicidal ideation[29] (level C–D). There was no attempt at comparison of proportions with age-matched peers, making it difficult to ascertain whether this reduction in mental health issues and suicidal intentions was a result of the hormone therapy or whether it was consistent with an average decrease in the general population as they age and mature.

Bone density

One study followed 34 trans boys at three time points: at the start of puberty suppression, at the start of GAHT and 24 months after starting GAHT[9] (level C). Following bone density mass decrease during puberty suppression, the addition of GAHT resulted in bone density returning to normal levels.

Cognition

One study investigated the effect of GAHT on visual-spatial functioning in 21 trans boys[16] (level C). After an average of 10 months of testosterone treatment, trans boys showed increases in brain activation in areas implicated in mental rotation. No harms of testosterone treatment on cognitive function were found.

Medical intervention 3: Gender-affirming surgery (top surgery)

Using our search criteria, we identified eight papers that considered the effect of surgical interventions on transgender adolescents and for which results specific to the impact of surgery could be extrapolated (Table 4). Three papers reported empirical studies of chest surgery in trans boys,[29,34,40] four papers were clinical practice guidelines for health professionals working with transgender children and adolescents[1,47,48,51] and one paper reviewed interventions, including surgery.[4] We did not include a commonly cited paper by de Vries[30] because: (1) even though participants were recruited into the study at a mean age of 13.6 years, the mean age for surgery was 19.7 years, which was outside the age range for this Evidence Check; and (2) it was not possible to disentangle the benefits and harms of surgical interventions from the benefits and harms of gender-affirming hormone treatment in this study. The quality of the empirical studies was low, with two being rated NHMRC level of evidence grade IV[29,30] and one unable to be graded as it was a qualitative study.[40] Overall, we rated the evidence as D (poor).

Three papers reported chest surgery in trans boys; however, only one paper[34] included quantitative evidence of surgery-related outcomes (level C–D). This study reported the outcomes of chest reconstruction surgery for 14 trans boys attending a gender management clinic in the US. These 14 individuals were the only ones from a population of 108 trans boys to undergo chest reconstruction surgery. The median age of participants when they had the surgery was 17.2 years (range: 13.4–19.7). All 14 were in advanced puberty (Tanner stage 5) and had support for the surgery from their parents or guardians. All participants reported a high level of satisfaction with the surgical outcomes in

terms of aesthetics and comfort. The average satisfaction score was 4.9/5. All subjects were pleased they no longer needed a binder to hide evidence of previous breast development. Participants and their families reported improvement in depressive and anxiety symptoms after the procedure in almost all cases. Of the 10 subjects whose depression-screening scores were available, only one scored in the high range following surgery. For reasons not explained by the authors, only 50% of participants were taking testosterone at the time of surgery. Differences between those taking testosterone and those not taking testosterone were not presented and the effect of testosterone on satisfaction with chest surgery was unclear. A recent single case qualitative study described a 16-year-old trans boy who experienced significant relief of dysphoria following chest surgery.[64]

As part of a larger study describing patient characteristics of young people receiving treatment for gender dysphoria, Khatchadourian et al.[29] reported that nine trans boys underwent a mastectomy with male chest contouring. The median age of trans boys undergoing surgery was 18.1 years with a range between 14.9 and 22.1 years. No data regarding outcomes of the surgery were reported. The authors argued that initiation of GnRHa at an earlier stage of puberty was preferable as it was associated with better surgical outcomes; however, they did not present any evidence from this study, or cite other studies, to support the claim (level D).

The review by Mahfouda et al.[4] included five empirical studies of surgical interventions, including one that was published before 2000, one that included participants whose mean age at the time of the survey was over 18 years and the aforementioned study by de Vries and colleagues.[30] In three of the studies participants had undergone both top and bottom surgery and the impact of the chest surgery alone could not be separated. The remaining two studies examined chest surgery for trans boys. Chest surgery was associated with reductions in gender dysphoria and improvements in overall mental health and quality of life. The measures used to assess gender dysphoria and mental health were not reported in the review. No regret was reported following surgery (level B).

A qualitative study of the experiences of 35 transgender children and adolescents identified only one individual who underwent chest surgery.[40] This individual, a trans boy, reported that of all the interventions he had experienced, chest surgery had the most significant positive impact on his wellbeing (level D). Most participants in the study were under the minimum age restriction for surgery and some reported they were not interested in surgery. Other participants, however, particularly those with acute gender dysphoria, considered surgery a crucial step to alleviate dysphoria.

Overall, the available guidelines agree there is a beneficial effect of chest surgery on gender dysphoria, general psychological wellbeing, satisfaction with body image and social acceptance of affirmed gender[47-49,51] (level B–C). It should be noted, however, that in the absence of studies specific to children and adolescents, expert opinion is largely based on clinical experience rather than controlled studies and by extrapolating evidence generated from adult samples.

Question 1b: What have been shown to be the risks or potential harms from medical interventions for children and young people with gender dysphoria?

Medical intervention 1: Puberty suppression

Some participants reported that they experienced a very long wait for puberty suppression treatment, which adversely affected their mental health. Additionally, some expressed concern about affordability of treatment, fear of possible cancer and fear of injections[40] (level D).

A more affordable puberty suppression treatment than GnRHa used in one study was bicalutamide.[24] In this study, there were no apparent side effects; however, as this was a very small retrospective chart review with only 13 participants these results should be treated with caution (level C–D).

Lynestrenol, another cheaper alternative that required no needles, was investigated for puberty suppression in one study.[27] A rise in haemoglobin was observed, which stabilised to normal male levels within three months. Although it was deemed less effective than injectable GnRHa, it effectively and significantly decreased the overall estrogenic to androgenic ratio within six months (level C).

The use of cyproterone acetate (CA) instead of GnRHa resulted in additional side effects of emotionality (29%), hunger (14%) and hot flushes in one study (14%).[12] In other studies, complaints, especially of fatigue, were relatively frequent during treatment with cyproterone acetate (CA).[27 45] These authors concluded CA would be a viable, safe and more affordable alternative to GnRHa in trans girls (level C–D). Harms of treating could also be concerns about social consequences of treatment: in one small qualitative study (N=5), the fear of withdrawal of parental support was voiced should the adolescent embark on puberty suppression and gender-affirming hormone treatment.[65]

Bone density

One of the most serious side effects of puberty suppression treatment is bone density loss, which is reported in 10 of the included papers.[1,4,8,9,40,43,45,47,48,49] Tack and colleagues[8] demonstrated limited normal bone expansion and less pubertal bone mass accrual, mostly at the lumbar spine, which was more pronounced in trans girls, in a study following late pubertal trans boys and trans girls using pro-androgenic or anti-androgenic progestins lynestrenol and cyproterone acetate for between four and 40 months (level C). In one qualitative study involving focus groups for TGD children and their parents, one participant using GnRH experienced a stress fracture[40] (level D). One study showed the loss of bone density continued throughout a 24-month treatment period[9] (level C).

Physical side effects

Participants of several studies reported side effects such as hot flashes, mood swings and (less commonly) headaches, knee pain and excessive thirst.[40] Weight gain and fatigue were common side effects of puberty suppression reported in one study[23] (level C–D).

In another study, one participant experienced sterile abscesses from injectable leuprolide acetate, which resolved when switched to triptorelin.[29] One participant also reported leg pain and headaches, which spontaneously resolved. One participant had weight gain of 19 kg in nine months[29]; however, his previous BMI was above the 85th percentile[29] (level C–D).

In one study, height gain velocity decreased in both trans boys and trans girls.[11] Lean body mass percentage significantly decreased during the first year of treatment, whereas fat percentage significantly increased. These authors recommended further studies to determine the extent to which changes in height and body composition that were observed during GnRHa treatment could be reversed during subsequent GAHT (level B–C).

Cognition

Adolescence is an important period for developing executive cognitive functions (e.g. working memory, flexible thinking, planning) and two studies examined whether puberty suppression treatment effects cognitive function. One study[42] examined the impact of GnRHa on performance on the Tower of London (ToL) task, which is a commonly used test of planning ability (level B–C). The researchers found no significant effect of GnRHa on reaction times or accuracy on the ToL task and concluded there were no detrimental effects of GnRHa on executive functioning. The second paper reported a single-subject case study of the effect of puberty suppression using GnRHa on white brain matter (WM) in a trans girl (level D).[37] The subject, who had low average cognitive functioning at baseline, showed no change in white matter fractional anisotropy over 28 months. In comparison, WM typically increases in adolescent males. A drop in operational memory was also observed. The authors were unable to determine whether the findings were due to the patient's low cognitive functioning at baseline or reduced serum testosterone levels.

Risks of not treating

In a very small case-study[25] (N=5), the authors proposed that harms from not treating gender dysphoria in a timely way would result in gender nonconforming youth turning to maladaptive behaviours to change their bodies, or self-harm the body that they perceived as a betrayal of their authentic gender. They cited adverse outcomes when parents refused to support gender identity (n=2) as well as another case of parent rejection of gender-affirming treatment (n=3), and a lack of timely referral to specialist gender clinics, which contributed to escalation of maladaptive behaviours, including eating disorders (level D).

Medical intervention 2: Gender-affirming hormone therapy (GAHT)

Risks or potential harms from gender-affirming hormone therapy for trans girls.

Irreversible changes

There were no eligible empirical studies in this Evidence Check that explored whether GAHT for trans girls was reversible, and most changes are thought to be at least partially reversible. The Endocrine Society Clinical Guideline[47] suggests fertility is likely to be compromised following GAHT, and gynecomastia (enlarged breast tissue) may be corrected by surgery.[48] Decreased growth velocity, which may be partially reversible, has also been noted in a recent systematic review.[45] (level B–C).

Physical side effects

Side effects from GAHT for trans girls can include breast tenderness, fatigue, mood swings and hot flushes.[23]

Body image

Although a small retrospective chart review reported improvement in body image in trans girls with eating disorders following hormonal treatment, one subject retained eating disorder thoughts.[25] (level D).

Alteration in biochemistry

In a small study (N=14) investigating metabolic profiles of trans girl adolescents using GAHT, there was a trend towards increasing triglycerides, high-density lipoproteins (HDL) and prolactin levels, although the values did not reach statistical significance.[32] Excessively elevated oestradiol levels and elevated liver enzyme levels have been observed with GAHT.[23] Elevated liver enzymes were also observed in another study, alongside other metabolic side effects of hypertriglyceridaemia, with possible increased risk of hypertension, hyperprolactinaemia or prolactinoma[48] (level C–D).

Fertility

Compromised fertility is a likely consequence of GAHT[47] and fertility discussion is recommended with transgender adolescents prior to commencement of GAHT.[49] For prepubertal transgender youth, the only feasible option of fertility preservation is testicular tissue cryopreservation, which is still experimental and not yet proven successful in humans[44] (level B–C).

Potentially serious side effects

Serious side effects of GAHT were few. In one study[14], ethinyl estradiol was used in two (of 28 participants) rather than estriol. One of the two trans girls using ethinyl estradiol developed hyperprolactinaemia and galactorrhoea, with no pituitary lesion seen. WPATH no longer recommends the use of ethinyl estradiol in GAHT because of a high risk of venous thromboembolism[48,51] (level B–C). An expert statement from the Pediatric Endocrine Society Special Interest Group[51] suggested the thromboembolic risk was higher with ethinyl estradiol than estradiol taken orally or using a patch. WPATH guidelines stated another potentially serious side effect was noted in trans girls using spironolactone, which can be used to reduce testosterone levels in trans girls.[48] In a retrospective cohort (N=117), one participant experienced low sodium and high potassium levels while taking spironolactone. In this study, the participant taking spironolactone had multiple comorbidities, which may have influenced the outcome.[33] (level D).

Risks or potential harms from gender-affirming hormone therapy for trans boys

Irreversible changes

There were no eligible empirical studies in this Evidence Check that explored whether the effects of GAHT for trans boys were reversible. Certain changes were thought to be irreversible: voice deepening[1,48,49], male pattern hair growth including increased bodily and facial hair and male pattern balding[1,29,49] and compromised fertility.[47,51] These statements were from standards of care and clinical guidelines from *The Endocrine Society* and the *Pediatric Endocrine Society Special Interest Group on Transgender Health* (level B–C).

Physical side effects

Voice deepening has been reported as an irreversible consequence of testosterone therapy.[1,48,49] Several studies reported increased (sometimes severe) acne.[17,23,27,29] In one study the incidence of

acne increased up to 12 months post-therapy but by 15 months post-therapy showed signs of lessening[17] (level C–D).

One study reported one case of androgenic alopecia[29] and another reported male pattern balding[27] (level C–D). Changes in hair patterns such as facial and body hair growth and scalp hair loss induced by hormone therapy in trans boys are unlikely to be reversible.[1] (level B–C).

Sleep apnoea[48] and fatigue have been reported[27], particularly when anti-androgen cyproterone acetate is used.[45] One retrospective chart review (N=45) reported one in four participants ceased treatment as a result of hot flushes.[27] Increased appetite has been noted with GAHT[23], which has also been implicated in increased BMI or weight gain for trans boys[32,33,48] (level C–D).

Mental health issues

Australian guidelines suggest many transgender youth (particularly those experiencing untreated gender dysphoria) have mental health comorbidities that are exacerbated as they start puberty, and are at high risk for depression, anxiety, isolation, self-harm and suicidality.[1] In our Evidence Check, few mental health issues were identified in trans boys (once they were receiving GAHT). Significant mood swings were reported by only one participant in a retrospective cohort study[29] (level C–D). In a qualitative study involving focus groups for TGD adolescents and their support people, some anxiety was voiced regarding the expense of the treatment and the long waiting time to be seen at the clinic[40] (Level D).

Bone density

In a prospective study involving trans boys who had started GnRHa treatment and had subsequently received testosterone treatment for more than six months, bone density scores were lower than pre-treatment levels after 12–24 months of testosterone treatment. This study investigated physical changes, laboratory parameters and bone mineral density during GAHT for trans boys[17] (level C–D). Dual-energy x-ray absorptiometry (DXA) or bone densitometry scans remain important in the follow-up of the bone health of transgender adolescents[9] (level C).

Alteration in biochemistry

A significant rise in systolic blood pressure was reported during the first six months of GAHT[17], as well as elevated red cell markers[23] (level C-D). Lipid abnormalities (mild dyslipidaemia) were reported in three participants in one study involving 37 participants[29] (level C–D). Significant increases in haemoglobin/haematocrit levels and decreases in high-density lipoprotein levels were recorded up to six months after starting testosterone treatment, which then stabilised[32,33] (level D). These effects were found to be higher in those taking larger doses of testosterone. Similarly, lipid metabolism shifted to an unfavourable HDL/LDL ratio in another study[27] (level C). In their recent review, Mahfouda and colleagues[4] reported concerns about acute hepatic dysfunction in trans boys during GAHT.

Fertility

Expert statements warn testosterone therapy for trans boys may lead to sterility[47,51] although it does not necessarily protect against unwanted pregnancy.[51] Ovarian reserve and fertility preservation should be discussed with trans boys starting GAHT.[27]

Potentially serious side effects

There was a single case study reporting pulmonary embolism without an underlying genetic thrombophilic condition in a 17-year-old trans boy taking ethinyl estradiol-containing oral contraceptive pills (for control of menses) for 10 months before simultaneously commencing testosterone cypionate injections for gender transition.[63] These authors recommended modification or elimination of other thrombotic risks factors before starting testosterone therapy in this population.

Breast cancer, ovarian cancer, uterine cancer and vaginal cancer have all been reported in trans men but it is uncertain whether an association with GAHT in adolescence is associated with higher risk[49] (level C–D).

Risks of non-treatment with GAHT

Australian and international guidelines suggest prolonged administration of puberty suppression and delay of GAHT is likely to be associated with a greater risk of relative osteopaenia.[1] In trans girls, delay in GAHT may result in distressing linear growth beyond expected final height, a result of delayed growth plate closure because of oestrogen and testosterone deficiency.[1,47] Delay in commencing GAHT may also contribute to or exacerbate mental health conditions such as distress, anxiety or depression because of the sense of social isolation that arises from the timing of puberty being out of sync with peers[47], with subsequent increase in self-harm or suicide risk.[1]

Long-term outcomes: Puberty suppression

We identified 18 papers that discussed long-term outcomes following puberty suppression. Ten of these papers were graded NHMRC III-2–III-3, with the remaining six papers NHMRC Level IV (NHMRC matrix levels B–D). Of these, five were guidelines, reviews or position statements[1,44,45,47,48] and 13 were empirical studies.[8,9,11,15,18,19,21,30,34,35,39,42,53] These papers were highly positive, particularly with regard to mental health outcomes following puberty suppression, with some recommending psychological support as an adjunct to this therapy to improve health outcomes. One limitation was that some papers assessed long-term outcomes of both puberty suppression and GAHT together as treatment for gender dysphoria. No studies assessed long-term fertility outcomes for those using puberty suppression.

Psychosocial outcomes

High levels of satisfaction following puberty suppression were reported by one study, with 55 participants followed up for 18 months after the start of treatment[30] (level D). In this study, the trans girls reported higher levels of satisfaction than trans boys, and none expressed regret. Two studies suggested mental health outcomes were higher following psychosocial support during puberty suppression[18,23], with one of these papers reporting that the impact plateaued after six months[18] (level B–C).

In a study that interviewed 89 TGD individuals up to the age of 36, the lifetime risk of suicidal ideation was lower in those who requested and received puberty suppression compared with those who requested puberty suppression and did not receive it.[53] One limitation of this study was that it was unclear whether these people also received GAHT, so it is difficult to attribute the effect only to puberty suppression treatment (level B–C). Another 18-month follow-up study (n=50) found reduced depression and suicidal ideation 18 months after commencing GnRHa[19] (level B–C).

Bone mineral density

There is consistent evidence in long-term follow-up, in a rigorously designed systematic review, that BMD is reduced with puberty suppression[47] (NHMRC level IV; NHMRC matrix level B). Bone health, especially at the lumbar spine, is of concern in trans girls, as bone mass accrual is severely affected by androgen suppressive therapy.[8] One study followed TGD individuals from the start of GnRH to the age of 22. These authors concluded that at the age of 22, BMD was below their pre-treatment potential and either attainment of peak bone mass had been delayed or peak bone mass itself was attenuated.[15] Another study detected a significant reduction in bone turnover over a two-year period, which was more pronounced in trans girls.[9]

One recent review[45] suggested there was insufficient evidence of the impact of GnRH on potential height loss because of a lack of heterogeneity of studies and inconsistent length of time of, or lack of, follow-up. This was demonstrated by a recent case study that found the BMD of a non-binary youth who used GnRH for more than two years dropped to the lowest 2.5th percentile (without any fractures). The youth was assessed as having reduced gender dysphoria and anxiety; however, this case demonstrates the clinical dilemmas experienced by care providers[66] (level B). In another case study, one trans boy had GnRH for four years from the age of 13, followed by GAHT. At the age of 22 (following use of GAHT) his bone mineral density was within normal parameters for his birth-assigned and cisgender peers[39] (level C–D).

Cardiovascular risk and biochemical profile

One recent study followed 192 TGD adolescents who had undergone puberty suppression and GAHT. During treatment and up to the age of 22, blood pressure, lipids, insulin resistance and BMI were measured. Limitations of this study included failure to adjust for confounders such as diet, activity and family history of obesity and dyslipidaemias. Lipid values for TGD at the age of 22 were similar to cisgender peers; however, TGD people were significantly more likely to be obese[35] (level B–C). Another study followed 116 adolescents taking puberty suppression for 12 months. Monitoring of creatinine and liver enzymes did not identify any pathology.[11]

Long-term outcomes: GAHT

We identified 10 papers that discussed long-term outcomes following GAHT, ranging from NHMRC level III-2– IV, with NHMRC matrix levels B–D. Of these, four were guidelines, reviews or position statements[1,4,23,47] and six were empirical studies.[8,14,17,21,35,36]

Psychosocial outcomes

The physical changes in line with affirmed gender that occur with GAHT have already been discussed in the previous section. These changes are sustained in long-term studies[8], with the effect less pronounced in trans men than trans women.[35] In another study involving 64 trans boys, not all had achieved the desired bodily changes by two years (not all had abdominal hair).[17] It is likely that voice deepening with testosterone therapy is irreversible[23], along with male pattern balding[8], for trans boys.

One study (n=148) assessed TGD adolescents 12 months after commencing GAHT, using validated tools for body satisfaction, depression and anxiety. This study reported large improvements in body satisfaction, and small to moderate improvements in self-reported depressive symptoms[21] (level C). The study's limitations included an absence of peer comparators and no details of protective factors

such as family support for participants. Another study reported that of the 2.5% (89/3494) of transgender adults who had requested intervention for gender dysphoria as children, those who received puberty suppression had lower lifetime odds of suicidal ideation compared with those who did not receive it[36] (level B–C).

Bone mineral density

Several studies reported restoration of bone mineral density with GAHT following BMD loss during puberty suppression.[8,9,14,17] In one study involving 26 trans girls, height gained was related to bone growth when they started taking GAHT. The bone age of those commencing GAHT was variable; if baseline bone age was 13–15 (younger bone age), those with advanced bone age grew slowly[14] (level C). In one study following 64 trans boys for two years after starting testosterone, BMD z-scores increased after starting GAHT, but at 12–24 months remained lower than pre-treatment values.[17] In another study assessing trans girls who had used GnRh (n=21), weight and BMI changes similar to age-matched peers were detected, with significant fat mass increase.[17]

Fertility

There is consensus that GAHT may affect fertility long term and many papers recommend fertility counselling before starting treatment[1,23,47] (level C).

Cardiovascular risk and biochemical profile

GAHT does not appear to confer significant risk for cardiovascular events and biochemical profile long term. However, in one study (n=192) the prevalence of obesity at age 22 was higher in trans women and trans men who had taken GAHT than in their cisgender peers.[35] In one five-year retrospective audit of 45 trans boys taking lynestrenol and testosterone esters, lipid metabolism shifted to an unfavourable high-density lipoprotein / low-density lipoprotein (HDL/LDL) ratio.[8] In another study, non-clinically significant elevations in systolic and diastolic blood pressure were observed after two years of testosterone treatment, and the collective consensus from a number of authors is that such changes observed in transgender adolescents do not pose a clinical risk.[4]

In a two-year follow-up study of 64 trans boys who were receiving testosterone therapy, haematocrit significantly increased in the first year but reverted to normal levels without interevention.[16] In one five-year study of trans girls taking GAHT, prolactin, Hct and HbA1c liver enzymes didn't change except for lower ALP in years two and three. Creatinine decreased in the second year except in one case, where it increased after a year but subsequently spontaneously normalised.[14] These authors concluded that regular biochemical monitoring for trans girls taking GAHT was unnecessary, but suggested precautionary prolactin monitoring (level C). They also suggested high doses of oestrogen (which has been given in cases of excessive height) may increase the risk of venous thromboembolism. Discouraging both smoking and long periods of immobilisation are important in this scenario.

Medical intervention 3: Gender-affirming surgery (top surgery)

Risks or potential harms from surgical interventions

No harms associated with chest surgery were reported by Pullen-Sansfaçon and colleagues[40], nor by Khatchadourian and colleagues.[29] In another study[34], the self-reported complication rate was relatively low, with 36% experiencing hypertrophied scar tissue (keloid) and/or a small and temporary fluid or blood collection. Most subjects had decreased or complete loss of sensation in the surgical and nipple area. No participants experienced serious adverse effects such as nipple necrosis or infection. Although reportedly not regretting having the procedure done, one participant stopped testosterone treatment about two months after surgery. This participant did not feel as elated as other participants about the outcome and later requested to return to the sex they were assigned at birth. One barrier to transgender youth accessing surgical options is financial: the cost of chest reconstruction surgery is expensive and may not be covered by insurance (level C–D).

The latest Endocrine Society Clinical Practice Guidelines[47] advise that surgery is partially irreversible. These guidelines, along with the position statement by Lopez and colleagues[51], also draw on studies from adult populations to note that long-term follow-up studies have found persistence of psychiatric comorbidity and death from suicide in transgender patients after gender-affirming surgery. However, Lopez et al.[51] cautions that these results should not be interpreted that sex reassignment increases morbidity and mortality given the overall mortality rate was only significantly increased for the group operated on before 1989. The reduced mortality rate since then may be due to improved healthcare for transgender adults during the 1990s and beyond, along with improved societal attitudes towards gender-nonconforming individuals (level B–C).

One qualitative study[40] was the only eligible paper to consider the harms of not treating. This study identified a lack of access to surgery as an important source of distress and reduced wellbeing (level D).

Summary: harms from surgical interventions

The absence of controlled studies with sufficient follow-up, combined with a lack of validated measures and adequate control of potential confounders, means assessments of the harms associated with gender-affirming surgery for children and adolescents relies heavily on evidence with a high risk of bias, including case studies and expert opinion. Thus, while relatively few harms associated with chest surgery have been documented this may be due to the absence of evidence rather than evidence of absence. To better understand potential harms associated with chest surgery in young people there is a need for more well-designed studies that examine a wide range of outcomes.

Quality of evidence: Gender-affirming hormone therapy (GAHT) and surgical interventions

Medical interventions

The quality of most included studies of medical interventions was low. Overall, although some reviews were extremely thorough and assessed the quality of included studies and available evidence, most studies had small sample sizes and in many cases missing data was not accounted for. Some relied

on expert consensus for treatment recommendations. Randomised controlled trials in this area are not ethically possible and control groups (if included) are usually age-matched peers not taking GAHT. Many studies had other methodological flaws such as not adjusting for potential confounders such as diet, lifestyle and exercise / strength training when examining change in body shape and composition with GAHT; and concurrent psychosocial interventions when assessing the effect of medical therapy on mental health status.

Six studies reporting GAHT involved the Center of Expertise on Gender Dysphoria at VU University Medical Center in the Netherlands.[9,14,16,17,26,30] It is unclear whether the participants in the various studies overlapped; that is, whether the same subjects participated in different studies. Duplication of data is likely to lead to an overestimation of intervention effects.

Many of the empirical studies used case notes retrospectively, from a cohort. Using records that were not designed for the study may result in the available data being of poor quality. Sometimes it is difficult to identify potential confounding factors if the data were recorded in the past, as well as to identify an appropriate exposed cohort and an appropriate comparison group. Losses to follow-up can also bias retrospective cohort studies.

Surgical interventions

The quality of evidence for chest surgery in transgender youth is low. There is a lack of studies in this area and only one study we identified included more than one individual who had undergone chest surgery. In the absence of empirical evidence, guidelines and standards of care rely heavily on expert opinion and by extrapolating evidence from studies of adults. Among the empirical studies we identified, only one reported any quantitative data and none used validated pre and post measures to determine the impact of the intervention on gender dysphoria, psychological wellbeing and physical health.[34]

The quality of evidence for risk of harm from gender-affirming surgery for children and adolescents is very low. Available guidelines note the potential harms of surgery, but the evidence is largely extrapolated from adult populations because of the lack of studies among younger people.

Question 1c: Is there variation in the effectiveness and risks associated with medical interventions for children and young people with gender dysphoria by factors listed below?

Variation in effectiveness: Medical interventions

Although some authors reported uncertainty as to the recommended age for GAHT[10], most studies recommended it should not begin until 16 years of age[26,48,50,51] because of some of the irreversible effects of treatment. In some cases (e.g. to halt excessively tall height development over 180 cm), GAHT was commenced in children at 15[14,51], some recommending starting earlier in special cases after expert multidisciplinary discussion.[4,47] In one study, significantly lower height standardised values were observed for trans girl adolescents only[15] (level B).

More recent authors appear to be moving away from recommending a particular age for GAHT. One advised commencement of GAHT at Tanner stage 4, after at least six months of treatment with cyproterone acetate.[12] Australian guidelines recommend considering treatment when the adolescent is competent to make an informed decision.[1] These authors suggest timing depends on the nature, history and presentation of gender dysphoria, duration of GnRH for those on stage 1 treatment, comorbid mental health and medical issues, and existing family support (level B–C).

For trans girls, there appears to be a more significant return to normal bone density if GAHT is started at a 'bone age' younger than 15 than at an older bone age.[9] The clinical significance of this is not clarified (level C).

It is as yet uncertain whether starting GAHT at a younger age is associated with improved quality of life of transgender adolescents or is associated with increased rates of regret or de-transition[4] (level B) / (level D).

One retrospective study (N=116) found a significant rise in haematocrit, high-density lipoprotein and body mass index in trans boys taking testosterone. These authors also pointed to another study in adult trans women taking oestrogen, where increased cardiovascular events and venous thrombosis were noted. These authors recommend closer surveillance of adolescents with medical comorbidities, as GAHT may increase risk of morbidity[33] (level D).

Variation in effectiveness: Surgical interventions

The paucity of studies investigating surgical interventions among transgender children and adolescents precludes any assessment of whether there is variation in the effectiveness or risk associated with such interventions.

The recommendations within the available guidelines typically reflect the World Professional Association for Transgender Health (WPATH) guidelines.[48] The Australian Standards of Care and Treatment Guidelines[1] recommend that chest surgery does not occur before 16 years of age and that the decision regarding surgery should be made jointly, with consensus between the adolescent, guardians and clinicians. The Endocrine Society Clinical Practice Guidelines[47] recommend that gender-affirming surgery does not occur before the age of 18, while WPATH[48] recommends that the young person has undergone at least one year of testosterone and spent sufficient time living in their desired gender role prior to surgery (level B–C).

Question 2: What are the effective psychosocial interventions for TGD children and young people and those with gender dysphoria?

We identified three papers investigating psychosocial or behavioural interventions among transgender adolescents or their parents / carers (Table 5). One paper investigated the effect of psychological support on global functioning among transgender adolescents.[18] Another paper[41] described a pilot program of group work for parents and carers of transgender adolescents and the third paper[38] reported a single subject case study in which a trans girl in a youth justice facility received intensive voice feminisation therapy.

Question 2a: What have been shown to be the most effective psychosocial interventions for treating children and young people with gender dysphoria?

There is a lack of evidence for the effectiveness of psychosocial interventions for transgender adolescents. We identified only three studies, all of which were low quality. While each of the three studies reported positive findings, the small self-selected samples, absence of control groups and failure to account for confounders means it is not possible to isolate the effect of the intervention from other factors. We did not identify any eligible studies comparing neutral psychological therapy versus gender-affirming therapy, nor any eligible studies investigating therapies to change gender identity (conversion therapy).

Psychosocial intervention 1: Psychosocial support vs psychological support and referral

The most robust study of psychosocial interventions was a prospective cohort study conducted by Costa et al.[18], who compared the global psychosocial functioning of 36 transgender adolescents who received psychological support and GnRHa with 35 transgender adolescents who received psychological support and referral to a mental health service. Participants were assessed four times over 18 months. Global psychosocial functioning among study participants was also compared with a normative sample of adolescents without psychological morbidity. At baseline, adolescents with GD had lower psychosocial functioning than a normative sample of adolescents. At six months, participants in both groups had significantly improved psychosocial functioning; however, only the group who also received GnRHa continued to improve. At 18 months, participants who received psychological support and GnRHa were comparable to a normative sample while participants who received psychological support alone continued to score lower than a normative sample.

Quality of evidence

The quality of this study was low to moderate. While the authors reported that all participants received psychological support for the duration of the study, the exact nature of the support and the dose of support received was not standardised and neither was it controlled for in the analysis. Therefore, it is not clear if there were differences in the amount or type of support between the two groups and to what degree this affected the outcomes. Additionally, because there was no control group it is not possible to isolate the cohort effects in which improved psychological functioning may be due to the young people naturally maturing. There was also substantial attrition throughout the study, with only 71 of the original 201 participants completing all phases. Differences between those who completed all phases of the study and those who dropped out were not reported.

Psychosocial intervention 2: Group therapy

One small study[41] described a six-session group therapy program for parents and carers of transgender adolescents. Attendees completed a brief evaluation questionnaire at the completion of the program which indicated that most participants found the sessions to be ‘helpful ’or ‘very helpful’. Key benefits of the program were parents’ self-reported feelings of diminished isolation and better understanding and knowledge of gender identity development.

Quality of evidence

The quality of this descriptive study was very low. It comprised a small, self-selected sample of parents and carers of adolescents enrolled in a UK gender identity clinic approximately 15 years ago. The lack of objective pre and post measures means that it is not possible to determine how much, if at all, attitudes shifted over the study period. The lack of a control group makes it impossible to separate the effect of group therapy from the effect of the adolescent being part of the gender identity clinic.

Psychosocial intervention 3: Voice feminisation therapy

One paper[38] described a case study of voice feminisation training in a trans girl in an Australian youth justice facility. Following treatment, the participant reported that their voice was having a less negative impact on their life. However, they were still not consistently perceived as female and had difficulty implementing feminine speech strategies in discourse. The authors concluded it was possible to achieve significant voice change within a limited time frame while working with transgender young offenders.

Quality of evidence

The quality of this study is very low, largely due to the single-subject design. Furthermore, the generalisability of this study to the broader population of transgender youth is limited by the unique circumstances of the participant and their complex social and criminal history and comorbid psychological and neurological issues.

Question 2b: What have been shown to be the risks or potential harms from psychosocial interventions for treating children and young people with gender dysphoria?

One study (which did not meet eligibility criteria as it included lifetime exposure to gender identity conversion therapy [GICT], not just childhood) identified a strong association between recalled exposure to the outdated practice of GICT and psychological distress and lifetime suicide attempts.53 This association was stronger when the recalled exposure was when the child was 10 years or younger. The authors concluded that this practice was harmful and concurred with policy statements from several professional organisations that have discouraged this now outdated practice.

We identified no other risks or potential harms of psychosocial interventions. Although the voice feminisation intervention38 did not succeed in completely inducing feminine speech strategies, no specific harms of the treatment were reported. Similarly, although some participants in the group therapy intervention41 reported that they found it difficult to follow some of the doctor's language, no harms were reported.

Because none of the studies included a control group it is not possible to quantify risks or harms associated with not administering treatment.

Question 2c: Is there variation in the effectiveness or risks associated with psychosocial interventions for treating children and young people with gender dysphoria by factors listed below?

The lack of studies investigating psychosocial interventions and the heterogeneity among the three studies that we identified precludes any assessment of whether or not there is variation in the effectiveness or risk associated with psychosocial interventions for children and adolescents with gender incongruence or gender dysphoria.

Gaps in the evidence

Although the preliminary evidence suggests gender-affirming treatments are associated with mental health benefits there are large gaps in the evidence base regarding the benefits and potential harms of both medical and psychosocial interventions for transgender children and adolescents. Key gaps in the evidence base are:

Understanding the characteristics of trans and gender diverse (TGD) youth

It was out of the scope of this Evidence Check to examine population studies of TGD youth in Australia. Hence, it is not possible to know how representative the subjects in existing studies are of the transgender youth population and the degree to which the findings can be applied to transgender youth more broadly.

Timing of gender-affirming medical interventions

There is a lack of studies examining the short- and long-term effects of initiating GAHTS and performing gender-affirming surgeries at different ages and developmental stages. It is not clear whether individuals who start such treatment earlier have varying degrees of regret, satisfaction, societal acceptance, quality of life and so forth than individuals who start treatment later.

Social isolation during puberty suppression

Some authors proposed that there is potential for the TGD child undergoing puberty suppression to experience (increasing) social isolation as their peers experience the many physical, emotional and social changes during puberty. Further studies could explore this issue.

The role of pubertal suppression and GAHT on the outcomes of surgery

Although expert commentary reports it appears to be generally accepted that starting puberty suppression at an earlier age improves the outcomes of surgery, we did not find much evidence to

support this. Further studies are needed to clarify the relationship between early pubertal suppression, surgery and a range of physical and psychosocial outcomes.

The effect of exercise and diet on bone density

None of the studies measured the effect of diet, exercise and vitamin D on bone density.

Long-term evaluations of medical intervention

More studies are needed on the long-term effectiveness and safety of gender-affirming treatment on mental health, social outcomes, metabolic and other physical variables.

A wide range of outcomes measured using validated instruments

The individual studies in this Evidence Check examined a relatively small range of outcomes and few used validated pre and post measures. A broader range of outcomes should be examined including family relationships, societal acceptance and quality of life. Future studies should use validated outcome measures across a range of domains.

The independent effect of medical interventions on psychological outcomes

The lack of studies that include a control group means it is not possible to determine the effect of medical interventions on psychological wellbeing independently of other factors such as growing maturity and the effect of being part of a TGD treatment program.

Type and effect of psychosocial interventions

There is a gap in our understanding of the effectiveness of psychosocial interventions for transgender children and adolescents. Future studies should explore which interventions are suitable for transgender children and adolescents at different ages and the effect of those interventions alone and in combination with medical interventions, although this poses the challenge of how to design a study that withholds medical or psychosocial intervention ethically.

Discussion

The aim of this Evidence Check was to identify evidence-based options to inform a state-wide clinical service for NSW to meet the needs of the vulnerable population of children and young people with gender dysphoria or who are trans and gender diverse (TGD). In January 2020, we conducted a literature search to identify published evidence. Following application of a range of search terms to seven databases, two reviewers independently screened and reviewed the abstracts and full texts of articles in Covidence.[58] Thirty-eight peer-reviewed studies, practice guidelines and reviews published since 2005 were deemed appropriate for inclusion. We examined the quality of all publications using the NHMRC levels of evidence.

Robust evidence of the benefits and harms of medical and psychosocial treatment for TGD children and adolescents is lacking, mainly due to the emerging nature of this field, low population prevalence of this group, and the ethical challenges of designing quality studies with control groups where treatment is potentially not provided to all participants. The paucity of quality empirical research reflects the emerging nature of healthcare for trans and gender diverse adolescents. More than half of the included empirical studies were retrospective, mainly derived from case notes. Some recent prospective papers improve the quality of the evidence base in this area. There are a relatively small number of studies for each of the interventions we examined and the quality of the evidence across almost all studies was low. Most of the evidence we identified was for puberty suppression and GAHT. Very few studies examined psychosocial interventions or top surgery in adolescents.

Puberty suppression

Strong evidence was found for the use of GnRHa in effectively and safely suppressing puberty. Although side effects such as hot flushes, acne, weight gain and mood swings are common, these appeared to be reasonably well tolerated by TGD children and adolescents.[12,29,40] There is weak to moderately strong evidence that anti-androgen medications such as cyproterone acetate or spironolactone may also relieve dysphoria in trans female adolescents.[23]

GnRHa is more expensive than other puberty suppressing treatments and may be problematic for adolescents who cannot tolerate injections. However, GnRHa is more effective than alternatives for suppressing puberty and does not have the serious adverse side effects that occasionally have been reported with alternatives such as cyproterone acetate and medroxyprogesterone.

Expert opinion indicates that there are several key benefits of puberty suppression. First, it allows the young person more time to explore their gender identity before initiating irreversible, or partially irreversible, gender-affirming treatments. Second, it reduces the potential of further psychological harm that may arise when the young person develops the unwanted secondary sexual characteristics of the sex they were assigned at birth. It has been reported that some young TGD children and adolescents attempt to self-harm by removing the body part they find incompatible with their affirmed gender.[25] It has been suggested that preventing the development of breasts in trans boys, and

testicular and penile development in trans girls may reduce such incidents of self-harm.[25] Third, gender-affirming hormone treatment and top surgery are more successful in achieving the desired aesthetic outcomes when puberty has been suppressed.

There is a lack of empirical studies into the impact of puberty suppression on gender dysphoria. The only quantitative study using validated pre and post measures found no change in gender dysphoria following GnRHa treatment.[13] This is not surprising as GnRHa does not change body composition; rather, it aims to stop changes in body composition. Similarly, the empirical evidence for the psychological benefits of puberty suppression is weak. Although several studies reported that puberty suppression was associated with improved psychological wellbeing, none included a control group of TGD adolescents not undergoing puberty suppression. The lack of a control group makes it difficult to conclude that puberty suppression itself has a causal role in improvements in mental health. It is possible that the observed improvements in psychological wellbeing are at least partially attributable to maturational effects of the adolescent and the effect of enrolling in a gender dysphoria clinic where, for example, they: (1) have their desired gender affirmed by health professionals; (2) might meet other TGD youth; and (3) are likely to receive psychological support. Indeed, a recent (unpublished) study at the Royal Children's Hospital Gender Service in Melbourne showed TGD children and adolescents attending a single session at a gender clinic reported multiple positive changes, including mental health, family functioning and quality of life.[67]

Investigation into the potential harms of puberty suppression have centred on bone mineral density (BMD). Puberty is a critical period for bone development and there are concerns that delaying puberty causes a loss of BMD, thus increasing the risk of osteoporosis and fractures in the future. Bone density issues for adolescents undergoing puberty suppression have been examined in several papers.[7-9,11,17,18,28,30,32,34] Some studies of puberty suppression and BMD conclude the changes in mean BMD are insignificant and argue that regular surveillance is unnecessary. However, a recent letter published in the *British Medical Journal*[74] points out that raw data from these studies reveal substantial heterogeneity among participants, with more than half losing BMD. Why some participants lose BMD and others do not is unclear. No studies we identified adequately accounted for important factors in bone development such as exercise and diet and there remain substantial gaps in our understanding of the relationship between puberty suppression and BMD. Regular monitoring of bone density during puberty suppression is widely recommended by expert consensus.

More recently, there has been a focus on the effect of puberty suppression on fertility. Fertility may be compromised if GnRHa is started early and followed by GAHT. The only feasible option for fertility preservation among prepubertal trans girls is testicular tissue cryopreservation, or harvesting of oocytes for trans boys, both of which are still experimental and invasive. Clinical guidelines are unanimous in recommending that fertility preservation counselling is conducted with the young person and their family before initiating puberty suppression.

Another potential harm noted by experts was the potential for the TGD child who remains prepubertal to experience (increasing) social isolation as their peers experience the many physical, emotional and social changes that puberty brings. Of note, however, we did not identify any studies exploring this phenomenon.

Recent papers endorsed by WPATH and expert consensus concur that there is no minimum age for puberty suppression. For trans boys, GnRHa is recommended at Tanner stage 2, and for trans girls, starting GnRHa at Tanner stage 2–3.

Gender-affirming hormone treatment

GAHT is effective in changing body composition in line with the desired gender. There is moderate evidence that an important benefit of GAHT is that it improves bone density following the loss observed during puberty suppression. Several studies found bone density was restored within three-to-six months of starting GAHT.

We found limited evidence of the psychological benefits of GAHT for children and adolescents; however, expert opinion indicates GAHT is associated with reductions in depression and gender dysphoria and increases in body satisfaction and self-esteem. Adult studies suggest reduction of sexual distress in TGD people after GAHT.[68]

There is conflicting evidence regarding haematological and metabolic changes during testosterone therapy. The largest study undertaken suggests monitoring lipids, liver function and cardiovascular parameters is important, particularly in the first three months of GAHT.[32] Common side effects include acne, hot flushes, mood swings, weight gain and, in trans boys, male pattern baldness. In general, these side effects appear to be tolerated although at least one study reported some participants discontinued GAHT because of hot flushes. One longitudinal study following 59 young people who had GAHT between the ages of 12 and 23 concluded that the use of hormones in transgender youth appeared to be safe over a treatment course of approximately two years despite alteration in some physiologic parameters that did not appear to have clinical significance.[10]

Some effects of GAHT are irreversible or only partially reversible. For trans boys, this includes voice deepening and male pattern balding. For trans girls, breast development may only be reversible through surgery. Although quality evidence is lacking, available evidence suggests fertility is compromised by GAHT.

Fertility preservation is an issue for adolescents undergoing GAHT.[44] A recent Australian study[69] reported that no trans boys opted for fertility preservation and suggested this population were electing to delay this procedure until they were older. However, 62% of trans girls underwent fertility preservation. The rate of trans girls undergoing fertility preservation was higher than that reported in studies from the US[70] or the Netherlands.[60] Pang et al.[69] suggested timely fertility preservation that did not substantially delay gender-affirming treatment explained the higher uptake. These authors suggested that being co-located with an onco-fertility centre and being publicly funded might explain the uptake rates. It is strongly recommended by expert consensus that fertility counselling be provided for all adolescents embarking on GAHT.

Historically, GAHT has rarely been started before 16 years of age. However, recent studies and expert consensus suggest the most appropriate stage at which to begin treatment should not be decided on age alone. The most recent Australian Guidelines[1] state that timing depends on the nature, history and presentation of gender dysphoria, the duration of GnRH for those on stage 1 treatment, comorbid mental health and medical issues, and existing family support. Decisions should be made by the informed and competent adolescent along with their support people and other health and allied health professionals involved. One study detailed the clinical dilemma sometimes faced by clinicians when adolescents request GAHT without parental support, and cited the difficulties of weighing up the perceived benefits of therapy with the potential for fractured family relationships.[52] These authors stipulated the practice of evaluating the risks of harm from withholding, delaying or initiating GAHT is vital to determine whether a proposed course of action (or refusal of an

intervention) would cross the 'harm threshold'. TGD children and adolescents who are well supported by their parents report positive health outcomes from GAHT.[2]

Top surgery

There are very few studies focusing on gender-affirming surgery in children and adolescents and clinical guidelines tend to have an over-reliance on expert opinion. This Evidence Check identified only three studies, all focusing on chest surgery in trans boys. The paucity of studies is to be expected given the age restrictions on gender-affirming surgery and the Evidence Check's inclusion criteria regarding age.

The evidence of benefits and harms of top surgery is limited. Small studies reported high levels of satisfaction with the outcome, but not all subjects experienced total satisfaction. Body image improvement and improvements in mental health outcomes were reported in small studies. Mild side effects were common but serious complications of the surgery were rare. The evidence for the effectiveness of chest surgery emerged from weaker study designs and should be considered preliminary. Keeping in mind the preliminary nature of the evidence, existing studies suggest most trans boys have a high level of satisfaction with chest surgery and that it is associated with a reduction in gender dysphoria and an improvement in psychological wellbeing. Mild side effects, such as scarring, were common but serious complications of top surgery were uncommon.

Psychosocial interventions

The lack of empirical evidence for psychosocial interventions for TGD youth was unexpected, especially given the elevated rates of psychological distress in this population and recommendations from multiple sources that mental health professionals should be involved in the care of TGD youth.[47,48,71] The absence of empirical research looking at psychological interventions has previously been described as an "*empirical black hole in the treatment literature*" for transgender youth.[72]

Due to the paucity of studies, there is limited evidence of the benefits or harms of any psychosocial interventions. The three studies in this Evidence Check all reported positive effects, although the design and interpretation of the studies was very weak. However, emerging evidence from the Royal Children's Hospital Gender Service in Melbourne suggests that even an initial bio-psychosocial assessment can have a beneficial impact on the lives of TGD children and adolescents and their families.

Limitations

This Evidence Check focused on TGD adolescents up until, but not including, the age of 18 years. Therefore, adult outcomes of treatments that began in childhood and adolescence were not included.

Overall, there are some serious limitations in the available evidence of the benefits and harms of treatment for TGD children and adolescents. In most studies, sample sizes are very small and rely on convenience sampling. The main disadvantage of convenience samples is that they are unlikely to be

truly representative of the population being studied. Thus, the degree to which the findings of such studies can be applied to the broader population of TGD children and adolescents is unclear.

Additionally, although many studies experienced substantial attrition, they did not report whether there were any systematic differences between participants who completed all assessments and those who did not. Non-random attrition skews the results. For example, if individuals who experienced serious side effects were more likely to drop out of a study, the results would suggest that treatment was associated with fewer side effects than the population experienced. In contrast, if individuals who experienced no side effects were more likely to drop out, the results would suggest that the treatment was associated with a higher rate of side effects. In most studies there were moderate to large amounts of missing outcome data and no attempt to determine if the data were missing at random or in a systematic way that would help in interpreting the results.

There was also substantial overlap of participants across studies. Just under a fifth (18%) of papers in the Evidence Check included a cohort of TGD youth recruited from the Center of Expertise on Gender Dysphoria, VU University Medical Center in the Netherlands.[9,14,16,17,26,30,,42] It was not possible to determine the independence of the samples analysed in each paper and it appears the same participants were included in multiple studies. Duplication of data is likely to lead to an overestimation of intervention effects.

Several studies were based on a retrospective chart review, which is highly biased as it depends on the information entered by the treating clinicians. Information that is unusual or unexpected is more likely to be entered into the chart than other information.

The absence of control groups, lack of consistent and validated measures, and the failure to account for salient confounders are particularly serious limitations in the literature on the benefits and harms of treatment for TGD children and adolescents. Study outcomes are frequently attributed to the treatment alone without sufficient consideration of other potential causes of observed change.

An additional issue with interpreting the results from empirical studies looking at puberty suppression and gender-affirming hormone therapy was the high variability of the different agents used in the different studies. The lack of homogeneity in the types of hormone used is likely to be attributed (at least in part) to the many countries represented in the samples and the use of generic hormone in some of the reviews and position statements.

Future research

Research into the treatment outcomes for TGD children and young people is an emerging field that is in the process of establishing a robust evidence base. It is anticipated that the quality of evidence will improve substantially over the next decade both internationally and within Australia. Although it may not be ethically feasible to conduct RCTs on this population, there are several ways in which the quality of the research could be enhanced.

First, researchers should clearly report the generalisability of their findings. This includes describing any sources of potential bias arising from the sampling technique that was used as well as the implications of non-random attrition from the study and the selection of statistical analysis methods (e.g. intention-to-treat analysis versus complete case analysis). Researchers should also describe

how the characteristics of the sample compare with aged-matched peers generally and TGD young people specifically. This will enable clinicians and decision makers to understand the degree to which findings from individual studies can be applied to the young people presenting for specific services. Results from a recent Australian study called *Trans Pathways*[57] provide an important data source from which future studies can draw to estimate the generalisability of their findings. *Trans Pathways* was an anonymous cross-sectional online survey of 859 young people aged 14–25 years living in Australia in 2016. The study collected data covering multiple measures and represented a significant step forward in understanding the characteristics of TGD young people. Unfortunately, *Trans Pathways* did not include children under the age of 14 years.

Secondly, future studies should be designed to measure outcomes across multiple domains using consistent, validated and standardised measures. Consistency of measures will enable findings from different studies to be compared, which provides a more reliable picture of the risks and benefits of individual treatments. Once again, there is progress in this regard in the Australian context. *Trans20* is a large prospective cohort study of TGD young people seen at the Royal Children's Hospital Gender Service (RCHGS) between 2017 and 2020.[73] At their first visit to the service, children and adolescents between three and 17 years of age will be recruited into the study and followed for up to 20 years. The study uses validated measures across multiple domains including, but not limited to, gender, physical and mental health, behaviour, schooling, family functioning, quality of life and experiences of care. *Trans20* provides an exemplar of the range of appropriate and validated measures available for use in studies of TGD children and young people.

Third, future research should be designed to measure and analyse potential confounders in the relationship between treatment and outcomes. The failure to consider the role of other factors in the observed outcomes is a notable weakness in the existing evidence base. Well-designed longitudinal cohort studies that compare outcomes for young people who receive a specific treatment with those who do not can provide more insight into the causal relationships between treatment and outcomes if they identify, measure and control for potential confounders a priori.

Applicability

Most studies in this Evidence Check are based on very small convenience samples recruited from gender dysphoria clinics or children's hospitals in Europe or the US more than 10 years ago. The degree to which these participants are representative of the NSW population of TGD children and adolescents is unclear. It is possible that individuals who enrolled in gender dysphoria clinics or who underwent treatment more than 10 years ago, when social acceptability of TGD was lower and treatment was harder to access, were more motivated to seek treatment because of higher levels of gender dysphoria and psychiatric comorbidity. Decision makers should consider whether potential differences between earlier cohorts of TGD children and adolescents seeking treatment and those currently seeking treatment in NSW are likely to affect the treatment outcome.

Nevertheless, although many questions remain, particularly concerning the psychosocial impact of treatments and the role of confounders on the outcomes, the evidence as to the efficacy, safety and side effects of interventions are highly applicable to the NSW context. *The Australian Standards of Care and Treatment Guidelines for Transgender and Gender Diverse Children and Adolescents*[1] inform the local context and reference other important guidelines such as the World Professional Association for Transgender Health (WPATH) guidelines.[48] Other key Australian papers inform the results of this Evidence Check and are particularly applicable to the NSW context.[1,4,43]

Conclusion

Trans and gender diverse (TGD) children and young people and those with gender dysphoria are a uniquely vulnerable population who are much more likely than their age-matched peers to experience stigma, marginalisation and other stressful events[1] that can increase their risk of social, educational and economic disadvantage, as well as depression, anxiety, self-harm and suicide.[2] In NSW, as elsewhere across Australia, TGD children and young people are presenting for clinical care in increasing numbers. As such, it is timely to review and refine the services provided for young TGD people and to do so considering current evidence regarding available treatments. The NSW Ministry of Health commissioned this Evidence Check to collate and evaluate evidence as to the benefits and risks of treatment for TGD children and young people.

The review examined the evidence regarding the effect of treatment on TGD children and young people up to, but not including, the age of 18 years. We looked at quantitative and qualitative empirical studies published since 2005 as well as reviews, clinical guidelines and clinical standards that were published after 2015. We limited papers to those written in English and from developed countries. Using our search criteria, we identified 46 papers, which included 34 empirical studies, six reviews and six guidelines or consensus statements. The additional papers identified in the August 2020 literature search for long-term follow-up did not add further information that would give rise to concern regarding puberty suppression therapy or GAHT.

Research into the outcomes of clinical care for young TGD and non-binary people is an emerging field and the quality of the current evidence base is low. Empirical studies relied on small convenience samples and frequently experienced substantial, and unexplained, attrition between baseline and follow-up. The representativeness of the study sample was rarely described and the degree to which the study's findings were generalisable to the broader population was generally unclear. Studies also used a narrow and inconsistent range of outcome measures and failed to account for confounding variables that may have influenced the outcomes. Randomised controlled trials, which are considered the gold-standard for research evidence, are absent in the studies we identified in this Evidence Check. The lack of RCTs is attributable to ethical concerns about withholding treatment for young people with gender dysphoria and is likely to remain a characteristic of this field of research. It is anticipated that the best quality evidence in the future will come from well-designed longitudinal cohort studies where young people who have a specific treatment are compared with those who do not have treatment, taking into careful consideration the differences between the two groups before starting the treatment.

Treatment for TGD youth identified in this Evidence Check falls into four categories: puberty suppression, gender-affirming hormone therapy, top surgery and psychosocial interventions. Puberty suppression prevents the development of secondary sexual characteristics and gives the young person more time to explore their gender identity before embarking on irreversible, or partially irreversible, treatment. Evidence for puberty suppression indicates that it is safe and well tolerated, despite most recipients experiencing minor side effects such as hot flushes and mood swings. Clinical guidelines argue that puberty suppression also prevents an exacerbation of the psychological distress

that some young people would experience if they developed secondary sexual characteristics different from their affirmed gender. Weak evidence supporting this argument is provided by one study that found that adolescents who received puberty suppression treatment in addition to psychological support had better global functioning than those who received psychological support alone.[41]

Evidence about the impact of puberty suppression treatment on bone mineral density (BMD) is inconclusive. It is unclear whether the use of GnRH agonists in adolescents causes slow bone accrual, static accrual or bone loss.[74] Furthermore, although some studies report that mean bone mass remained stable during puberty suppression[9], Ferguson et al.[74] point out that more than 50% of the cohort actually lost bone mineral density, which indicates substantial heterogeneity in responses to puberty suppression treatment. More research is needed to understand why some young people, but not others, experience a loss of BMD while undergoing puberty suppression treatment. Another concern about puberty suppression treatment is its potential adverse impact on future fertility; however, our search criteria (which was limited to people younger than 18 years) did not identify any empirical studies exploring this outcome.

GAHT is used to induce physical changes in line with an individual's gender identity. It is effective in altering body composition in the desired direction and some of these changes are irreversible or only partially reversible (e.g. voice deepening and increased facial and body hair in trans boys; development of breast tissue in trans girls). Minor side effects, such as acne, hot flushes, mood swings and weight gain, are common although they appear to be well tolerated. There is some evidence that changes in body composition as a result of GAHT are associated with improved psychological wellbeing, including a reduction in gender dysphoria. There is also moderate evidence that GAHT reverses at least some of the bone density loss observed during GnRH.

Potential risks associated with GAHT include a change in cardiovascular markers and compromised fertility. Several studies reported that testosterone therapy was associated with haematological and metabolic changes that may increase future cardiovascular risk; the evidence is conflicting, however. Although quality evidence is lacking, available evidence also suggests fertility is compromised by GAHT.

Gender-affirming surgery in people under the age of 18 years is rare. As a result, there is very weak evidence for either the benefits or risks of this treatment. However, preliminary evidence suggests trans boys are very satisfied with the outcomes of chest reconstruction surgery.[34]

There is little evidence regarding the potential benefits and harms of psychosocial interventions for TGD children and young people and those with gender dysphoria. Studies identified using our search criteria were of very low quality and only one study reported a psychological intervention targeting a cohort of TGD children or adolescents.[18] The other two studies described a voice feminisation case study and a parental support group.[38,41] Costa et al. (2015)[18] found psychological functioning improved over time in young people receiving psychological support. However, the absence of a control group and the lack of consideration of confounding factors makes it difficult to estimate how much of the improvement in psychological functioning can be attributed to the intervention itself. We did not identify any studies that attempted to change an individual's gender identity, which is not surprising given that conversion therapies have long been discredited by medical and psychological bodies across Australia and internationally.[1,75]

Overall, research on the impact of treatment for TDG children and young people is in an emergent phase and it is anticipated that the quality of evidence will improve in the coming years. Future research should clearly establish the generalisability of findings so clinicians and decision makers can estimate the degree to which findings from individual studies can be applied to the young people presenting for specific services. Studies should also be designed to measure outcomes across multiple domains using validated and standardised measures that enable findings from different studies to be compared. Although it may not be possible to conduct RCTs on this population, appropriate consideration and treatment of potential confounders in a study's analysis will provide more insight into the causal relationship between the treatment and the observed outcomes.

The *Trans20* study[73], which is under way in Victoria, will add important information to the evolving evidence base of the natural history of TGD children and adolescents and the outcomes for those receiving interventions in the longer term. Findings from *Trans20* will be highly applicable to the Australian context; however, they will be most specific to the service provided at the Royal Children's Hospital Gender Service. A paediatric gender service in NSW might consider adding to this study or creating a similar study that would provide findings specific to the NSW context.

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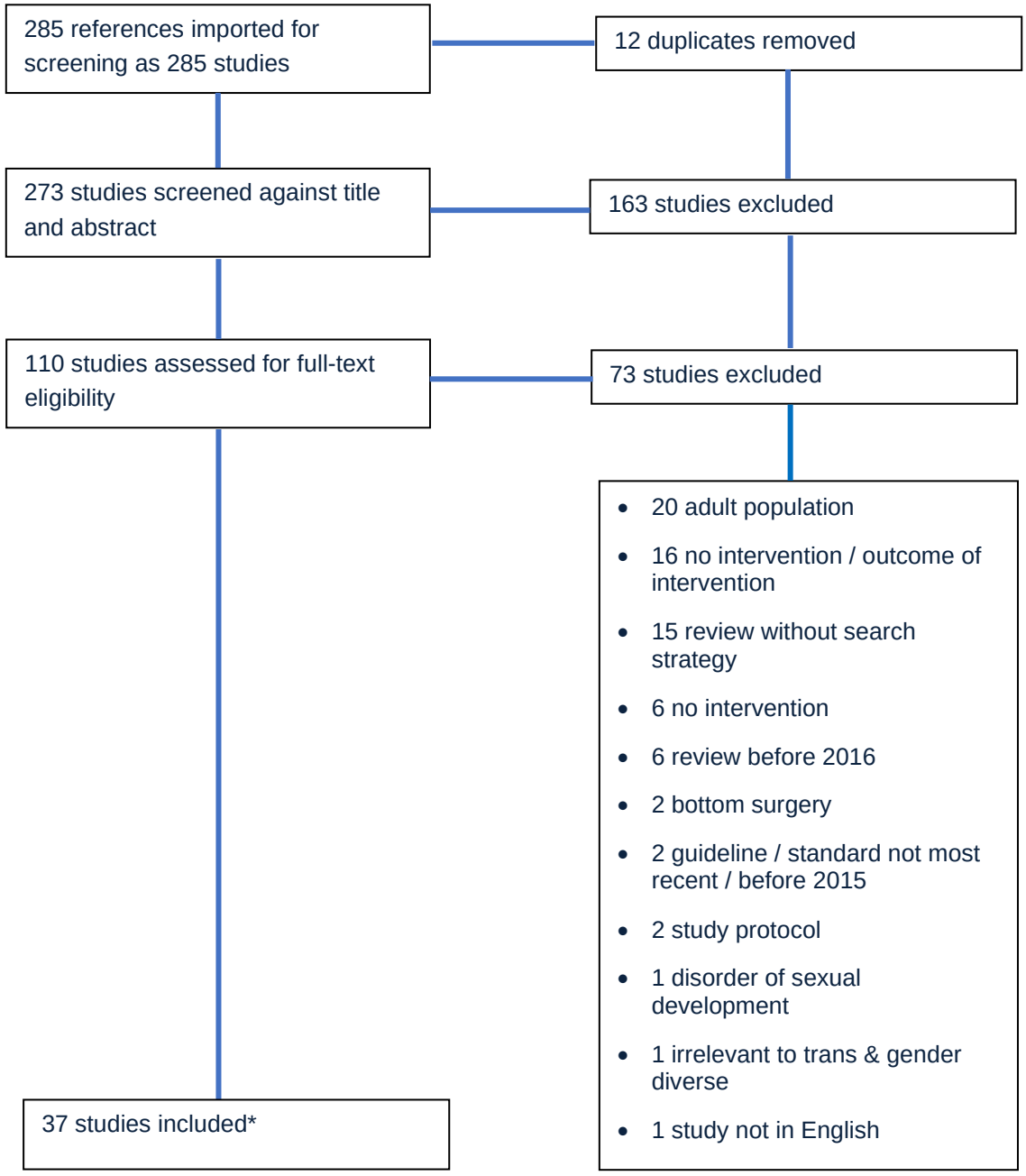
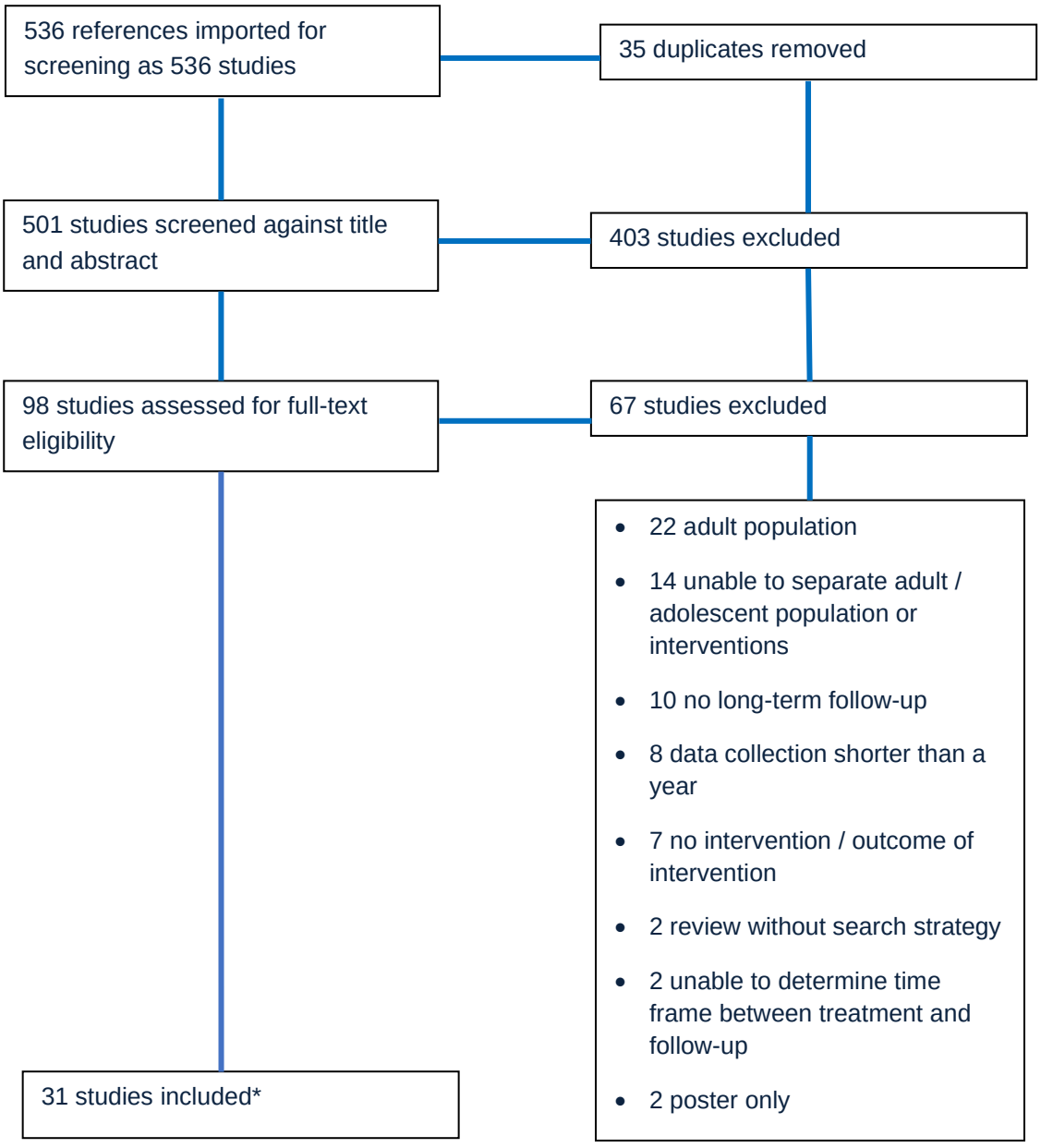
Appendices

Appendix 1a: Literature search flow chart (February 2020)



Appendix 1b: Literature search flow chart (August 2020, long-term follow-up)



*This includes 24 papers about long-term outcomes identified in previous search, seven new papers about long-term outcomes and one new paper about short-term outcomes

Appendix 2: List of included studies and quality assessment

Authors (date)	Title	NHMRC level of evidence NHMRC evidence grade
Achille C et al. (2020)[19]	Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results	III-3 B–C: good applicability1
ACOG (2017)[49]	Committee Opinion No. 685: Care for Transgender Adolescents	NA: committee opinion C: satisfactory
Baram S et al. (2019)[44]	Fertility preservation for transgender adolescents and young adults: a systematic review	NA: good quality review (no meta-analysis) B–C Good applicability
Beking T et al. (2020)[20]	Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls	III-2 C–D: uncertain applicability
Burke SM et al. (2016)[16]	Male-typical visuospatial functioning in gynephilic girls with gender dysphoria—organizational and activational effects of testosterone	III-2 C: satisfactory
Chew D et al. (2018)[45]	Hormonal treatment in young people with gender dysphoria: A systematic review	NA: review without meta-analysis B
Cohen Kettenis P et al. (2011)[39]	Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up	IV: single case study C–D: uncertain applicability
Coleman E et al. (2012)[48]	Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7	NA: review, no lit search C: best available evidence
Costa R et al. (2015)[18]	Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria	III-3 B–C: good applicability
de Vries ALC et al. (2014)[30]	Young adult psychological outcome after puberty suppression and gender reassignment	IV D: poor
de Vries ALC et al. (2011)[13]	Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study	IV C–D: uncertain applicability
Di Ceglie D and Thümmel EC (2006)[41]	An experience of group work with parents of children and adolescents with gender identity disorder	NA: qualitative C–D: poor; reasonable applicability

Authors (date)	Title	NHMRC level of evidence NHMRC evidence grade
Donaldson AA et al. (2018)[25]	Multidisciplinary care considerations for gender nonconforming adolescents with eating disorders: A case series	IV D: poor; limited applicability
Esteva de Antonio I et al. (2015)[50]	Position statement: Gender dysphoria in childhood and adolescence. Working Group on Gender Identity and Sexual Development of the Spanish Society of Endocrinology and Nutrition	NA: position statement D: poor; low applicability
Hannema SE et al. (2017)[14]	Efficacy and safety of pubertal induction using 17β-Estradiol in transgirls	III-2 C: good applicability
Hembree WC,et al. (2017)[47]	Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline	IV B: good quality, applicable
Jarin J et al. (2017)[33]	Cross-sex hormones and metabolic parameters in adolescents with gender dysphoria	III-2 D: uncertain applicability
Jensen R et al. (2019)[23]	Effect of concurrent gonadotropin-releasing hormone agonist treatment on dose and side effects of gender-affirming hormone therapy in adolescent transgender patients	III-3 C–D: poor; uncertain applicability
Khatchadourian K et al. (2014)[29]	Clinical management of youth with gender dysphoria in Vancouver	IV C: probable applicability
Klaver M et al. (2018)[26]	Early hormonal treatment affects body composition and body shape in young transgender adolescents	IV C: reasonable applicability
Klaver, M et al. (2020)[35]	Hormonal treatment and cardiovascular risk profile in transgender adolescents	III-2 B-C: Good applicability
Klink D et al. (2015)[15]	Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria	III-3 B: good; good applicability
Kuper LE 2020[21]	Body dissatisfaction and mental health outcomes of youth on gender-affirming hormone therapy	III-3 C: Reasonable applicability
Lopez X et al. (2017)[51]	Statement on gender-affirmative approach to care from the Pediatric Endocrine Society Special Interest Group on Transgender Health	NA: review without meta-analysis B–C: good applicability
Lynch MM et al. (2015)[28]	Retrospective study of the management of childhood and adolescent gender identity disorder using medroxyprogesterone acetate	IV: case series D: unclear applicability

Authors (date)	Title	NHMRC level of evidence NHMRC evidence grade
Mahfouda S et al. (2019)[4]	Gender-affirming hormones and surgery in transgender children and adolescents	III-2 B: good; good applicability
Mahfouda S et al. (2017)[43]	Puberty suppression in transgender children and adolescents	NA: review (no meta- analysis) B–C good; good applicability
Marinkovic M and Newfield RS (2017)[34]	Chest reconstructive surgeries in transmasculine youth: Experience from one pediatric center	IV C–D: unclear applicability
Neyman A et al. (2019)[24]	Bicalutamide as an androgen blocker with secondary effect of promoting feminization in male-to-female transgender adolescents	IV: retrospective case C–D: unclear applicability
Pang K et al. (2020)[66]	Long-term puberty suppression for a nonbinary teenager	IV: single case study B: good applicability
Pullen Sansfaçon A et al. (2019)[40]	The experiences of gender diverse and trans children and youth considering and initiating medical interventions in Canadian gender-affirming speciality clinics	NA: qualitative D: poor; uncertain applicability
Quinn S and Swain N (2018)[38]	Efficacy of intensive voice feminisation therapy in a transgender young offender	IV: single case study D: poor; low applicability
Schagen SEE et al. (2016)[11]	Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents	III-2 B–C: likely applicability
Schneider MA (2017)[37]	Brain maturation, cognition and voice pattern in a gender dysphoria case under pubertal suppression	IV: single case study D: poor; low applicability
Sequeira GM et al. (2017)[10]	Impact of gender expression on disordered eating, body dissatisfaction and BMI in a cohort of transgender youth	III-2 C–D: poster abstract, little detail
Staphorsius AS et al. (2015)[42]	Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria	III-2 B–C: good; reasonable applicability
Stoffers IE et al. 2019[17]	Physical changes, laboratory parameters and bone mineral density during testosterone treatment in adolescents with gender dysphoria	III-2 C–D: satisfactory; uncertain applicability
Tack LJW et al. (2018)[8]	Proandrogenic and antiandrogenic progestins in transgender youth: Differential effects on body composition and bone metabolism	IV C: satisfactory; likely applicability

Authors (date)	Title	NHMRC level of evidence NHMRC evidence grade
Tack LJW et al. (2017)[12]	Consecutive cyproterone acetate and estradiol treatment in late-pubertal transgender female adolescents	III-3 C: satisfactory; likely applicability
Tack LJW et al. (2016)[27]	Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis	III-3 C: satisfactory; likely applicability
Telfer M et al. (2018)[1]	Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents. Melbourne, The Royal Children's Hospital. Version 1.1	NA B–C: Australian guidelines using best available evidence
Trotman G et al. (2014)[32]	Metabolic profiles in a transgender adolescent population receiving steroid hormone therapy: A pilot study	III-2 D: uncertain applicability due to small sample
T'Sjoen G et al. (2019)[46]	Endocrinology of transgender medicine	NA: review; no meta-analysis C–D: likely applicability
Turban JL et al. (2020)[53]	Association between recalled exposure to gender identity conversion efforts and psychological distress and suicide attempts among transgender adults	III-2 B–C: likely good applicability
van der Miesen A et al (2020)[22]	Psychological functioning in transgender adolescents before and after gender-affirmative care compared with cisgender general population peers	III-2 B: good applicability
Vlot MC et al. (2017)[9]	Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents	III-2 C: satisfactory; likely applicability

Appendix 3: List of included tables

Table 1a—NHMRC levels of evidence

Level of evidence	Study design
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls (i.e. non-randomised experimental trials, cohort studies, case-control studies, interrupted time series studies with a control group)
III-3	A comparative study without concurrent controls (i.e. historical control study, two or more single-arm studies, interrupted time series studies without a parallel control group)
IV	Case series with either post-test or pre-test/post-test outcomes

Table 1b—NHMRC matrix to summarise the evidence base

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base[A]	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review or multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency[B]	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty regarding clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Generalisability	Population/s studied in body of evidence are the same as the target population in question	Population/s studied in body of evidence are similar to the target population in question	Population/s studied in body of evidence differ from target population in question, but it is clinically sensible to apply this evidence to target population	Population/s studied in body of evidence differ from target population and it is hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian context	Applicable to Australian context with few caveats	Probably applicable to Australian context with some caveats	Not applicable to Australian context

[A] Level of evidence determined from the NHMRC evidence hierarchy as in Table 1.

[B] If there is only one study, rank this component as 'not applicable'.

National Health and Medical Research Council (2009) ***NHMRC levels of evidence and grades for recommendations for guideline developers.*** Canberra: National Health and Medical Research Council. Available from: https://edit.nhmrc.gov.au/sites/default/files/images/NHMRC%20Levels%20and%20Grades%20(2009).pdf

Table 2—Medical intervention 1: Puberty suppression

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample characteristics	Main outcomes	Benefits	Harms	Limitations, comments
Pullen Sansfaçon, 2019[40] To understand experiences of TG youth regarding gender-affirming care	Canada Qualitative study 3 Canadian gender dysphoria clinics	*Puberty suppression and CSHT combine* Trans girls: n=14 Trans boys: n=22 Specific age GnRH started not recorded Aged 9–17	Experiences of care and treatment	Improved mental wellbeing (i.e. reduced dysphoria; increased optimism)	Common side effects: Hot flushes, mood swings. Less common side effects: Headaches, knee pain, polydipsia, stress fractures, anxiety relating to injections, potential loss of BMD, prospect of cancer, affordability, waiting for treatment	Recommend: Flexible protocols as young people mature & increasing opportunities for young people to take greater agency in decision-making re care Some clinical protocols may need adjustment and flexibility to meet the needs of non-binary youth
Jensen, 2019[23] To compare dosages of gender-affirming hormones in those taking GnRHa & those not taking GnRHa	US Retrospective chart review Paediatric gender clinic	*Intervention:* *Leuprolide (n=17)* *Histrelin (n=1)* Trans girls: 14.5 years (range 11.4–15.7) Trans boys: 13.9 years (range 12.9–15.6)	Health conditions and medications, GnRHa and gender-affirming hormone regimens and reported side effects	Patients who initiated treatment with GnRHa before gender-affirming hormones required lower doses of hormones than those who did not use GnRHa	65% experienced side effects including: hot flushes, mood swings, weight gain, fatigue 59% ceased GnRHa, mainly due to loss of insurance coverage	Gender-affirming hormone regimens are highly individualised, which presents a significant challenge for data collection and analysis
Neyman, 2019[24] To describe the use of bicalutamide for	US Design: Retrospective	*Bicalutamide (BC) 50 mg daily* N=13	Breast development. Liver function tests at baseline in 3 patients and between 6.3 and	85% had breast development (Tanner 2–5) at ~6 months. Liver enzymes were	No apparent adverse effects of bicalutamide	How bicalutamide compares with other androgen receptor blockers in terms of safety

Table 2—Medical intervention 1: Puberty suppression

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample characteristics	Main outcomes	Benefits	Harms	Limitations, comments
puberty suppression	chart review Department of Pediatrics, Indiana University and Riley Hospital for Children	Trans girls: 100% Mean age at start of BC 16 years ±1.77 (range: 12–18.8) Majority were Tanner stage 3	29.3 months after starting bicalutamide in the remainder. Estradiol concentrations and testosterone levels	normal. Estradiol levels were above 20 pg/dl for 12/13 subjects. All patients positive about breast development and less facial hair/ acne. Bicalutamide less expensive than GnRHa		and efficacy in the adolescent age group is unknown Risk for liver toxicity needs to be investigated in larger samples and over a longer period
Donaldson, 2018[25] To identify themes across disciplines in 5 TG youth with an eating disorder (ED)	US Retrospective chart review Weight management children's clinic	*GnRHa* N=5 Trans girls/gender fluid: n=1 Trans boys: n=3 Gender queer: n=1 Aged 13–22 at presentation	Key themes: Risk of self-harm; Lack of timely referral treatment delay associated with adverse psychiatric & medical outcomes; Lack of parental support for treatment	Harms from NOT treating: Escalation of ED symptoms; Self-harm of the body they perceive is inconsistent with authentic gender	One trans girl with multiple psychiatric issues attempted suicide and was readmitted to psychiatric care	Recommendations: Need for collaboration across disciplines to better focus attention on addressing needs of TG adolescents Larger-scale examination of these themes will help establish best practice guidelines and approaches to care
Klaver, 2018[26] To examine changes in body shape & composition from the start of GnRHa until 22 years of age	Netherlands Retrospective cohort study Center of Expertise on Gender Dysphoria, VU University	*GnRHa* N=192 Trans girls: n=71 Trans boys: n=121 Minimum age: 12 years Tanner stage B2 / G2	Outcomes: Anthropometry, lab measurements and whole-body DXA collected 3 times: start of GnRHa, addition of CSHT, and at 22 yrs of age (range 20.5–23.5 yrs) Results at 22 yrs were	Benefits: The largest bodily changes in trans girls conforming to affirmed gender were seen during GnRHa monotherapy (i.e. testosterone suppression) Knowing long-term	No harms reported. However, authors noted changes in subcutaneous and visceral fat may have implications for future cardiometabolic outcomes	Comments: One of several studies using same cohort from VU University Medical Center Unclear whether the larger increase in body fat during GnRHa monotherapy in trans girls is due to direct absence of testosterone

Table 2—Medical intervention 1: Puberty suppression

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample characteristics	Main outcomes	Benefits	Harms	Limitations, comments
	Medical Center	At start of GnRH: mean=14.5; +/– 1.8. At start of CHT: mean 16.4 +/– 1.1. At final assessment: 22 years (range 20.5–23.5)	compared with age-matched peers	body shape and composition will help TG youth have realistic expectations about desired body phenotype		action or hypogonadal state
Schneider, 2017[37] To review the effects of puberty suppression on the brain white matter (WM) during adolescence	Brazil Single subject clinical report Hospital gender identity program	*GnRH (Leuprorelin)* N=1 Age 11 years 11 months Trans girl: 100% Tanner stage 2	White matter fractional anisotropy (FA), voice & cognitive functions were assessed before /during treatment. MRI scans before and after 22 / 28 months of hormonal suppression	White matter: Affective and social domains improved Voice: Variability in the fundamental frequency during the evaluation period	Lack of significant variation in brain WM FA during treatment. Global IQ slightly reduced during follow-up. Teachers reported difficulties in maths / science)	Longitudinal studies comparing cognition among TG adolescents under puberty suppression and age-matched controls are needed to confirm the findings
Vlot, 2017[9] To investigate the effect of GnRHa & GAHT on bone turnover markers / mineral apparent density (BMAD) in TG adolescents	Netherlands Retrospective cohort study Center of Expertise on Gender Dysphoria, VU University Medical Center	*GnRHa (triptorelin) subcutaneously monthly* N=70 Mean age at start of GnRH: Trans boys: 15.1 years (range 11.7–18.6). Trans girls 13.5 years (range 11.518.3).	P1NP (formation markers), osteocalcin, ICTP (resorption marker) and BMD of lumbar spine (LS) and femoral neck (FN) were measured 3 times, : (1) D0: at start of GnRHa treatment; (2) C0: at start of CSHT; and (3) C24: at 24 months after C0. BMAD and z-scores were calculated	None reported	Decrease of P1NP and ICTP indicating decreased bone turnover. BMAD z-scores of predominantly the LS decreased, especially in young transwomen. 24 months after CSHT, bone turnover markers (BTMs) P1NP and ICTP were even more	

Table 2—Medical intervention 1: Puberty suppression

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample characteristics	Main outcomes	Benefits	Harms	Limitations, comments
		Tanner stage 2 / 2–3B			decreased in all groups except for older trans boys	
Tack, 2016[27] To assess effects & biochemical changes in trans girls taking cyproterone acetate (CA) alone & in combination with oestrogens	Belgium Retrospective cohort study Ghent University Hospital	*Cyproterone acetate orally daily* N=27 Trans girls: 100% Tanner stage IV for CA; GnRH if earlier. Mean age: 16.6 years	Anthropometrics, reported beneficial and side effects, safety parameters, and hormone levels	Effectively decreased facial hair growth in most adolescents and induced breast development in one-third Affordable	Breast tenderness 2/27 (7.4%), emotionality 3/27 (11%), fatigue 10/27 (37%), hot flushes 1/27 (3.7%). No suppression of gonadotropins	CA may be a safe alternative for GnRHa, especially for older adolescents. However, high doses of CA, as used in androgen deprivation therapy, have been associated with severe liver dysfunction. Monitoring liver function during treatment is important
Sequeira, 2017[10] To evaluate associations between initiating CSHT, BMI, disordered eating and body image.	US Prospective cohort study Children's Hospital of Pittsburgh	*GnRH* N=50 Trans girl: n=18; 15.7 years Trans boy: n=32; 14.3 years Uncertain age for puberty suppression	Body dissatisfaction, disordered eating	Significantly reduced body dissatisfaction and disordered eating compared with those who did not start hormone therapy	Trans girls had 1.20 kg/m2 higher and trans boys 1.31 kg/m2 lower BMIs than cisgender controls	Future studies should investigate the role of comorbid psychiatric diagnoses in body dissatisfaction & disordered eating & develop evidence-based weight management program for TG youth
Schagen, 2016[11] To describe physical	Netherlands Observational	*GnRH (triptorelin)* N=116	Physical examination and Tanner stage assessed every 3	Gonadotropins & sex steroid levels suppressed within 3	Height decreased in boys and girls. Lean body mass	Monitoring creatinine and liver enzymes did not identify any pathology,

Table 2—Medical intervention 1: Puberty suppression

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample characteristics	Main outcomes	Benefits	Harms	Limitations, comments
and biochemical puberty changes during GnRHa & evaluate efficacy	prospective Center of Expertise on Gender Dysphoria, VU University Medical Center	 Trans girls: n=49 Trans boys: n=67 Trans girls: 13.6 years (range 11.6–17.9). Trans boys: 14.2 years (range11.1–18.6)	months. Blood samples drawn at 0, 3, and 6 months and then every 6 months. Body composition was evaluated using dual energy x-ray absorptiometry	months. All subjects sufficiently suppressed without adjustment. No sustained abnormalities of liver enzymes or creatinine. Alkaline phosphatase decreased. None discontinued because of side effects	percentage significantly decreased during 1st year of treatment in girls and boys, while fat percentage significantly increased	suggesting routine monitoring of gonadotropins, sex steroid levels, renal function and liver enzymes during treatment is not necessary. Further studies should determine the extent to which changes in height & body composition observed during GnRHa treatment are reversible during later CSHT
Tack, 2016[27] To examine effects of lynestrenol on trans boys, Tanner stage B4+	Belgium Retrospective cohort study Adolescent gender clinic, Ghent University Hospital	*Lynestrenol (L) (Orgametril®) monotherapy* N=45 Trans boys: 100% Mean age 15 years 10 months. Tanner stage 4B	Anthropometry, side effects, safety parameters, and hormone levels	L = 13 x cheaper than GnRH & no needles needed. Rise in Hb, but stabilised & within normal male levels. Effectively decreases overall oestrogenic to androgenic ratio within 6 months	Headaches, hot flushes, fatigue. Less effective than GnRHa in inducing total amenorrhea & in suppressing gonadotropins and hence development of secondary sex characteristics	Lynestrenol is indicated in adolescents with advanced pubertal development and where GnRHa is not reimbursed. Its use may reduce psychological burden while waiting for cross-sex hormone treatment
Staphorsius, 2015[42] To determine if performance on a cognitive functioning task is altered in youth treated with	Netherlands Case-control study Center of Expertise on	*Triptorelin* N=40 Trans boys: n=22 (12 treated with GnRHa; 10 not	Performance on the *Tower or London* task	No effect of GnRHa on reaction times or accuracy among TG youth Puberty suppression appeared to alter some	Control boys had significantly higher IQ scores than suppressed trans girls (but uncertain baseline homogeneity)	No evidence for detrimental effects of GnRHa on executive functioning

Table 2—Medical intervention 1: Puberty suppression

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample characteristics	Main outcomes	Benefits	Harms	Limitations, comments
GnRHa	Gender Dysphoria, VU University Medical Center	treated) Trans girls: n=18 (8 treated with GnRHa; 10 not treated). Controls: 24 cis girls; 21 cis boys Age: Male: 14.9 +/– 1.5 Female: 14.4 +/– 1.8 Age for GnRH: 12+ / Tanner stage 2–3		aspects of brain functioning in line with natal sex	Suppressed trans girls had significantly lower accuracy scores than the control groups compared with control boys and control girls	
Lynch, 2015[28] To determine the efficacy and safety of medroxyprogesterone (MPA)	US Retrospective chart review Gender Identity Clinic at University of Texas, Galveston	*Medroxyprogesterone acetate.* Treatment for between 6 months and 3 years N=14 Trans girls: n=7 Trans boys: n=7 Treatment started between Tanner stage 2 and 4. Age: 15.6 years (range 13–18)	Main outcomes: Patient's medical record was reviewed to determine safety and efficacy. Variables of interest were not specified a priori. Testosterone levels were checked every 3–6 months	MPA effectively suppressed puberty in most participants. Most effective when started in early puberty. It is a low-cost oral alternative to more expensive injectable or implant GnRH analogues Oral administration makes it a good alternative for those with needle phobia	MPA was not always successful in suppressing testosterone Three patients discontinued MPA because of psychiatric / psychosocial reasons rather than because of adverse side effects	Outcomes not specified a priori and decisions on which results in the medical chart are reported in the paper are highly subjective. Generalisability is low. Small sample and high proportion of comorbid psychiatric/neurological conditions (12/14 had depression/anxiety, ADHD, Asperger's, bipolar or seizures)
Khatchadourian, 2014[29]	Canada Retrospective	*GnRH (leuprolideacetate)*	Age at the start of GnRHa and cross-sex hormone therapy;	Treatment prevented the development of unwanted secondary	Sterile abscesses (n=1): switched to triptorelin. Leg pains	Early initiation of GnRHa prevents development of unwanted secondary sex

Table 2—Medical intervention 1: Puberty suppression

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample characteristics	Main outcomes	Benefits	Harms	Limitations, comments
To describe characteristics of TG youth at presentation, during treatment and in response to treatment	chart review Columbia Children's Hospital	N=27 Mean age: 14.7 years (±1.9) Trans girls: 14.7 years (±1.7) Trans boys: 14.8 years (±2.1) At least Tanner stage 2	Tanner stage at initial visit (breast for natal females, genital for natal males) and before initiating GnRHa and cross-sex hormones; medical and psychiatric comorbidities and complications related to medical treatment(s)	sexual characteristics, which can alleviate distress	& headaches (n=1, spontaneously resolved). Weight gain 19 kg in 9 months (n=1, previous BMI was >85 percentile). Expensive: $425 CDN per 7.5 mg kit	characteristics. Fertility considerations for trans girls: Assess desire for biological children Discus option of sperm banking. Consider delaying GnRHa to allow semen cryopreservation
			Anti-androgen spironolactone	Normal electrolyte and urea/creatinine levels		
de Vries, 2014[30] To determine if gender-dysphoric youth improve over time with medical intervention consisting of GnRHa, GAHT and gender-affirming surgery	Netherlands Retrospective cohort study Center of Expertise on Gender Dysphoria, VU University Medical Center	*GnRHa (NOS)* N=55 Trans girls: n=22 Trans boys: n=33 Mean age: 14.8 years +1.8	Gender dysphoria; body image; psychological functioning; depression; anger; anxiety; behaviour Assessed 3 times: (1) pre-treatment; (2) after GnRH & at initiation of CSHT; (3) one-year post surgery	Suppression caused participants' bodies to cease (further) development contrary to their affirmed gender Improvements in multiple measures of psychological functioning	None reported	One of several studies on the same cohort from the Center of Expertise on Gender Dysphoria. Difficult to quantify results specific to changes occurring from pre-treatment to post puberty suppression
de Vries, 2010[13] To compare psychological	Netherlands Prospective cohort study	*GnRHa (NOS).* N=70 Trans girls: n=33	Main outcomes: Participants were assessed twice: (1) before starting GnRHa;	Benefits: General functioning improved significantly during GnRH.	Harms: Changes over time were equal for both sexes but trans boys	Not possible to isolate the effects of puberty suppression from the effects of enrolling in a

Table 2—Medical intervention 1: Puberty suppression

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample characteristics	Main outcomes	Benefits	Harms	Limitations, comments
functioning & gender dysphoria before and after puberty suppression in GD adolescents	Center of Expertise on Gender Dysphoria, VU University Medical Center	Trans boys: n=37 Mean age at first assessment: Trans girls: 13.14 years ±1.55. Trans boys: 14.10 years ±1.99. Mean age at pubertal suppression: Trans girls: 14.25 years ±1.79) Trans boys: 15.21 years ±1.95	and (2) before starting cross-sex hormone treatment Assessments included: Behavioural and emotional problems, depressive symptoms, anxiety and anger, general functioning, gender dysphoria and body satisfaction	Behavioural & emotional problems & depressive symptoms decreased. Anxiety, anger, gender dysphoria & body satisfaction were unchanged	were older when they started GnRH & had more problematic behaviour at 1st & 2nd assessment	gender dysphoria clinic. Effects of the latter may include: Relief at formal recognition of gender identity, opportunity to meet other adolescents with GD, increased parental acceptance, receipt of psychological support
van der Miesen, 2020[22] To investigate the possible effect of transgender care involving puberty suppression	Netherlands Prospective cohort study Center of Expertise on Gender Dysphoria, VU University Medical Center	*GnRH* 1. Adolescents referred to a specialised gender identity clinic yet to receive any GnRH n=272 2. Transgender adolescents receiving puberty suppression n=178 3. Dutch high school cisgender adolescents from the general population n=651	The Dutch version of the Youth Self Report was used to assess internalising and externalising problem behaviour, self-harm / suicidality and poor peer relations	TG adolescents receiving GnRHa had fewer emotional and behavioural problems than the group that had just been referred to transgender care, and had similar or fewer problems than their same-age cisgender peers on the Youth Self-Report domains	None reported	Need studies from other healthcare settings

Table 2—Medical intervention 1: Puberty suppression

Guidelines

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age / stage	Treatment		Non-treatment	Key recommendations / comments
			Benefits	Harms	Harms	
Telfer, 20181 Australia	Healthcare providers	Goserelin Tanner stage 2–3 (trans boys)	Reversible Reduced distress Allows emotional / cognitive development prior to GAHT / surgery decisions	Impacts bone mineral density	Distress related to development of secondary sexual characteristics	Medical transitions depend on adolescent's capacity and competence to make informed decisions, duration of time on puberty suppression, coexisting mental health and medical issues, and existing family support. Regular monitoring of bone mineral density. Encourage optimising bone health with adequate calcium intake, vitamin D supplementation (if indicated) and weight-bearing exercise
		Cyproterone acetate or spironolactone	Induces amenorrhea. Reduces dysphoria. Cheaper than GnRH. Oral administration			
American College of Obstetricians and Gynecologists, 201749 US	Obstetricians and gynaecologists	GnRHa Tanner stage 2: After an established diagnosis of TG identity	Most effects are reversible	Decreased bone mineral density. Changes in growth velocity		Transgender patients are an at-risk population. Preventive interventions are imperative to their health. This includes proper screening for sexually transmitted infections, screening for suicidal thoughts and mental health issues and appropriate vaccination
Lopez, 201751 US Position statement	Academic societies involved in the care of children and adolescents	Intervention: GnRH Tanner stage 2				Includes limited assessment of quality of studies. Recommendations: Important to counsel all patients on fertility, which is likely to be compromised if GnRH agonists are started in early puberty. Offer sperm and oocyte retrieval and banking
Hembree, 201747 US, Netherlands,	Treating physicians	Intervention: Long-acting GnRH analogues	Benefits: Reduce psychological harm.	Harms: Adverse effects on		Offer vitamin D supplements. BP monitoring before and during treatment. It is recommended that any use of pubertal

Table 2—Medical intervention 1: Puberty suppression

Guidelines

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age / stage	Treatment		Non-treatment	Key recommendations / comments
			Benefits	Harms	Harms	
Belgium Clinical practice guidelines from Endocrine Society		Timing: Following diagnosis of GD by mental health professionals who meet criteria listed. Tanner stage 2	Fully reversible. Improved physical outcome compared with initiating physical transition after puberty has been completed	bone mineralisation. Compromised fertility if GnRH at early age or if treated with sex hormones later. Unknown effect on brain development. Possible arterial hypertension Hot flushes, fatigue, mood alterations		blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Specifically: Height / weight/ sitting height / BP, Tanner stages every 3–6 m. LH, FSH, E2/T, 25OH & vit D every 6–12m. DXA scan, bone age L hand if indicated every 1–2 years
		Long-acting GnRH antagonists	Cheaper than GnRH analogues			Uncertain safety and efficacy profile
		Depot and progestin preparations (e.g. lynestrenol)	Effective. Appropriate where GnRHa not available. Good option for those with needle phobia	Gonadotropins not fully suppressed. Acne, fatigue, headaches, hot flushes. Potential for metrorrhagia		

Table 2—Medical intervention 1: Puberty suppression

Guidelines

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age / stage	Treatment		Non-treatment	Key recommendations / comments
			Benefits	Harms	Harms	
Esteva de Antonio, 201550 Spain Position statement	Clinicians & inter-disciplinary staff	GnRHa 12+ years; Tanner stage 2; or later stage of puberty		Partially or totally irreversible		Careful diagnosis and evaluation is essential. The professional making the diagnosis should be trained in developmental psychopathology in childhood and adolescence and be competent in the diagnosis and treatment of mental problems. A wide understanding of GD is also required
Coleman, 201248 US, Europe WPATH Standards of Care	Clinicians, voice therapists, mental health services	GnRH analogues At least Tanner stage 2; usually 12+ years	May avert social / emotional consequences of gender dysphoria if used early	Cost may be prohibitive. Possible bone development issues. Height issues		Recommended over other puberty suppression agents Trans girls who start GnRH analogues early in puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques

Table 2—Medical intervention 1: Puberty suppression

Reviews

Author, date, aims	Target users / included studies	Intervention Age or stage of puberty suppression	Benefits	Risks / harms	Key recommendations
Baram, 201944 To synthesise literature on fertility preservation (FP) for	Not specified	Ovarian stimulation via either antagonist or low-dose agonist protocols	In two cases, patients retrieved preserved oocytes, resulting in delivery of healthy twins in both cases	Significantly reduced semen parameters in TAYAs with current GAHT, compared with both past and no treatment.	For young prepubertal transgenders, the only feasible option is testicular tissue cryopreservation (TTC), which is still experimental and not yet proven successful in humans. When counselling about TTC, both

Table 2—Medical intervention 1: Puberty suppression

Reviews

Author, date, aims	Target users / included studies	Intervention Age or stage of puberty suppression	Benefits	Risks / harms	Key recommendations
TG adolescents and young adults (TAYAs)		and oocyte cryopreservation. Undertaken prior to initiating CSHT		Trans girls have poorer semen quality on most parameters, particularly a higher proportion of oligospermia. Trans girls' sperm more cryosensitive	the patient and guardian need to be aware that it is relying on the emerging technologies of tissue reimplantation or spermatogonial stem cells (SSC)
Mahfouda, 20194 Review evidence on GAHT & surgical interventions in TG children & adolescents	12 studies: 2 assessing psychological outcomes, 1 assessing cognitive effects, 2 assessing BMD or body composition, and 7 assessing safety outcomes	GnRH & testosterone Mean age 16.1. Optimal age & developmental stage for initiating CSHs and performing gender-affirming surgeries remains to be clarified	6-month testosterone (mean age 16) associated with higher levels of mean Hb & haematocrit	Reduced HDL after 6 months of testosterone. Elevations in systolic and diastolic blood pressure with testosterone observed after 2 years. Significant increases in AST, ALT, K+, TSH & free thyroxine. Authors conclude that changes observed in transgender adolescents do not pose a clinical risk	Monitoring BMD parameters in transgender adolescents is recommended before & during GAHT Re high AST/ALT, K+, TSH, free thyroxine: additional studies are warranted to clarify long-term safety
Chew, 201845 Review evidence for the physical, psychosocial and cognitive effects of GnRHa, gender-affirming hormones, anti-androgens and	13 papers: GnRHa (n=9) Oestrogen (n=3), testosterone (n=5) and anti-androgen cyproterone (n=1) and	GnRHa N = 9 studies Age / stage not reported	*GnRHa associated with significant improvements in global functioning, depression, behavioural problems. *After 1 year of GnRHa, no changes in carbohydrate or lipid metabolism as measured by fasting	Harms: Menopausal-like symptoms, especially in post-pubertal subjects. Adolescents' lumbar spine bone mineral density (BMD) z-scores decreased after GnRHa monotherapy. Mean reduction in z-score only significant for those	Low-quality evidence suggests hormonal treatments for transgender adolescents can achieve their intended physical effects, but evidence regarding their psychosocial and cognitive impact is generally lacking There is a lack of reporting of pubertal stage at treatment commencement, which makes interpretation of some changes difficult,

Table 2—Medical intervention 1: Puberty suppression

Reviews

Author, date, aims	Target users / included studies	Intervention Age or stage of puberty suppression	Benefits	Risks / harms	Key recommendations
progestins on transgender adolescents	progestin lynestrenol (n=1)		glucose, insulin, cholesterol, low density lipoprotein (LDL), and high-density lipoprotein (HDL) levels. *The effects of GnRHa on anger and anxiety remain unclear, with conflicting results	with a bone age <15 years. One study: significantly lower height standardised values for trans girls. No studies tested whether subjects given GnRHa achieved their predicted final height after GAHs. After 1 year on GnRHa, subjects had significant increase in body fat % and BMI, accompanied by a decrease in lean body mass * no significant effect on symptoms of GD	especially BMD Although researchers in 2 studies have now examined growth and height characteristics in transgender youth receiving GnRHa their relatively short follow-up times (≤3 years) precluded determination of the effects of GnRHa on final height
		Progestin lynestrenol	Reduced SHBG, reduced LH, increased free testosterone	No cessation of menses. Headaches 12%, hot flushes 10%, acne increased from 15%–29%. Increased weight and BMI after 6 months with return to normal after 12 months. Significant adverse lipid profile: Lower HDL & higher LDL after 12 months	Only 1 study. Therapeutic impact of progestins for menses suppression and psychological outcomes unclear from current literature
Mahfouda, 2017[43] Australia.	8 papers: 3 longitudinal (psychiatric	*GnRH agonists, e.g. triptorelin acetate*	Most potent method of suspending puberty, especially in early Tanner	Expensive. Significant bone mineral density reduction (which	Monitoring of renal function and liver enzymes during GnRH agonist treatment, as stipulated in current Endocrine Society guidelines, is not

Table 2—Medical intervention 1: Puberty suppression

Reviews

Author, date, aims	Target users / included studies	Intervention Age or stage of puberty suppression	Benefits	Risks / harms	Key recommendations
Review empirical evidence on cognitive, physical and surgical implications of puberty suppression in TG youth	and psychosocial outcomes), 1 cross-sectional (executive function), and 4 longitudinal (physical & metabolic parameters). WPATH guidelines reviewed	Tanner stage 2. The most appropriate time to start treatment remains to be clarified	stage. Allows opportunity to explore gender expression. Progression of sexual development ultimately ceases and can even regress somewhat if started early enough. Reversible. Renders some cosmetic procedures redundant or less invasive, e.g. bilateral mastectomy / chest recontouring / facial feminisation	increases again during GAHT). Leuprolide acetate SE sterile abscess (n=10 and treatment changed to triporelin). Multiple other side effects reported from numerous studies including hot flushes, headache, fatigue, atrial hypertension. Papilloedema and increased intracranial pressure in one case	necessary Gaps: studies testing whether GnRH alleviates distress in adolescents; physical and cognitive function during treatment. Studies to identify which patients benefit most, and which are at higher risk of regret, changed wishes, or poorer quality-of-life outcomes; the most appropriate time to start treatment Relevant articles in references were included
		Progestins e.g. lynestrenol Timing: At least Tanner stage 4	Cheaper than GnRHa. Pro-androgenic progestins can induce amenorrhoea in female-to-male candidates with advanced puberty	Less effective than GnRHa	
		Cyproterone acetate & spironolactone	Lessens the effect of testosterone in trans girls Can reduce frequency of shaving or need for future hair removal		

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	**Country, design, setting**	***Intervention*** **Sample N= age, gender identity**	**Main outcomes**	**Benefits**	**Harms**	**Limitations / flags / comments**
Jensen, 2019[23] To compare dosages of gender-affirming hormones in those taking GnRHa & those not taking GnRHa	US Retrospective chart review Pediatric gender clinic	*Estradiol tablets with GnRHa, varying from 1.9mg/day to 4.6mg/day* (trans girls) N=66	GnRHa use before oestrogen was associated with a significantly lower average dose of oral estradiol	Rates of side effects of gender-affirming hormones were similar regardless of concurrent GnRHa use	Breast tenderness, excessively elevated oestradiol levels, elevated liver enzyme levels	Small sample. Concurrent GnRHa may decrease doses of hormones needed to achieve desired physiologic changes
		Subcutaneous testosterone cypionate. +GnHRa 37.9mg/week to GnRHa 51.7mg/week (SD 8.4, n=48) (trans boys) N=18	Side effects that were reported in the patients' charts	GnRHa use correlated with lower doses of subcutaneous testosterone cypionate	Acne, mood changes, increased appetite and elevated red blood cell markers	Recommendations: patient monitoring in gender-affirming hormone treatment
Donaldson, 2018[25] To identify themes across disciplines in 5 TG youth with an eating disorder (ED)	US Retrospective chart review Weight management children's clinic	*Estradiol* N=5 Trans girls/gender fluid: n=1 Trans boys: n=3 Gender queer: n=1 Aged 13–22 at presentation	Themes: increased risk for self-harm/suicide, complex psychiatric & medical implications of delay in treatment for gender dysphoria / disordered eating; & the importance of collaborative management to maximise care and facilitate healthy development to adulthood	Improved body satisfaction and less reported suicidal ideation and self-injurious behaviour Weight gain	Participants continued to have symptoms of an eating disorder	
Klaver, 2018[26]	Netherlands	*17b-oestradiol /*	Data obtained during	In transmen, the	Harms / adverse	Comments: Missing data

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
To examine change in body shape & composition from the start of GnRHa until 22 years of age	Retrospective cohort study Center of Expertise on Gender Dysphoria, VU University Medical Center	*mixed testosterone esters* N=192 Trans girls: n=71 Trans boys: n=121 At start of GAHT: mean 16.4 +/–1.1	routine medical check-ups on anthropometry, laboratory measurements, & whole-body DXA. Collected at: (1) start of GnRHa; (2) when GAHT started; & (3) at 22 years of age (range 20.5–23.5 years) Measures at 22 years were compared with age-matched peers	largest change in body shape / composition was after the start of testosterone treatment. Therefore, the suppression / addition of testosterone has a greater impact than suppression / addition of oestradiol	effects: None reported	not accounted for. Confounders not measured: diet, lifestyle & exercise / strength training
Stanley, 2018[63] To present a case study of a trans girl receiving both oestrogen and testosterone therapy, who developed a pulmonary embolism	US Single-subject case study Emergency department, children's hospital	*Ethinyloestradiol-containing OCPs (for control of menses) and testosterone cypionate injections (25 mg weekly for 4 months) for gender transition* N=1 Age: 17 years Trans girl: 100%	Clinical presentation	Not reported	Developed a pulmonary embolism without an underlying genetic thrombophilic condition Presented to ED with 48 hours of shortness of breath and left-sided pleuritic chest pain	Recommendation: Modification or elimination of other thrombotic risk factors should be explored before starting testosterone therapy in this population. A thorough discussion of all risks and benefits should occur with patients considering hormonal therapy
Hannema, 2017[14] To evaluate the efficacy and safety of	Netherlands Prospective cohort study	*Estrogen (estradiol [E] or ethinylestradiol [EE]) was added to Triptorelin.*	Participants were assessed over 3 years, comprising a physical exam every 3 months,	Estrogen treatment effectively slowed height growth. Estradiol was found to	Ethinyloestradiol: One of the 2 participants on EE developed	Comments / limitations Small sample. One of several studies using the same cohort

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
estrogen treatment for pubertal induction in trans girls	Center of Expertise on Gender Dysphoria, VU University Medical Center	*Triptorelin had been administered for a median of 24.8 months before starting oestrogen* N=28 Trans girls: 100% Mean age at start of oestrogen treatment: 16.0 years (range, 13.9 –18.9). Note: In 5 participants, oestrogen commenced before 15.5 years because of tall stature (≥180cm)	blood tests every 6 months and radiological testing once a year Measures included: Tanner stage, anthropometry, laboratory parameters, bone age and body composition	effectively induce breast development and female fat distribution in trans girls. Breast development started within 3 months in 83%. After 3 years, 86% had Tanner breast stage 4–5. Hip circumference increased and the waist/hip ratio decreased	hyperprolactinaemia and galactorrhoea. No pituitary lesion. The use of EE is no longer recommended because of high risk of VTE. Estradiol: Creatinine slightly decreased during 2 years of E. One participant had a creatinine level > than normal range at 12 months, which normalised spontaneously. An adult dose of estradiol 2 mg does not always result in appropriate serum estradiol levels	from the Center of Expertise on Gender Dysphoria at VU University Medical Center. Only 57% assessed at 3 years Further studies are needed to establish effective and safe methods to limit growth
Sequeira, 2017[10] To evaluate associations between initiating GAHT, BMI, disordered eating and body image	US Prospective cohort study Children's Hospital of Pittsburgh	*GAHT (not defined)* N=50 Trans girl: n=18 Trans boy: n=32 Trans girls: 15.7 years Trans boys: 14.3	Measures of body dissatisfaction and disordered eating behaviours using the Stunkard Figure Rating Scales and Eating Attitudes Tests	Individuals who initiated hormone therapy by six months (n¼18), had lower levels of body dissatisfaction (t(31)¼2.31, p<.05) and disordered eating	Harms were not reported. Of note was that at baseline (prior to GAHT), transmen had greater overall body dissatisfaction than transwomen and cisgender controls	Noted in Table 1. Conference abstract

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
		years Uncertain age for GAHT		(t(31)¼1.78, p<.05) than those who did not		
Tack, 2016[27] To assess effects & biochemical changes in trans girls taking cyproterone acetate (CA) alone & in combination with oestrogens	Belgium Retrospective cohort study Ghent University Hospital	*Estrogen (Progynova) & cyproterone acetate* (trans girls) N=21 Trans girls: 100% Commenced at Tanner stage G4; 6 months after starting CA	Anthropometrics, reported benefits and side effects, safety parameters and hormone levels		Breast tenderness 12/21 (57%), emotionality 6/21 (29%), hunger 5/21 (14%), hot flushes 3/21 (14%) Complaints of hypogonadism, especially fatigue, were relatively frequent during CA	If favourable biochemistry is confirmed, CA could offer a safe and cost-effective alternative to GnRHa Single-centre retrospective chart review. Semen cryopreservation offered before starting CA
Tack, 2018[8] To report effects of lynestrenol on trans boy adolescents Tanner stage B4+	Belgium Design: retrospective cohort Setting: Adolescent gender clinic, Ghent University Hospital	*Lynestrenol and testosterone esters (TE), Sustanon®* (Trans boys) N=44 From age 16	Anthropometry, side effects, safety parameters,and hormone levels	Increased facial / body hair, libido, muscle mass, skin oiliness. Clitoromegaly, voice deepening, cessation of menses, redistribution of fat mass. Significant increase in weight gain compared with age-matched natal sex peers. Rise in Hb but not exceeded natal sex age-matched peer parameters	Male pattern balding In this study, lipid metabolism shifted to an unfavourable HDL/LDL ratio; metrorrhagia & significant increase in acne; fatigue 1:4 stopped treatment because of hot flushes	Further research in transsexual adults focusing on early determinants of cardiovascular disease such as adiponectin or carotid artery intima media thickness is warranted. Regular blood controls to check safety parameters or hormonal levels and for medication abuse

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	**Country, design, setting**	***Intervention*** **Sample N= age, gender identity**	**Main outcomes**	**Benefits**	**Harms**	**Limitations / flags / comments**
Vlot, 2017[9] To investigate the effect of GnRHa & GAHT on bone turnover markers / mineral apparent density (BMAD) in TG adolescents	Netherlands Retrospective cohort study Center of Expertise on Gender Dysphoria, VU University Medical Center	*17-β-oestradiol orally daily* N=22 Trans girls: 100% Age: 16.0 years (range 14.0–18.9)	P1NP (bone formation markers), osteocalcin, ICTP (resorption marker) and BMD of lumbar spine (LS) and femoral neck (FN) were measured 3 times: (1) Day 0: at start of GnRHa treatment; (2) at start of GAHT; and (3) at 24 months after start of GnRH. BMAD and z-scores were calculated	Bone density returned towards normal levels, especially in lumbar spine	Not reported	The added value of evaluating bone turnover markers seems to be limited and DXA scans remain important in follow-up of bone health of transgender adolescents
		Testosterone esters (Sustanon) Trans boys: 16.3 years (range 15.9–19.5) N=34	P1NP, osteocalcin, ICTP and BMD of lumbar spine & femoral neck measured: (1) at start of GnRH; (2) at start of GAHT; and (3) 24 months after start of GAHT. BMAD & DXA scans	Bone mineral apparent density (BMAD) increased		The added value of evaluating bone turnover markers seems to be limited and DXA scans remain important in follow-up of bone health of transgender adolescents
de Vries, 2014[30] To determine if gender dysphoric youth improve over time with medical	Netherlands Retrospective cohort study Center of	*GAHT (NOS)* N=55 Trans girls: n=22 Trans boys: n=33	Participants were assessed 3 times: (1) pre-treatment; (2) after puberty suppression treatment and at initiation of GAHT; (3)	Not reported	The age criterion of 16 years for the start of GAHT may be problematic, especially for transwomen,	One of several studies on the same cohort from the Center of Expertise on Gender Dysphoria at VU University Medical Center. Physical changes not

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
intervention consisting of GnRHa, GAHT, and gender-affirming surgery	Expertise on Gender Dysphoria, VU University Medical Center	Mean age: 16.7 years ±1.1	one-year post surgery		because growth in height continues as long as cross-sex steroids are not provided	assessed. Substantial missing data
Khatchadourian, 2014[29] To describe patient characteristics at presentation, treatment and response to treatment in youth with gender dysphoria	Canada Retrospective chart review Children's Hospital. See previous entry	*Oral micronised 17-β-oestradiol* (trans girls) Median age at initiation of oestrogen: 17.9 years (range 13.3–22.3) N=37	Measures included: age at the start of GnRHa and gender-affirming cross-sex hormones; Tanner stage at initial visit (breast for natal females, genital for natal males) and before initiating GnRHa and cross-sex hormones; medical and psychiatric comorbidities and complications related to medical treatment(s)	None reported	12/37 trans boys (32%) using testosterone developed minor complications: severe acne needing isotretinoin (n=7) early-onset (age <20 years) androgenic alopecia (n=1), mild dyslipidaemia (n=3), significant mood swings (n=1). No minor / severe complications (blood / liver issues) with oestrogen use	Although it cannot be attributed to GAHT specifically, suicide attempts and/or emergency department visits for suicidal ideation decreased from 12% (n=10) before the first visit to the transgender clinic to 5% (n=4) afterwards. This may suggest a reduction of emotional problems and suicidality when puberty blockers or cross-sex hormones are started. Small sample
		Injectable testosterone enanthate and/or cypionate (trans boys)		Suicide attempts 3% (n=1), reduced from 5% before being seen in the clinic and being prescribed GAHT	Severe acne (n=7); early-onset (age <20 years) androgenic alopecia (n=1), mild dyslipidaemia (n=3), & significant mood	

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
		Median age at initiation of testosterone: 17.3 years (range 13.7–19.8) N=45			swings (n=1)	
Trotman, 2014[32] To identify patterns and changes in metabolic profiles of TG adolescents undergoing GAHT	US Poster abstract Retrospective chart review Children's hospital clinic	*Oestrogen* (route and dose not reported) N=14 Trans girls: n=6	Outcomes: Baseline values and trends in body mass index (BMI); biologic markers including lipid markers; testosterone, oestradiol level, liver function tests, prolactin level, HgbA1c, CBC and electrolytes	Not reported	A non-significant trend towards increasing triglycerides, HDL and prolactin levels	Recommendations: Our results support the need for larger-scale studies in this population
		Testosterone (route and dose not reported) N=14 Trans boys: n=8		Significant increase in haematocrit levels. Trend towards increasing total cholesterol, LDL and BMI with a decrease in HDL levels		
Jarin, 2017[33] To identify patterns in metabolic and cardiovascular parameters in	US Retrospective cohort study Three hospital	*Oestrogen: orally daily / IM monthly / trans-dermally weekly; testosterone weekly* (trans girls)	Outcomes: BP, BMI, serum testosterone & oestrogen, prolactin, electrolytes, LFTs, Hb / haematocrit, & HbA1c3.	Physiologic levels reached after 6m. Most had testosterone levels higher than pubertal female range (although lower than before	One subject had low sodium level and high potassium level when taking spironolactone (subject had multiple	Recommendations: Metabolic and cardiovascular parameters safe short-term for GAHT. In the absence of pre-existing medical conditions

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
transgender adolescents receiving cross-sex hormone therapy	clinics	N=116 Trans girls: n=44 Mean age Trans girls: 16 years (range: 13–22)	Time points: Before therapy, 1–3 months after starting, at 4–6 months & 6 months+	GAHT) A significant increase in haemoglobin / haematocrit levels and BMI, & decrease in HDL	comorbidities)	and medications, low sodium / high potassium unlikely with spironolactone. Long-term oestrogen: Clinical follow-up, lifestyle modification and lab testing needed because of higher prevalence of AMI, thrombosis, CVS
		Spironolactone			Risks: An isolated but clinically important event involving low sodium / high potassium in one subject, who had multiple medical comorbidities	
		Testosterone (trans boys) N=116 Trans boys: n=72 Trans boys: Mean 18 years (range: 14–25)	BP, BMI, serum testosterone & oestrogen, prolactin, electrolytes, LFTs, Hb / haematocrit, & HbA1c3. Time points: before therapy; 1–3 months after starting; at 4–6 months; & 6 months+	Significant increase in haemoglobin / haematocrit levels and BMI & decrease in high-density lipoprotein level. No significant changes were found in any other parameter tested	A statistically significant decrease in HDL level among affirmed male subjects taking testosterone	Recommendations: Monitor haematologic and metabolic parameters 3 months after starting therapy. Frequent monitoring after this not supported (little further changes). Closer surveillance for trans boys taking 50 mg+ weekly as effects more pronounced with higher doses

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	**Country, design, setting**	***Intervention*** **Sample N= age, gender identity**	**Main outcomes**	**Benefits**	**Harms**	**Limitations / flags / comments**
Stoffers, 2019[17] Assess virilisation, BMI, bone density during testosterone treatment	Netherlands Prospective cohort observational Hospital clinic	*GnRHa (Decapeptyl-CR) median 8 months followed by testosterone (Sustanon; 250 mg) treatment for 6 months+* N=62 Trans boys: Age 17.2 years (range 14.9–18.4)	Virilisation, anthropometry, laboratory parameters and bone mineral density (BMD)	Increased hair growth (extremities / facial) in all by 15 months; abdominal / chest hair in 79% after 12 months; voice deepening in 85% by 3 months	Increased acne up to 12 months: prevalence reduced by 15m. Systolic BP increased from 118 mm Hg to 124mm Hg in 1st 6 months, then stabilised. BMD z-scores at 12–24 months lower than pre-treatment values	Monitor haematocrit (increased risk of cardiovascular events) Long-term follow-up studies of lipid profile Encourage good bone diet (including adequate calcium and vitamin D intake), physical exercise, no smoking, and limit alcohol Non-validated and inconsistent outcome measures
Pullen Sansfaçon, 2019[40] To understand goals, feelings about care / interventions & regrets of trans youth receiving gender-affirming care at specialty clinics	Canada Qualitative study Canadian Gender Dysphoria clinics (n=3)	*Testosterone* Trans boys: n=22 Specific age at commencing testosterone not recorded Aged 9–17 (4 aged 9–11; 14 aged 13–15; 17 aged 16 & 17)	Experiences of care and treatment from prepubertal and pubertal adolescents (not all received hormone treatment, but all were included in the focus groups as their intervention included psychosocial)	Voice deepened, facial and body hair increased and, in several cases, shape of upper body and face changed. Self-reports of being happier, less anxious or less dysphoric, & more positive about body	None expressed regrets / doubts regarding the medical interventions. Some anxious re expense, & concern about waiting time for clinic	Small sample
Burke, 2016[16] To examine changes	Netherlands Prospective	*Testosterone ester OR testosterone*	Brain activation, as measured by an fMRI,	Trans boys showed male-typical, rather	No harms / adverse effects reported	One of several studies on the same cohort from the

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
in cognitive function in trans boys before and after starting testosterone treatment	cohort study, parallel group Center of Expertise on Gender Dysphoria, VU University Medical Center	*undecanoate* N=21 trans boys (mean age 16.1 years ±0.8) 21 cis female age matched controls (mean age 16.3 years ±1.0) 20 cis male age matched controls (mean age: 15.9 years ± 0.6)	during a mental rotation task. Participants were tested before starting testosterone treatment and after ~10 months of testosterone treatment	than female-typical, visuospatial functioning before starting testosterone treatment. After an average of 10 months of testosterone treatment, trans boys' performance on a mental rotation task improved		Center of Expertise on Gender Dysphoria at VU University Medical Center Findings suggest different sexual differentiation of the brain in natal girls with GD compared with boys; suggests organisational and activational effects of testosterone on visuospatial cognitive functioning. Flaw: Social influence not accounted for. Clinical application of results is unclear. Limited usefulness in informing care Missing data
de Vries, 2011[13] To compare psychological functioning & gender dysphoria before and after puberty suppression in gender-dysphoric adolescents	Netherlands Prospective cohort study Center of Expertise on Gender Dysphoria, VU University Medical Center	*GnRHa (NOS)* N=70 Trans girls: n=33 Trans boys: n=37 Mean age at first assessment: Trans girls: 13.14 years +1.55. Trans boys: 14.10 years +1.99.	Participants were assessed twice: (1) before starting GnRHa; and 2) shortly before starting cross-sex hormone treatment Assessments measured the following: Behavioural and emotional	General functioning improved significantly during GnRH. Behavioural & emotional problems & depressive symptoms decreased. Anxiety, anger, gender dysphoria & body satisfaction did not change	Adverse events: None reported	One of several studies on the same cohort from the Center of Expertise on Gender Dysphoria at VU University Medical Center It is not possible to isolate the effects of puberty suppression on psychological functioning from the effects of enrolling in a gender dysphoria

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Empirical studies

Author, date, aims	Country, design, setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
		Mean age at pubertal suppression: Trans girls: 14.25 +1.79. Trans boys: 15.21 yrs +1.95	problems; depressive symptoms; anxiety and anger; general functioning; gender dysphoria; and body satisfaction			clinic itself. Effects of participation in the clinic may include: happiness / relief at formal recognition of gender identity, opportunity to meet other adolescents with GD, greater parental acceptance of gender identity, receipt of psychological support

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Guidelines / position statements

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age or stage of puberty suppression	*Methods / literature review* Benefits	Risks / Harms	Key recommendations / comments
American College of Obstetricians and Gynecologists, 2017[49] Aim: To review	Obstetricians and gynae-cologists	Oestrogen and androgen blockers 16 years	*Literature review not described. Committee members not identified* Hormone therapy has been shown to decrease depression	Trans boys: Voice deepening & facial hair growth may be irreversible (expert opinion). Potential risks: polycythemia, hyperlipidaemia, hypertension, mood changes & hepatitis. Breast, ovarian, uterine and	Fertility preservation options need to be discussed The clinical healthcare provider who administers the hormones will check laboratory values and anthropomorphic measures regularly, but a gynaecologist

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Guidelines / position statements

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age or stage of puberty suppression	*Methods / literature review* Benefits	Risks / Harms	Key recommendations / comments
current recommendations for management of gender non-conforming youth			and increase self-esteem among transgender patients	vaginal cancer have all been reported in trans boys receiving androgen therapy. However, these cases are uncommon & there is insufficient data to conclude androgen therapy increases the risk of any gynaecologic malignancy	should understand the adverse effects. Currently, there are large gaps in training, knowledge and comfort with transgender patients among obstetricians / gynaecologists
Telfer, 2018[1] Australia Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents	Healthcare providers working with TGD children and adolescents in Australia	*Trans girls: Oestradiol valerate (e.g. Progynova) oral / transdermal patch* *Trans boys: Testosterone enanthate* Tanner stage 2–4	*Literature search strategy not defined. Four authors, with acknowledgments to multiple contributors and stakeholders (nationwide) including consumers. Endorsed by Australia and New Zealand Professional Association for Transgender Health (ANZPATH)* Feminise /masculinise the appearance by inducing the onset of secondary sexual characteristics Start when adolescent	Daily dose may be affected by user compliance issues Trans girls: Irreversible breast growth. Delay in use of GAHT (with prolonged GnRH) likely associated with greater risk of relative osteopaenia and linear growth beyond expected final height due to delayed growth plate closure. Delay may also cause distress, anxiety and depression with subsequent increase in self-harm or suicide risk Trans boys: Unlikely to be able to reverse facial and body hair growth and scalp hair loss; irreversible deepening of voice (from Endocrine Society Guidelines)[47]	Comments: Timing depends on the nature / history / presentation of gender dysphoria, duration of GnRH for those on stage 1 treatment, comorbid mental health and medical issues and existing family support Mostly based on expert consensus & non-randomised trials but highly applicable to Australian context

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Guidelines / position statements

Author, date, aims	**Target users (e.g. GPs)**	***Intervention*** **Age or stage of puberty suppression**	***Methods / literature review*** **Benefits**	**Risks / Harms**	**Key recommendations / comments**
			is competent to make an informed decision. See comments		
Lopez, 2017[51] Texas, US Pediatric Endocrine Society position statement for transgender health	Target users: Academic societies involved in the care of children and adolescents	*Gender-affirming hormone therapy* Start at age 16, or younger if indicated	*Search strategy for literature review not included. Five authors, on behalf of the Pediatric Endocrine Society.* Benefits: One study demonstrated complete resolution of gender dysphoria and psychological outcomes similar or better than non-transgender age-matched young adults. In addition, none of these patients regretted their decision to transition[26]	Harms: Trans girls: Thromboembolic risk (higher with ethinyloestradiol than oral and patch ß-oestradiol) Trans boys: Does not protect against pregnancy Also may lead to sterility (expert opinion)	
Hembree, 2017[47] Endocrine Society guidelines Task force initiated	See previous entry	17ß-oestradiol (transdermal for hypogonadal females) Trans boys:	*Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)*	Harm: Potential compromised fertility (expert opinion): Recommendation that all embarking on GAHT have fertility counselling	Key recommendations: GAHT not recommended in prepubertal children. Recommended after children first show physical evidence of puberty.

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Guidelines / position statements

Author, date, aims	**Target users (e.g. GPs)**	***Intervention*** **Age or stage of puberty suppression**	***Methods / literature review*** **Benefits**	**Risks / Harms**	**Key recommendations / comments**
for these guidelines, and input from national and international stakeholders		testosterone	*system to describe the strength of recommendations and the quality of evidence, which was low or very low* Benefits: Not discussed Start at about 16 years (possibly beforehand in special cases after expert multidisciplinary discussion)	Potential risks / harm to BMD and the sense of social isolation from the timing of puberty being out of sync with peers Pregnancy was reported in trans boys who had prolonged androgen treatment & discontinued testosterone but did not have genital surgery	Addition of progestin if uterine bleeding Initiate Rx using gradually increasing dose schedule after multidisciplinary team has confirmed persistence of GD, and sufficient mental capacity for consent. Monitor clinical pubertal development every 3–6 months, & lab parameters every 6–12 months during hormone Rx, including prolactin levels and lipid profiles, and diabetes screening. Based on literature review in guidelines
de Antonio, 2015[50] Position statement Aims: Report recommendations for evaluation & treatment of GD in children & adolescents in Spain	Target: Clinicians & inter-disciplinary staff working with adolescents with GD	Cross-sex hormone therapy Age: 16+	*Developed by GIDSEEN (Working Group on Gender Identity and Sexual Differentiation of the Spanish Society of Endocrinology and Nutrition) (20 members from across Spain)* *No search strategy defined*	Harms: Partially or totally irreversible consequences of hormone therapies	Recommendations: Care for TGD adolescents should be preceded by a diagnosis, with adequate monitoring, in the setting of a multidisciplinary team and following a specific protocol recorded by the competent bodies It is mandatory that minors and their guardians be informed about the effects of these treatments on fertility and psycho-emotional maturation
Coleman, 2012[48]	Target: Clinicians,	Oestrogens, oral, for 2+ years.	*Process of developing guidelines outlined.*	Risks: Ethinyloestradiol not recommended because of	Recommendations: Close communication with the patient's

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Guidelines / position statements

Author, date, aims	**Target users (e.g. GPs)**	***Intervention*** **Age or stage of puberty suppression**	***Methods / literature review*** **Benefits**	**Risks / Harms**	**Key recommendations / comments**
WPATH standards of care US, Europe	voice therapists, mental health services	Transdermal not oral advised for those with risk factors for VTE Age 16 years	*International advisory group appointed. Members of WPATH committee named. Review of literature undertaken but search strategies not identified* Benefits trans girls: Breast growth (variable), decreased erectile function, decreased testicular size and increased percentage of body fat compared with muscle mass Benefits trans boys: Deepened voice, clitoral enlargement (variable), growth in facial and body hair, cessation of menses, atrophy of breast tissue and decreased percentage of body fat compared with muscle mass	increased risk of venous thromboembolism (VTE). Testosterone has limited efficacy in suppressing menses. Voice deepening irreversible Harms: Likely increased risk of VTE (risk higher with oral than transdermal); gallstones; elevated liver enzymes; weight gain; acne & alopecia (trans boys); hypertriglyceridaemia. Possible increased risk of hypertension; hyperprolactinaemia or prolactinoma. Also possible increased risk of type 2 diabetes (oral higher than transdermal)	primary care provider. Baseline laboratory values are important both to assess initial risk and evaluate possible future adverse events. Fertility counselling beforehand

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Guidelines / position statements

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age or stage of puberty suppression	*Methods / literature review* Benefits	Risks / Harms	Key recommendations / comments
		5-alpha reductase inhibitors	Beneficial effects on scalp hair loss, body hair growth, sebaceous glands and skin consistency		
		GnRH agonists, e.g. goserelin, buserelin, triptorelin		Harms / disadvantages: Expensive. Only available as injectables or implants	
		a. spironolactone b. cyproterone to reduce testosterone		Benefit: Most cost-effective agents	Recommendations: Monitor blood pressure & electrolytes; potential for hyperkalaemia
		Medroxyprogesterone		Trans boys: Can be used for a short period of time to assist with menstrual cessation early in hormone therapy	

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Reviews

Author, date, aims	**Country / Studies included / *Search strategy***	***Intervention*** **Age or stage of puberty suppression**	**Benefits**	**Harms**		**Key recommendations**
Mahfouda, 2019[4] Aim: To review the evidence, safety and cognitive and physical effects of GAHT & surgical interventions in TG children and adolescents	Australia 12 studies: Psychological outcomes (n=2); cognitive and activational effects (n=1); bone metabolism / body composition (n=2); safety (n=1) *Search terms and search strategy detailed. 24 studies (and 3l guidelines) included*	*Oestrogen (oral / transdermal) testosterone* The optimal age / stage for GAHT & surgeries unclarified	Reduced gender dysphoria in youth taking GAHT[26] Initiation of puberty suppression in early puberty was associated with closer resemblance to the body composition of the affirmed gender when GAHT taken[16]	Trans girls: (VTE) Venous thromo-embolism risk. Oestrogen therapy alone insufficient for feminising effects; spironolactone added but can cause hyper-kalaemia Oestradiol valerate / cyprionate needs to be given weekly / fortnightly. Concentrations difficult to monitor	Trans boys: Concerns over acute hepatic dysfunction, and rarely, occurrence of meningiomas. Use of smaller doses (12·5 mg) substantially reduced the risk of these side effects	Uncertain which factors contribute to compromised bone mineral density values in trans girls prior to GAHT. Unclear safety profile of high-dose oestradiol preparations in trans girls (used to limit height) Monitor bone density[47] Trans boys: Gonadal suppression is recommended to be continued during GAHT Possibly compelling reasons to initiate GAHT in TG < 16 years. The optimal age /stage for initiating GAHT & surgery not yet clarified Authors conclude that it is uncertain whether starting CSH at a younger age is associated with improved quality of life of transgender adolescents, or is associated with increased rates of regret or de-transition
Chew, 2018[45] Aims: To review evidence for the physical,	Departments of Pediatrics and Psychiatry, Melbourne	GAHT N=10 studies in total (Estrogen n=3, testosterone n=5,	Trans girls. Combined oestrogen and cyproterone acetate benefits: 67% reached Tanner stage B3 after	Trans girls. Combined oestrogen and cyproterone acetate harms: Majority not satisfied with degree of breast development. Side effects included breast tenderness		Trans girls. Combined oestrogen and cyproterone acetate: Potential psychosocial effects unclear Anti-androgen cyproterone acetate:

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Reviews

Author, date, aims	Country / Studies included / *Search strategy*	*Intervention* Age or stage of puberty suppression	Benefits	Harms	Key recommendations
psychosocial & cognitive effects of GnRHa, gender-affirming hormones, anti-androgens and progestins on TG adolescents	Medical School, University of Melbourne. *Search terms and search strategy detailed. 13 studies included*	anti-androgen cyproterone n=1, progestin lynestrenol n=1) Age / stage not reported	cyproterone acetate and oestrogen for 6 months. Within 6 months serum oestradiol reached female reference range. After 3 months total testosterone outside male ref range. Reduced growth velocity. No significant changes in lipid profile Estrogen monotherapy: Increases in BMD for those who had GnRH, but after 2 years still lower than age/birth-assigned norm. Total BMI increased in first 6 months then stabilised. Most studies showed few biochemical changes with lipids Trans girls. Anti-androgen cyproterone acetate: Reductions in testosterone; marked increase in prolactin.	(57%), emotional lability (29%), fatigue (14%), hot flushes 14%. Significant increase in creatinine; one study found reduced growth compared with age-matched peers while another study found no difference Trans girls. Anti-androgen cyproterone acetate: Only partially reversible. Cyproterone acetate was evaluated to be relatively safe. Most common side effect was fatigue (37%) Cyproterone acetate resulted in a decrease in growth velocity compared with age-matched peers. No clinically significant changes in body weight and BMI. Breast development, outcomes were subjectively less in size than expected in majority of recipients Trans boys. Lynestranol: Did not stop menses. Side effects of heavy periods, headaches[17]	One study only. Successfully suppresses testosterone but its potential psychosocial benefits are unclear Authors conclude that, overall, hormonal treatments for transgender youth were observed to be relatively safe but not without potential adverse effects

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Reviews

Author, date, aims	**Country / Studies included / *Search strategy***	***Intervention*** **Age or stage of puberty suppression**	**Benefits**	**Harms**	**Key recommendations**
			Reduced facial hair. Few biochemical changes Trans boys. Lynestranol: Safe; resulted in reduced SHBG & LH, & increase in free testosterone		
Baram, 2019[44] Aim: To synthesise the psychosocial and medical literature on fertility preservation (FP) for transgender adolescents and young adults (TAYAs)	Canada *19 psychosocial-based research papers and 21 medical-based research papers. Search strategy according to PRISMA detailed*	Family planning discussions / counselling provided to TGD young people; knowledge, attitudes and beliefs of TGD young people and caregivers, and medical interventions related to fertility	GAHT (not specified)	Not all providers in studies conducted routine fertility discussion prior to hormone treatment. Significantly reduced semen parameters among those with current GAHT compared with both past and no treatment. Trans girls have poorer semen quality for most semen parameters, particularly a higher proportion of oligospermia. Trans girls' sperm to be more cryosensitive Trans males: Eight studies evaluated the effects of GAHT on fertility hormone levels, ovarian morphology and histology, as well as oocytes, with conflicting results. Most studies were with	Limitation for this review: Several studies included had young people > 18 years. For young prepubertal transgender people, the only feasible option regarding fertility preservation is testicular tissue cryopreservation (TTC), which is still experimental and not yet proven successful in humans. When counselling about TTC, both the patient and guardian need to be aware that it is relying on the emerging technologies of tissue reimplantation or spermatogonial stem cells (SSC) There are many barriers preventing TAYAs from pursuing FP: Lack of awareness of options, high costs, invasiveness of procedures & potential

Table 3—Medical intervention 2: Gender-affirming hormone therapy

Reviews

Author, date, aims	Country / Studies included / *Search strategy*	*Intervention* Age or stage of puberty suppression	Benefits	Harms	Key recommendations
				participants >18yo	psychological impact of the FP process. The available data regarding reproductive effects of GAHT are diverse, and while detrimental effects are anticipated, the extent to which these effects are reversible is unknown

Table 4—Medical intervention 3: Gender-affirming surgery

Empirical studies

Author, date, aims	Country / design / setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
Pullen Sansfaçon, 2019[40] Understand goals, feelings about treatment & regrets of receiving gender-affirming care	Canada Qualitative study 3 Canadian gender dysphoria clinics	*Chest surgery* N=1 17 years Trans boy	Experiences of care and treatment	Promoted comfort about body. "It (top surgery) was probably the one that made the biggest difference"		
Marinkovic, 2017[34] To present data about chest reconstructive surgeries in TG youth from a paediatric gender management clinic	US Retrospective cohort study Children's hospital	*Chest reconstruction surgery* (keyhole or double incision). N=14 Trans boys: 100% Age for chest surgery: 17.2 years (range 13.4–19.7). Three subjects < 16. All at Tanner stage 5	Satisfaction with the aesthetic outcome of the procedure	High satisfaction with aesthetics and comfort. All subjects pleased they did not need a binder anymore. Improvements in depression & anxiety after the procedure in almost all cases. Out of 10 subjects whose depression-screening scores were available, only one had high depression scores	Self-reported complication rate was low: 5/14 had hypertrophied scar tissue (keloid) and/or a small and temporary fluid or blood collection. None experienced serious adverse effects (e.g. nipple necrosis, infection). Most had decreased or complete loss of sensation in the surgical and nipple area. 1 participant stopped testosterone about 2 months after surgery and later requested return to natal gender. Chest surgery is usually not covered by insurance in US	A letter from a mental health provider was required in order to perform the procedure, as per WPATH recommendation. Larger, multicentre studies with long-term follow-up and international collaboration are necessary to gather data about surgical practices and outcomes in youth. Continued advocacy is vital for securing improved insurance coverage for this and other fundamental procedures that are medically necessary for transgender individuals

Table 4—Medical intervention 3: Gender-affirming surgery

Empirical studies

Author, date, aims	Country / design / setting	*Intervention* Sample N= age, gender identity	Main outcomes	Benefits	Harms	Limitations / flags / comments
Khatchadourian, 2014[29] Describe patient characteristics at presentation, treatment, and response to treatment	Canada Retrospective chart review Columbia Children's Hospital	*Mastectomy with male chest contouring* N=9 Trans boys: 100% Median age 18.1 yrs (range 14.9–22.1)	Patient characteristics, clinical management and response to treatment	Trans boys treated early with GnRHa who undergo mastectomy have a more favourable postoperative result	Not reported	Authors concluded treatment with GnRHa and/or cross-sex hormones, in collaboration with transgender-competent mental health professionals, appears to be appropriate in carefully selected youth with gender dysphoria. Long-term follow-up studies are needed to determine the safety of these treatments in this age group

Table 4—Medical intervention 3: Gender-affiming surgery

Guidelines

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age / stage	Treatment		Non-treatment		Key recommendations / comments
			Benefits	Harms	Benefits	Harms	
Telfer, 2018[1] Australian standards of care and treatment guidelines for transgender and gender-diverse	Healthcare providers working with TGD children and adolescents in Australia	*Chest surgery* Not before 16 years of age	Most effects are reversible Benefits / harms not reported		Benefits / harms not reported *Literature search strategy not defined. Four authors, with acknowledgments to multiple contributors and stakeholders (nationwide) including consumers. Endorsed by Australia and New*		Decision regarding surgery being in the adolescent's best interest should be made jointly, with consensus between the adolescent, guardians and clinicians

Table 4—Medical intervention 3: Gender-affiming surgery

Guidelines

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age / stage	Treatment		Non-treatment		Key recommendations / comments
			Benefits	Harms	Benefits	Harms	
children and adolescents					*Zealand Professional Association for Transgender Health (ANZPATH)*		
Lopez, 2017[51] US Statement on gender-affirmative approach to care from the Pediatric Endocrine Society special interest group on transgender health	Academic societies involved in the care of children and adolescents	*Gender-affirming surgery*	Studies show HRT and gender-affirming surgery are associated with reduced gender dysphoria and increased quality of life in adults	One longitudinal study in the Netherlands revealed persistence of psychiatric comorbidity and death from suicide in transgender patients after gender-affirming surgery[26]	Non-treatment benefits / harms not reported *Search strategy for literature review not included. Five authors, on behalf of the Pediatric Endocrine Society*		Results should not be interpreted that sex reassignment increases morbidity and mortality as overall mortality rate was only significantly increased for the group operated on before 1989. The results might be due to improved healthcare for transgender adults during the 1990s, along with improved societal attitudes towards gender-nonconforming individuals
Hembree, 201747 International Endocrine treatment of gender-dysphoric / gender-incongruent persons: An Endocrine Society clinical practice guideline	Endocrinologists	Gender-affirming surgery Not before 18 years of age	1 study showed increased satisfaction with breasts, genitals and femininity. Surgery seen as a key option for trans girls	Irreversible Several studies report significant long-term psychological pathology	No benefits / harms of non-treatment reported Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low		Surgery only after mental health professional and responsible clinician agree it is necessary and would benefit overall health/wellbeing. Because of the lack of controlled studies, incomplete follow-up and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. The authors recommend more studies with appropriate controls that

Table 4—Medical intervention 3: Gender-affiming surgery

Guidelines

Author, date, aims	Target users (e.g. GPs)	*Intervention* Age / stage	Treatment		Non-treatment		Key recommendations / comments
			Benefits	Harms	Benefits	Harms	
							examine long-term quality of life, psychosocial outcomes and psychiatric outcomes to determine the long-term benefits of surgical treatment
Coleman, 201248 US, Europe Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7	Clinicians, voice therapists, mental health services Process of developing guidelines outlined. International advisory group appointed. Members of WPATH committee named. Review of literature undertaken but search strategies not identified	Chest surgery After ample time of living in the desired gender role and after one year of testosterone treatment	Beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective wellbeing, cosmesis, and sexual function		Expensive Infections and capsular fibrosis are rare complications of augmentation mammoplasty in trans females. Scarring is likely. Complications of subcutaneous mastectomy can include nipple necrosis, contour irregularities and unsightly scarring		Informed consent necessary: alternatives; advantages/disadvantages of each type; risks; before and after photos
		Hysterectomy with bilateral salpingo-oophorectomy or salpingectomy, and possible neophallus creation 18 years					*Mastectomy* May be considered before 18

Reviews

No reviews identified

Table 5—Evidence for psychosocial interventions

Empirical studies

Author, date, aims	Country / design / setting	*Intervention* Sample, age, gender identity	Main outcomes	Benefits	Harms	Limitations / comments
Quinn, 2018.[38] Aim: To investigate intensive voice feminisation therapy in a trans girl in a youth justice facility	Australia Experimental case study Youth Justice Facility	*Voice training* targeting fundamental frequency and oral resonance. N=1 Age 17 Trans girl: 100%	Acoustic analysis of vocal femininity, self-ratings of vocal satisfaction, a post-treatment structured interview and pre- and post-treatment completion of the Transsexual Voice Questionnaire (TVQ).	Score decreased from 100 to 81 on the TVQ, indicating that their voice was having a less significant negative impact on their life."	Client was still not consistently perceived as female following treatment and had difficulty implementing feminine speech strategies	Suggests it is possible to achieve significant voice change within a limited timeframe among transgender young offenders. Limited generalizability: Participant had a complex social, psychological and substance abuse history, potentially compromised vocal health, and incomplete course of hormone therapy
Costa, 2015.[18] Aim: To assess global functioning after psychological support and puberty suppression.	UK Prospective cohort study. Gender Identity Development Service	N= 71 36 subjects received psychosocial support and GnRHa. 35 subjects received psychosocial support and referral to mental health services. Mean age=15.52 ±/- 1.41 years	Utrecht GD Scale (UGDS). Children's Global Assessment Scale (CGAS). Assessed at 4 time points: baseline, 6 months, 12 months, 18 months. Participants were compared with a sample of young individuals without observed psychological/	Baseline CGAS scores were significantly lower than a normative sample of adolescents. Adolescents who received psychological support + GnRHa had significantly improved functioning over time and were comparable to a normative sample of adolescents. Adolescents who received psychological support only had significantly better psychosocial functioning after	None reported	Indicates that puberty suppression in addition to psychological support is associated with superior psychological outcomes compared to psychological support alone

Table 5—Evidence for psychosocial interventions

Empirical studies

Author, date, aims	Country / design / setting	*Intervention* Sample, age, gender identity	Main outcomes	Benefits	Harms	Limitations / comments
			psychiatric symptoms	six months but did not have further improvement over time. They continued to score lower than a normative sample of adolescents		
De Ceglie, 2006.[41] Aim: To describe a model of group therapy for parents/carers of children or adolescents with gender identity disorder and to report the results of an evaluation of the program	UK Case report Gender Identity Development Service	*Parent support group held once a month for 1.5 hours for 6 months.* N = 10 parents / carers of 8 children. Age range of children: 9 - 17 yrs. Gender identity of children was unclear	Exploration of parents and carers' experiences of the group therapy program.	7 evaluation questionnaires were returned. The majority rated aspects of the group experience as 'very helpful' or 'helpful'. Qualitative results indicated that parents' feelings of isolation were diminished, and they gained a better understanding and knowledge of gender identity development. The group also provided a good basis to link with an ongoing self-help organization with families who had already participated in previous groups.	The least helpful aspects of the group included the 'tendency for sometimes one or two parents to dominate' and 'difficulty in understanding the way the doctor explained things'	Overall, the result suggests that group work for parents and carers of children and adolescents with gender incongruence is helpful.

Guidelines

No guidelines identified

Reviews

No reviews identified

Table 6—Long-term follow-up

Psychological

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
Achille, 2020[19] US	Single-centre, longitudinal Stony Brook University Hospital	*Pubertal suppression*	Trans boys and girls (n=50)	Follow-up: 18 months (6-monthly intervals)	Endocrine intervention may improve mental health in transgender youths in the US. This effect was observed in both male-to-female and female-to-male youths, but appears stronger in the former	There were fewer youths with depression scores/suicidal ideation who had undergone endocrine intervention compared with those who had not, while quality of life scores showed positive associations with intervention in transgender youths over time in the US The effects of testosterone in FTM transgender persons takes 6–12 months to become apparent and is not fully apparent until after several years of exposure
Baram, 2019[44] Canada	Review paper: TGD before GAHT	Psychosocial-based (n=19) & medical (n=21) papers that explore fertility-related aspects	Comment: FP counselling should begin as early as possible as a standard of care before GAHT to allow time for informed decisions. The current lack of high-quality medical data specific to FP counselling practice for this population means there is a reliance on expert opinion and extrapolation from studies in the cisgender population. FP counselling and support services should be the standard of		Another major barrier for both trans boys and trans girls was the concern of stopping or delaying the start of GAHT for FP when they already found it stressful to cope with gender dysphoria (Nahata et al., 2017; Chiniara et al., 2019). Prior to undergoing FP, individuals	FP counselling should begin as early as possible as a standard of care before GAHT to allow time for informed decisions

Table 6—Long-term follow-up

Psychological

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
			care		who have started GAHT must discontinue treatment for several months to allow sperm production or ovulation to resume	
Cohen-Kettenis, 2011[39] Netherlands	Single case study	*GnRH* analogs at 13 years of age; *GAHT* treatment at 17 years; *gender-reassignment surgery* at 20 and 22 years	N=1	Follow-up: Age 13–22	Was satisfied with surgery At 22, he was physically in good health and his metabolic and endocrine parameters were within reference ranges. Bone mineral density was within the normal range for both sexes. His final height was short as compared with Dutch males but proportionally normal	
Coleman, 2012[48] Europe; North America	WPATH (World Professional Association for Transgender Health) Standards of Care	*Psychotherapy*			Psychotherapy—although highly recommended—is not a requirement for gender dysphoria	
		Family therapy			Can assist clients with making thoughtful decisions about communicating with family members and others about their gender identity & treatment decisions	

Table 6—Long-term follow-up

Psychological

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
		E-therapy, online counselling or distance counselling				Until sufficient evidence-based data on this use of e-therapy is available, caution in its use is advised
		Voice and communication therapy	Treatment may involve individual and/or group sessions. The frequency and duration of treatment will vary according to a client's needs		Specialists can best serve their clients by taking the time to understand a person's gender concerns and goals for gender-role expression	
Costa, 2015[18] UK	Gender Identity Development Service Prospective cohort study	*GnRH & psychological support* n=36		Follow-up: 18 months	CGAS scores were significantly higher after 6 months of psychological support for both groups	
		Psychological support and mental health referral + delayed GnRH n=35	Mean age 16 Two groups: immediately eligible (started GnRHa immediately after assessment and diagnosis) and delayed eligible (not ready to start		The delayed eligible group continued to score lower than a sample of children/adolescents without observed psychological/psychiatric symptoms, even after 18 months of psychological support	

Table 6—Long-term follow-up

Psychological

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
			treatment until further psychological support)			
de Vries, 2014[30] Netherlands	Prospective cohort study University Medical Center, Amsterdam	*GnRH*	55 young adults from cohort of 70 adolescents who were prescribed puberty suppression	Follow-up: from GnRH to 12 months post-surgery	Transwomen reported more satisfaction over time than transmen. None (trans men/women) expressed regret	
		GAHT	Transmen more satisfied after GAHT than pre-GnRH. Reduced anger and anxiety for transmen. Stable for transwomen		Depression scores increased from the time of GAHT to the time of surgery	Comment: The age criterion of 16 years for the start of GAHT may be problematic especially for transwomen, as growth in height continues as long as GAHT is not provided (as this causes the growth plates to close)
Kuper, 2020[21] US	Prospective cohort study Multidisciplinary program in Dallas, Texas	TG adolescents with *GnRHa and GAHT* survey 'SCARED'. Body dissatisfaction (validated tools).	TGD adolescents taking GnRHa and GAHT n=148 Ages 9–18 years; mean age 14.9 years	Follow-up: 12 months	A significant decrease in body dissatisfaction, self-reported depressive symptoms & total anxiety symptoms during follow-up. Decreases in anxiety symptoms significant (p=0.05). No change in clinician report of depressive symptoms. A significant	Interesting that the patients reported a decrease in depression and anxiety but the clinicians found overall no change

Table 6—Long-term follow-up

Psychological

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
		Clinicians reported impression of depression and suicidality			change in self-reported depressive symptom categories (P<0.001) but not clinician-reported categories	
Marinkovic 2017[34] US	Retrospective cohort study Children's hospital clinic	*Chest surgery*	Trans boys GAHT and chest surgery n=14	Average follow-up was 1.6 years but it ranged from 0.1–3.6 years	All reported high personal satisfaction with the surgical outcomes (aesthetics/comfort). All pleased that postoperatively they no longer needed a binder. Average satisfaction score 4.9/5. Almost all reported improvement in depression and anxiety post op. Out of 10 subjects whose depression-screening scores are available, assessed through PHQ-9 screen in the postsurgical period, only one continued to have high depression scores	All patients' satisfaction 5 or 4.5 (3) on a scale of 1–5. All happy they no longer needed a binder Family reported decrease in depression at semi-structured interview
Telfer, 2018[1] Australia	Standards of care and treatment guidelines	*GnRHa, GAHT, psychological support, transition to adult care*	Trans boys and trans girls	While most TGD children and their families may benefit from psychological support, the level of support depends on the clinical & psychosocial circumstances. There is growing evidence to suggest that for children, family support is associated with better mental health outcomes. When a child's medical, psychological and/or social circumstances are complicated by coexisting		The discussion about transition to adult care needs many years of preparation If possible, the same practitioner is used to retain continuity of care,

Table 6—Long-term follow-up

Psychological

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
				autism spectrum disorder, mental health problems, learning or behavioural difficulties, trauma, abuse or significantly impaired family functioning, a more intensive approach with input from a skilled mental health clinician with expertise in child cognitive and emotional development and child psychopathology, and experience in working with children with gender diversity and gender dysphoria, is required		which is especially important for those in rural areas. Mental health assessments should continue throughout the process Where there are coexisting mental health difficulties, more intensive input from a mental health practitioner is beneficial
		Social transitioning		Social transition should be led by the child and can reduce a child's distress and improve their emotional functioning. Evidence suggests transgender children who have socially transitioned demonstrate rates of depression, anxiety and self-worth comparable to their cisgender peers		Can assist adolescents in the development of skills which enable them to communicate in a manner consistent with their gender identity
		Fertility counselling and preservation procedures		TGD youth who present in the latter stages of pubertal development (Tanner stage 3–5) should be counselled on the benefits of storing semen for cryopreservation either through masturbation or surgical extraction		
Turban, 2020[53] US	Cross-sectional survey about adolescent therapy and depression and	*Pubertal suppression*	Adults 18–36 years of age who had or wanted to have puberty suppression	Follow-up: 12 months from puberty suppression to up to age 36	Treatment with pubertal suppression among those who wanted it was associated with lower odds of lifetime suicidal ideation when compared with	No difference detected in the odds of lifetime or past-year suicide attempts or attempts resulting in

Table 6—Long-term follow-up

Psychological

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
	suicidality		as a youth n=89		those who wanted pubertal suppression but did not receive it	hospitalization
Brain						
Beking, 2020[20] Netherlands	Quasi-experimental	*Testosterone* Trans boys	Trans boys n=21; cisgender boys n=20; cisgender girls n=21	Length of follow-up: 12 months after GAHT	Cis boys: more activation in the right amygdala than girls during the perception of emotional faces. Lateralisation index in trans boys shifted towards the right amygdala after testosterone, & the cumulative dose of testosterone treatment correlated significantly with amygdala lateralisation after treatment. No significant group differences in lateralisation. Testosterone concentrations predicted rightward amygdala lateralisation only in the cis boys, but not in cis girls or trans boys	There is uncertain clinical significance in the changes noted in the lateralisation index, i.e. whether this would actually make any significant difference in functioning

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
Chew, 2018[45] Australia	Systematic review of papers regarding GnRHa and GAHT	*GnHRa*	13 papers total: GnRHa (n=9) oestrogen (n=3), testosterone (n=5), anti-androgen cyproterone (n=1), and progestin lynestrenol (n=1)	Follow up: variable	Low-quality evidence suggests hormonal treatments for TGD adolescents can achieve intended physical effects, but evidence regarding their psychosocial and cognitive impact are generally lacking. Lack of reporting of pubertal stage at treatment commencement, which makes interpretation of some changes difficult, especially BMD	Although researchers in 2 studies have now examined growth and height characteristics in transgender youth receiving GnRHa[21,29], their relatively short follow-up times (≤3 years) precluded determination of the effects of GnRHa on final height, and future researchers should address this knowledge gap
		Oestrogen monotherapy	Increases in BMD for those who had GnRH, but after 2 years of Rx, still lower than age/birth-assigned norm. Total BMI increased in first 6 months then stabilised. Most studies showed few biochemical changes with lipids			
		Testosterone	Virilisation, lower voice, clitoral enlargement, masculinised hair pattern within 6 months. Most had testosterone reaching normal male range after 6 months. Reduced oestrodiol levels after 6 months. Significant increase in BMD in those treated with GnRH but did not achieve age & birth-assigned sex control norms. Increased growth velocity and weight. No significant changes in carbohydrate and lipid metabolism. Improvement in mental rotation tasks			There is uncertain clinical significance in the changes noted in the mental rotation tasks, i.e. whether this would actually make any significant difference in functioning
Cohen-Ketteris, 2011[39] Netherlands	Single case study	*Triptorelin*	Trans boy n=1	Follow-up age 13–22	He was physically in good health and metabolic and endocrine parameters were within reference ranges. Bone mineral density was within the normal range for both sexes. His final height was	

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
					short as compared with Dutch males; however, his body proportions were within the normal range	
Hannema, 2017[14] Netherlands	Prospective cohort study	*Oestradio*	Trans girls n=28	Follow-up: 5 years	Height gain was related to bone growth when they started. Bone age variable if baseline bone age 13–15; those with advanced bone age grew slowly	
Hembree, 2017[47] Authors from US, Netherlands, Belgium	Endocrine Society Guidelines	*Long-acting GnRH analogues recommended*	TGD	GnRHa: adverse effects on bone mineralisation, compromised fertility if subsequently treated with sex hormones, unknown effect on brain development. Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRHa for precocious/early puberty. Hot flushes, fatigue and mood alterations because of pubertal suppression. Puberty suppression at an early stage may compromise fertility Offer vit D supplements. BP monitoring pre & post treatment. Recommended: fertility discussion before puberty suppression and GAHT. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Specifically: Height/ weight/ sitting height/ BP, Tanner stages every 3–6 m. LH, FSH, E2/T, 25OH & Vit D every 6-12m. DXA scan, bone age L hand if indicated every 1–2 years		Outcomes for all as there are not a lot of really long-term follow-ups. They have suggested a series of long-term follow-up monitoring in the prevention of harm. Section 4 of the recommendations address this with 7 points. No studies of vitamin D supplementation in this context. If GnRH treatment not available, trans girls may be treated with anti-androgen that directly suppresses androgen synthesis or action
Klaver, 2018[26]	Retrospective cohort study	*17ß-oestradiol*	71 transwomen	All started GnRH before 18	Body composition conformed to ciswomen with GAHT and this was seen	

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
Netherlands	VU University Medical Center			years of age and followed after age 20	to greater effect than for trans men	
		Mixed testosterone esters (Sustanon)	121 transmen		Body composition conformed with GAHT to trans men but less so than transwomen	
Klink, 2014[15] Netherlands	Longitudinal observational study at a tertiary referral centre	*GnRH*	TG n=34 who had started puberty suppression and subsequently had gonadectomy	Follow-up: from start of GnRH to age 22	Between the start of GnRHa and age 22 years, lumbar area BMD z-score (for the sex they were assigned at birth) in transwomen decreased significantly from 0.8 to 1.4 and in transmen there was a trend for decrease from 0.2 to 0.3. This suggests BMD was below their pretreatment potential and either attainment of peak bone mass has been delayed or peak bone mass itself is attenuated	Limitations: It could not be determined whether the loss of bone mass at age 22 can be attributed to the duration of GnRHa, initial low GAHT dosage scheme, or the pharmacodynamic characteristics of GAHT. Most patients were late pubertal at start and therefore part of their bone mass development had already occurred and GnRHa monotherapy therapy was relatively short before start of GAHT Limitation: The data on z-scores were limited. At the time of start of the study non-dominant femoral region aBMD z-scores

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
						were not available and only a small number of subjects could be compared from pretreatment to age 22 years
Mahfouda, 2019[4] Australia	Review of TG papers	*GnRH & testosterone*		In accordance with the Endocrine Society Guidelines, 12 monitoring BMD parameters in transgender adolescents is recommended both prior to and during gender-affirming hormonal treatment		
Pang, 2020[66] Australia	Single case study	*Puberty suppression for more than 2 years*	Non-binary youth (n=1)	Follow-up: 24 months+	Dilemma: use of blockers long-term involves 2 main risks: impaired fertility in the future and low bone density. TBMD decreased to lowest 2.5 percentile by 15. No fractures	This is a complex discussion by 3 experts with a 4th comment at the end on whether the health risks are outweighed by the psychological risks

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
Tack, 2018[8] Belgium	Prospective cohort study Ghent University Hospital	*Progestins*	Trans boys n=44	Follow-up: prior to GnRH and after starting GAHT	Proandrogenic and antiandrogenic progestins induce body composition changes in line with the desired appearance within one year of treatment. Bone health (especially at lumbar spine) is of concern in trans girls, as bone mass accrual is severely affected by androgen suppressive therapy	Appropriate grip strength, body composition, lean mass decreases. Bone development is interfered with, especially with trans girls on CA, even with supplementations. Z-scores were lower at baseline. Less activity than peers and z-scores decreased with GnRHa, and CA did not make it any better. CA had a negative affected on trabecular bone
		Orgametril (L)			Weight and BMI gain more pronounced than age-matched peers. Lean mass increased and fat mass decreased; increased muscle strength P1NP (marker for bone formation) decreased by 9.3%, BMD slightly decreased	

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
		Trans girls: 50mg *cyproterone acetate* (CA) daily. *Vitamin D* supplements 25,000 IU/month was added to the treatment, & all advised to take daily *dietary calcium* of at least 1500 mg	Trans girls n=21		CA limited normal bone expansion and impeded pubertal bone mass accrual, mostly at the lumbar spine [z-score: 20.765 to 21.145 (P = 0.002)]. Bone health, especially at the lumbar spine, is of concern in trans girls, as bone mass accrual is severely affected by androgen suppressive therapy	
		Androcur™ (Cyproterone acetate)			Weight and BMI changes similar to age-matched peers. Significant fat mass increase P1NP decreased by 46.5%. Decreased BMD. Cross-sectional muscle near radius significantly decreased	
		Vitamin D	Trans boys and girls		Mean levels of vitamin D increased. No difference between trans boys and girls	

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
Stoffers, 2019[17] Netherlands	Retrospective cohort Department of Pediatrics, Leiden University Medical Centre, Leiden	*GAHT*	Trans boys n=64 Received *testosterone therapy* for a minimum of 6 months and seen 2010–2018	Follow-up: 2 years	Even after 2 years, not all had abdominal hair. Increased acne up to 12 months: prevalence reduced by 15 months. Only 5 grew 2 cm+ during follow-up. Systolic BP increased from 118 mm Hg to 124mm Hg in 1st 6 months, P=.003), after which it did not change. BMD z-scores at 12–24 months lower than pretreatment values. Hematocrit significantly increased in 1st year 0.422–0.466, P<.001)	Although the hematocrit normalised without intervention, monitoring is important because erythrocytosis is associated with an increased risk of neuro-occlusive or cardiovascular events. Adolescents should be counselled about these concerns and advised about factors known to influence cardiovascular and bone health, such as diet (including adequate calcium and vitamin D intake), physical exercise, smoking and alcohol Long-term follow-up studies of lipid profile with testosterone treatment in adolescence are necessary to assess cardiovascular outcomes. To know long-term sequelae of these changes and potential CVD and bone disease, longer term studies will be needed

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
Vlot, 2017[9] Netherlands	Retrospective cohort study VU University Medical Center	*GnRHa (triptorelin)* Trans boys and girls n=70	*All were treated with GnRHa triptorelin and GAHT was added in incremental doses from the age of 16 years*	Follow-up: 2 years	Decrease of P1NP (formation markers) and 1CTP (resorption marker) during GnRHa treatment, indicating decreased bone turnover (young transmen 95% CI−74 to−50%,p= 0.02, young transwomen* (<15 years) 95% CI−73 to−43,p= 0.008). Bone mineral apparent density (BMAD) z-scores of predominantly the LS decreased, especially in the young transwomen. 14 months after GAHT, bone turnover markers (BTMs) P1NP and ICTP were even more decreased in all groups except for the old transmen* (>15 years)	Value of following bone turnover markers (BTMs) seems limited especially when they go on to GAHT, DXA scans remain important in transgender youth Lumbar spine (LS) bone mineral apparent density (BMAD) z-score decreased in young transwomen after GnRHa
		GAHT 17β-oestradiol			In older trans boys, increase of BMAD & BMAD z-scores predominantly in the LS as a result of treatment with GAHT is accompanied by decreasing BTM concentrations after 24 months of GAHT 2 years after GAHT, BTMs P1NP and ICTP were even more decreased in all groups except for the old transmen.* During GAHT BMAD increased and z-scores returned towards normal, especially of the LS (young transwomen* CI 95% 0.1–0.6, p=0.01, old transwomen* 95% CI 0.3–0.8, p=0.04)	No real change in BMAD at 24 months. LS BMAD z-score decreased in young transwomen* after GnRHa but increased in all transwomen after 24 months of GAHT

Table 6—Long-term follow-up

Bone mineral density

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at interventions	Age / years of follow-up	Outcomes	Comments
		GAHT Testosterone esters (Sustanon)			Bone mineral apparent density (BMAD) increased After 24 months young transmen decreased resorption marker ICTP concentrations. Young and old transmen* increased BMAD seen in LS increased BMAND z-score. LS (greater change) and FN differ in BMAD, probably reflecting state of puberty at initial GnRHa	The added value of evaluating bone turnover markers (BTMs) in transgender adolescent seems to be limited and requires further research. Meanwhile, DXA-scans remain important in follow-up of bone health of transgender adolescents

*Before treatment, the patients were categorised into a young and old pubertal group, based on their bone age. The young transmen had a bone age of 14 years and the old transmen had a bone age of ≥14 years. The young transwomen group had a bone age of 15 years and the old transwomen group ≥15 years.

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
Achille, 2020[19] US	Single-centre, longitudinal Stony Brook	*Pubertal suppression*	Trans boys and girls (n=50)	Follow-up: 18 months (6-monthly intervals)		

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
Cohen-Ketteris, 2011[39] Netherlands	Single case study	*Triptorelin*	Trans boy n=1	From puberty suppression to age 35	He was physically in good health and metabolic and endocrine parameters were within reference ranges. BMD was within the normal range for both sexes. His final height was short compared with Dutch males; however, his body proportions were in the normal range At age 35, general health markers, such as hematological parameters (Hb, haematocrit, erythrocytes), renal function and liver enzymes, were all within the normal reference value ranges	
Coleman, 2012[48] Europe, North America	WPATH (World Professional Association for Transgender Health) Standards of Care	*Oestrogens* Trans girls NB: ethinyloestradiol not recommended because of increased risk of		Trans girls	Likely increased risk: Venous thromboembolic disease (risk higher with oral than transdermal), gallstones, elevated liver enzymes, weight gain, hypertriglyceridaemia. Possible increased risk: Hypertension, hyperprolactinaemia or prolactinoma. Possible increased risk (oral higher	Baseline laboratory values are important both to assess initial risk and evaluate possible future adverse events. Fertility counselling prior General preventive healthcare for TR people: Include VCD, osteoporosis and some cancers—breast,

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
		VTE			than transdermal): Type 2 diabetes	cervical, ovarian, uterine and prostate. Ongoing research?
		a. Spironalactone b. cyproterone		Trans boys		Blood pressure and electrolytes need to be monitored because of the potential for hyperkalaemia
		Testosterone		Trans boys	Voice deepening irreversible. Gynomastia may be reduced by surgery. Likely increased risk: Polycythaemia, weight gain, acne, androgenic alopecia (balding), sleep apnoea. Possible increased risk: Elevated liver enzymes, hyperlipidaemia	
Hannema, 2017[14] Netherlands	Prospective cohort study	Estradiol *2 mg daily* 2–6 mg oral estradiol at the end of pubertal induction and increase the estradiol dose if the serum estradiol levels are low,	Trans girls n=28	Follow-up: 5 years	After 5 years height gain was related to bone growth according to pubertal stage when GnRH was started. Body fat increased in 3rd year. GnRH suppressed in all but one. Prolactin, HCT, HbA1c liver enzymes did not change except the lower ALP in the 2 and 3rd years. Creatinine decreased in 2nd year except	An adult dose of 2 mg does not always result in appropriate serum estradiol levels. [Australian guidelines: increase the dose to 2 mg oral daily depending on clinical effect at 6 or 12 months. Further increases may be

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
		especially in the presence of a high serum LH and low mineral bone density. No need to monitor haematocrit, creatinine, liver enzymes or HbA1c during pubertal induction with estradiol. Prolactin level monitoring is recommended			in one where it increased after a year but it did normalise. Bone age variable if baseline bone age was 13–15. Those with advanced bone age grew slowly: may not always reach adult levels of estradiol, especially when LH high	necessary over time to a maximum dose of 2–4 mg oral daily.[1]] Further studies are needed to establish effective and safe methods to limit growth [reduced growth is desirable for trans girls; with the converse applicable to trans boys] No value in monitoring renal function, liver enzymes HCT and HbA1c. Further studies need to limit growth safely
		Ethinylestradiol (E2) (n=2)				Use of ethinylestrodial no longer recommended because of high risk of VTE Prolactin monitoring

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
		Ethinylestradiol (n=4) High dose of E2 because of excessive height			Successful slowing down of growth	High doses of oestrogen may increase risk of VTE. Discouraging smoking and long periods of immobilisation are important Need studies to assess the safety and efficacy of estradiol and to determine optimal dose to prevent excessively tall stature
Hembree, 2017[47] Authors from US, Netherlands, Belgium	Endocrine Society Guidelines	*Long-acting GnRH analogues recommended*	TGD		Outcomes for all as there are not a lot of really long-term follow-ups; they have given a series of long-term follow-up monitoring in the prevention of harm. Section 4 of the recommendations addresses this with 7 points [a. 3-monthly physical monitoring for 1st 12 months then six monthly; b. Periodic monitoring of prolactin for trans girls; c. CVR risk factor monitoring; d. BMD if risk identified, especially in those who stop GAHT after surgery; e. BreastScreen monitoring for trans boys as	If GnRH treatment not available, trans girls may be treated with anti-androgen that directly suppresses androgen synthesis or action Recommendations: Offer vit D supplements. BP monitoring before / during treatment. Any use of pubertal blockers (and subsequent use of GAHT) include

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
					per national protocols; f. prostate cancer monitoring for trans girls; g. Clinicians to determine need for oophorectomy & hysterectomy as part of gender-affirming surgery	discussion about fertility implications. During treatment, monitor for negative effects of delaying puberty, including a halted growth spurt & impaired bone mineral accretion. Specifically: Height/ weight/ sitting height/ BP/ Tanner stages every 3–6 m. LH, FSH, E2/T, 25OH & vit D every 6–12m. DXA scan, bone age L hand if indicated every 1–2 years
		17ß-oestradiol (transdermal for hypogonadal females)			Initiate Rx using gradually increasing dose schedule after multidisciplinary team has confirmed persistence of GD and sufficient mental capacity for consent. Monitor clinical pubertal development every 3–6 months & lab parameters every 6–12 months during hormone Rx, including prolactin levels and lipid profiles and diabetes screening	Authors are uncertain regarding the potential benefits of waiting until about age 16 years to initiate sex hormones versus the potential risks/ harm to BMD and the sense of social isolation from having the timing of puberty out of sync with peers

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
Klaver, 2020[35] Netherlands	Retrospective cohort study VU University Medical Center	*GnRHa*	71 transwomen & and 121 transmen		Treatment with gonadotropin-releasing hormone agonists and gender-affirming hormones in transgender adolescents is generally safe in relation to cardiovascular risk factors	
		GAHT			In transmen at 15 years, obesity was already more prevalent (5.0%) than in transwomen (1.4%), reference men (1.8%), or reference women (1.5%). For total cholesterol at 22 years, an almost similar or lower prevalence was seen in transwomen (0%) and transmen (5.3%) compared with reference men (4.4%) and reference women (6.6%). The prevalence of low HDL cholesterol levels at 22 years was slightly higher in transwomen (2.9%) compared with reference women (0.0%) At the age of 22, the prevalence of obesity was higher in transwomen (9.9%) and transmen (6.6%) than in reference men (3.0%) or	The cardiovascular risk profile in transgender persons using GnRHa and GAHTs was comparable with that in the general population during treatment, except for a higher prevalence of obesity in young adulthood. Long-term studies needed to clarify whether this hormonal treatment exerts a higher risk for cardiovascular events in the future of these transgender people who started treatment in their teenage years

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
					reference women (2.2%)	
Mahfouda, 2019[4] Australia	Review of TG papers	*GnRH*			Does starting puberty suppression in early puberty negatively affect peak bone mass accrual and thus increase the risk of osteoporosis in transgender youth later in life?	
		Oestrogen			Venous thromoembolism risk. Oestradiol alone insufficient for feminising effects; spironalactone added but can cause hyperkalaemia	Which factors contribute to compromised bone mineral density values in transgender female adolescents before receiving oestrogen? What is the safety profile of high-dose oestradiol preparations in transgender females, often used to limit height?
		Cyproterone acetate				Concerns over acute hepatic dysfunction and, rarely, occurrence of meningiomas. Use of smaller doses (12·5 mg) has substantially reduced the risk of

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
						these side effects
		GnRH & testosterone			Testosterone: reduced HDL after 6 months. Elevations in systolic and diastolic blood pressure with testosterone treatment have been observed after 2 years. Significant increases in AST, ALT, K+, TSH & free thyroxine. Collectively, the consensus among the authors of these studies is that the changes observed in transgender adolescents do not pose a clinical risk	Re high AST/ALT, K+, TSH, free thyroxine: additional studies are warranted to clarify long-term safety. Additionally, two of these studies used progestins (lynestrenol in trans boys[36], cyproterone acetate in transgender adolescent females[40]) with the GAHT regimen, rather than GnRH
Neyman, 2019[24] US	Retrospective chart review Indiana University School of Medicine and Riley Hospital for Children, Indianapolis	*Bicalutamide 50 mg daily*	N=13 trans girls	Follow-up: 12 months	Increased testosterone levels (but no clinical sequelae) Effective in decreasing androgen exposure and increasing feminisation; results are preliminary	13 patients exclusively bicalutamide. Only 5 patients had a second follow-up and of these only 4 were over 12 months. All had breast development from T1 to 2,3 or 4. The authors conclude this may be because of the effect of bicalutamide on the androgen receptor, leading to increased testosterone levels

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
						which are subsequently aromatised to oestrogen
Tack, 2016[8] Belgium	Retrospective chart analysis Ghent University Hospital	*Lynestrenol (L) (Orgametril®) 5 mg*	45 gender-dysphoric trans boys who had received hormonal treatment over a period of at least 6 months from 2010 until September 2015	6–12 months	This treatment was 13 x cheaper than GnRH & does not require injections. Rise in Hb but stabilised by 6 months; did not exceed normal male parameters. Effectively and significantly decreased the overall oestrogenic to androgenic ratio within 6 months	Headaches, hot flushes, fatigue. Probably less effective than GnRHa in inducing total amenorrhea, in suppressing gonadotropins and hence development of secondary sex characteristics
		Lynestrenol and testosterone esters (TE), Sustanon®			Increase in facial and body hair, libido, muscle mass and oiliness of the skin. It will also result in clitoromegaly, a deeper voice, cessation of menses, redistribution of fat mass. Significant increase in weight gain compared with age-matched peers who were of the sex they were assigned at birth. Rise in HB but did not exceed age-matched peers of the sex they were assigned at birth's parameters	Side effects: Male pattern balding. Lipid metabolism shifted to an unfavourable high-density lipoprotein (HDL)/low-density lipoprotein (LDL) ratio; metrorrhagia & significant increase in acne were the main side effects, followed by fatigue. Need for further research in TGD adults focusing on early determinants of

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
						cardiovascular disease such as adiponectin or carotid artery intima media thickness is warranted. Regular blood controls allow screening for physiological changes in safety parameters or hormonal levels and for medication abuse
Tack, 2017[12] Belgium	Retrospective cohort study Ghent University Hospital	*Cyproterone acetate (CA)*	Trans girls n=27	12 months	High doses of CA, as used in androgen deprivation therapy, have been associated with severe liver dysfunction. Consider periodic monitoring of liver function during treatment important. Side effects: Breast tenderness 2/27 (7.4%), emotionality 3/27 (11%), fatigue 10/27 (37%), hot flushes 1/27 (3.7%). Did not result in suppression of gonadotropins	Although lack of direct comparative studies, if confirmed, CA could offer a safe and valuable alternative for GnRHa
		Oestrogen and CA	Trans girls n=21	12 months	Breast tenderness 12/21 (57%), emotionality 6/21 (29%), hunger 5/21 (14%), hot flushes 3/21 (14%)	If favourable biochemistry is confirmed, CA could offer a safe and valuable alternative for

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
						GnRHa
Schagen, 2016[11] Netherlands	Observational prospective VU University Medical Center from 1998–2009	*GnRHa & triptorelin*	Trans girls n=49 Trans boys n=67	12 months follow-up	GnRHa treatment using triptorelin is effective in suppressing gonadotropins and sex steroids and results in a decrease in testicular volume and cessation of menstrual bleeding. No creatinine / liver enzymes pathology	Monitoring of creatinine and liver enzymes did not identify any pathology. Routine monitoring of gonadotropins, sex steroid levels, renal function and liver enzymes during GnRHa treatment using triptorelin considered unnecessary
Stoffers, 2019[17] Netherlands	Retrospective cohort Department of Pediatrics, Leiden University Medical Centre, Leiden	*GAHT*	Trans boys n=64 Received testosterone therapy for a minimum of 6 months and seen 2010–2018	Up to 2 years	Extremity hair increased by 12 months. Facial hair continued to grow and still present at 15 months. At 2 years, 79% had abdominal and chest hair, but not all had abdominal hair. Increased acne up to 12 months; prevalence reduced by 15 months. Only 5 grew 2 cm+ during follow-up, with height overall increasing, but slightly less than age-matched peers. Systolic BP increased from 118 mm Hg to 124mm Hg in 1st 6 months (P=.003), after which it did not change.	Although the haematocrit normalised without intervention, monitoring is important because erythrocytosis is associated with an increased risk of neurooccluisve or cardiovascular events. Long-term follow-up studies of lipid profile with testosterone treatment in adolescence are necessary to assess cardiovascular

Table 6—Long-term follow-up

Biochemical markers and cardiovascular disease

Author, year, country	Design / setting	*Intervention* Sample characteristics	Population, age at intervention	Age / years of follow-up	Outcomes	Comments
					BMD z-scores at 12–24 months lower than pretreatment values. Haematocrit significantly increased in 1st year (0.422–0.466, P<.001). Haematocrit levels were higher for those who started GAHT after the age of 16 and had higher doses initially than those who started earlier. Cholesterol stabilised by 2 years; HDL decreased and remained so over 2 years. Creatinine continued to rise over the two years.	outcomes. Adolescents should be counselled about these concerns and advised about factors known to influence cardiovascular and bone health, such as diet (including adequate calcium and vitamin D intake), physical exercise, smoking and alcohol

Appendix 4: Tanner stages or Sexual Maturity Rating

Breast

- Tanner Stage 1. Prepubertal (no glandular tissue palpable)
- Tanner Stage 2. Breast and papilla elevated as small mound; areolar diameter increased
- Tanner Stage 3. Breast and areola enlarged, no contour separation
- Tanner Stage 4. Areola and papilla form secondary mound
- Tanner Stage 5. Mature; nipple projects, areola part of general breast contour.

For penis and testes:

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

Marshall WA, Tanner JM (1970). "Variations in the pattern of pubertal changes in boys". Arch. Dis. Child. 45 (239): 13–23