Commission on Human Medicines report on proposed permanent order to restrict the sale and supply of gonadotrophin-releasing hormone agonists in children and young people under 18 years of age for the purpose of puberty suppression in gender incongruence and/or gender dysphoria

Issue

The Secretary of State for Health and Social Care and the Minister of Health for Northern Ireland are considering proposals to introduce a permanent order restricting the sale and supply of gonadotropin-releasing hormones (GnRH) agonists in children and young people under 18 years for the purpose of puberty suppression in respect of gender dysphoria, gender incongruence, or a combination of both, via restrictions to UK private and European Economic Area (EEA) prescriptions. Under section 62(3) of the Medicines Act 1968, there is a requirement to consult with an expert group on any such proposal.

The Secretary of State for Health and Social Care on behalf of both ministers has requested the Commission on Human Medicines (CHM) provides advice, and this note provides the view of CHM on the proposal.

Recommendations

CHM recommendations in respect of the order

Recommendation 1 The current prescribing and care pathway for GnRH agonists for gender incongruence and/or gender dysphoria presents an unacceptable safety risk for children and young people under 18 years without significant additional safeguards, including those detailed in the 2 recommendations below. The current restrictions that are set out in the temporary prohibition order should continue indefinitely for prescribers registered outside the UK.

Recommendation 2 For UK private prescribers, the current restrictions that are in the temporary prohibition order should continue and there should be a review of the order in April 2027 and, if required, at a later appropriate date, but no later than the end of the puberty suppressing hormone trial. When reviewing the order, the Secretary of State for Health and Social Care and the Minister of Health for Northern Ireland should assess whether and how the evidence and safety environment have evolved, including whether the additional safeguards set out in recommendation 3 have been put in place. The purpose of the assessment should be to consider whether at that point GnRH agonists could be considered to have a safety profile that would enable them to be prescribed off label by competent clinicians working to common minimum care standards within an appropriate governance and multidisciplinary framework in the UK.

Recommendation 3 The additional safeguards which should be put in place to facilitate safe UK prescribing of GnRH agonists for gender incongruence and/or gender dysphoria outside the puberty suppressing hormone trial include:

a. prescribers should complete a risk acknowledgment form with the patient and/or parents or carers when prescribing GnRH agonists for puberty suppression in children and young people under 18 years of age. This form should be identical across the UK's 4 nations. CHM recommends that the Secretary of State for Health and Social Care and the Minister of Health for Northern Ireland should ask prescribers to do this and should write to their counterparts in Wales and Scotland asking them to do the same
b. it is important that a set of consistently audited common care standards for specialist gender services is developed for children and young people under 18 years of age, adopted and implemented for use in all parts of the UK by April 2027, in both public and private sectors, and adherence regularly assessed by the healthcare regulators. CHM recommends that the Secretary of State for Health and Social Care and the Minister of Health for Northern Ireland collaborate with their counterparts in Wales and Scotland on how to do this
c. there is an absence of long term safety and efficacy data for this population. The Department of Health and Social Care (DHSC) should facilitate the development of a funded strategy for capturing and reporting long term safety and efficacy data across all UK gender specialist services. All children and young people who were prescribed GnRH agonists at the time of the temporary ban coming into place should be given the opportunity to participate in and co-design the studies

CHM recommendations in respect of wider **implementation considerations**

Recommendation 4 Mental health and wellbeing support for all children and young people with gender incongruence and/or gender dysphoria should be expedited and enhanced, irrespective of whether the prohibition order is made permanent or not.

Recommendation 5 We have noted the reports that an unknown number of children and young people have been unable to find an NHS prescriber willing to manage prescribing of their GnRH agonists, where the prescribing had previously been by an EEA prescriber. Through the planned communication strategy (see recommendation 8), such young people should be invited to present to the NHS, through whichever route, and the NHS should ensure that they receive appropriate rapid specialist assessment of their needs, and access to other support as required. Where a decision is made to continue regularly prescribed GnRH agonists in these legacy individuals, this should be undertaken by specialist gender services.

Recommendation 6 Those children and young people identified within recommendation 5 represent a vulnerable at-risk population. There should be an accelerated mental health service triage made available for all those children and young people aged under 18 who have experienced withdrawal of GnRH agonist treatment for puberty suppression as a direct result of the prohibition order.

Recommendation 7 The planned puberty suppressing hormone trial will recruit children and young people under 18 years who have not had previous exposure to GnRH agonists. A clear exit strategy needs to be put into place for continuation of GnRH agonists when exiting the trial if this is the pathway agreed with the patient

and/or parents or carers. This should be accompanied by data collection on the efficacy and safety of the GnRH agonists.

Recommendation 8 An ongoing co-produced patient and/or parents or carers, and GP communication strategy should be prepared by DHSC working in collaboration with the 4 UK health services. This should include a plan detailing the timetable for enacting all the accepted CHM recommendations. The importance of further research in this area to understand the long term efficacy and safety of the GnRH agonists should also be included in the communications plan.

Report

1. The evidence underpinning this report was evaluated and the final report text agreed by members of CHM who are listed in appendix 3.
2. The process was led by Professor Steve Cunningham, MBChB PhD FRCPCH FRCP (Vice-Chair), Professor of Paediatric Respiratory Medicine, University of Edinburgh and Honorary Consultant, Royal Hospital for Children and Young People, NHS Lothian, Edinburgh.

Background

3. CHM is an advisory non-departmental public body, who advise ministers on the safety, efficacy and quality of medicinal products. Formulations licensed for other GnRH agonist indications can be considered to be of appropriate quality. CHM cannot comment on products which are accessed via unregulated services on the internet, where there may be a risk of counterfeit products. As such, this advice is focused on the safety and efficacy implications of the proposal, which the Secretary of State for Health and Social Care and Minister of Health are required to take into consideration before making a permanent order.
4. In developing this report, CHM has considered all available evidence, including but not limited to:
    - the written responses to the targeted consultation
    - 9 representation meetings with those who were consulted and wished to share their feedback directly with CHM:
        a. Clinical Advisory Network on Sex and Gender
        b. British Association of Gender Identity Specialists
        c. Genspect
        d. LGBT Foundation
        e. Mermaids
        f. Stonewall
        g. TransActual
        h. a transgender medicine academic, Glasgow University
        i. TransLucent
    - meetings with Dr Baroness Hilary Cass (author of the Cass report), Professor Jane Hewitt (lead for Cass report systematic reviews), NHS England (Professor James Palmer and Dr Jeremy Glyde), Professor Emily Simonoff (chief investigator of the planned puberty suppressing hormone study), Professor Tim Cheetham and Professor Indi Banerjee (consultant paediatric endocrinologists)
    - research evidence as identified through online searches, consultation or representation, and systematic reviews
    - safety data from the UK Yellow Card and European Medicines Agency or US Food and Drug Administration (FDA) sources

5. CHM has been asked to advise on 4 specific points related to the proposal:

a. the safety considerations that should be made when prescribing to those under 18 years
b. the safety considerations that should be made if there is an interruption to supply of GnRH agonists for puberty suppression in under 18 years for those already on a course of treatment
c. any gaps CHM can identify in support for those currently receiving GnRH agonists for puberty suppression, or those who may have had treatment withdrawn or removed as an option for their care who may have been expecting it
d. any other factors CHM thinks the Secretary of State for Health and Social Care and Minister of Health should consider when making a decision on making permanent the existing order

6. In providing this advice, CHM was not asked to provide a perspective on the Cass review or the indication of GnRH agonists for puberty suppression (that is, whether or not they should be used to achieve puberty suppression).
7. In preparing this advice, CHM has made consideration in relation to off-label prescribing for paediatric practice in the UK, and where possible to data that could support licensing of the indication for the use of GnRH agonists for puberty suppression in children and young people with gender incongruence and/or gender dysphoria.
8. As a range of medicines can act to impede pubertal development, we refer to the medicines under the order as GnRH agonists for pubertal suppression, rather than the colloquial term ‘puberty blockers’.
9. Due to the process and timelines required to deliver this requested advice, CHM has not attempted to provide a systematic approach to evidence assessment. This has been done by others, and we have taken their work into consideration.
10. CHM provides advice for each of the 4 specific points requested and leads each section with summary statements.

Point 1

The safety considerations that should be made when prescribing GnRH agonists for puberty suppression to those under 18 years of age

11. The summary statements are as follows:

- from a medicine safety perspective, GnRH agonists could be prescribed off label by competent clinicians working to common minimum care standards for the indication of gender incongruence and/or gender dysphoria acting within the provisions of recommendation 3
- CHM identified no data that from a medicine safety perspective would preclude appropriately trained and resourced clinicians from prescribing

GnRH agonists to adolescents acting within the provisions of recommendation 3

- CHM identified specific safety considerations that would require additional multidisciplinary specialist competence when prescribing GnRH agonists in adolescence, including impacts on gender and sexuality maturation, bone health and fertility
- CHM noted the absence of long term safety and efficacy data for this population. A funded strategy and process to capture and report long term safety and efficacy data across all UK gender specialist services should be made
- CHM observed evidence of information and healthcare provided to children and young people by private practitioners that appeared unsafe from a prescribing medicine safety perspective and would likely not be considered to have fulfilled Gillick competence, safe prescribing practice, or be consistent with General Medical Council (GMC) guidance

General safety of GnRH agonists

12. CHM has reviewed the safety data of GnRH agonists for licensed indications (including precocious puberty, prostate cancer, endometriosis, and so on) and finds this acceptable for these indications. This would not therefore by itself usually preclude off label use in children and young people (that is, for an off-label indication) within a regulated environment.

Use of medicines off label (that is, outside the licensed indication) in children and young people

13. It is common practice to prescribe medicines off label in paediatric practice in the UK (under 18 years of age). This is a result of too few medicines having licensed indications for the range of conditions experienced by children and young people. Off-label prescribing is carried out in line with GMC advice, which specifically identifies and provides examples of the need to consider off-label prescribing in children (reference 1). Doctors must take a (named) individual responsibility for prescribing and provide sufficient information to patients (parents and/or carers) to allow them to make an informed decision. Doctors must have the capability and capacity to ensure Gillick competence is assessed and met when including children and young people in the decision-making process.
14. The evidence of safety and efficacy required by doctors to prescribe off label is not the same as that required by regulators to license a medicine for that indication. It is uncommon for off-label indications in children and young people to have randomised trial evidence to support their use.
15. The use of GnRH agonists to suppress puberty in children and young people with gender dysphoria is an off-label indication. Extrapolation of safety data from younger age licensed indications (precocious puberty) and use in older age

licensed indications (endometriosis, cancer [prostate, breast] and so on) would not usually preclude off label use to an adolescent age range (10 to 19 years).

16. The reasons for the dramatic increase in the use of GnRH agonists to suppress puberty over the past 10 to 15 years remains unexplained. CHM found no evidence that previous populations in this age range identified as transgender in the volume currently doing so or that similar volumes expressed regret at not receiving GnRH agonists for the suppression of puberty. Of those receiving GnRH agonists for pubertal suppression, the majority do not regret their use when asked 6 to 10 years later (reference 2). Some suggest this data supports the use in this population. Others consider this a self-fulfilling prophecy (reference 3). One in 18 do regret the decision and may have lifelong impact from GnRH agonist use. There are valid concerns to be addressed that social constructs are driving behaviours for some transgender youth where children and young people and parents or carers feel compelled to seek pubertal suppression.

17. One postulate reported to CHM is that a significant proportion of those who enter puberty suppression are homosexual by nature and given time would relate more comfortably with their sexuality without the need for a change in gender by puberty suppression with the associated safety risks (reference 3).

18. A common theme from transgender support organisations within the consultation and in their representations was that current safety data should be considered sufficient to allow off-label prescribing. CHM found this was only partially supported as there are important additional safety considerations in this population that need to be addressed, including a capacity to deliver further research.

Reported safety data

19. Yellow Card safety reporting data (up to 14 October 2024) in children and young people using GnRH agonists contained 2 reports associated with use for gender dysphoria, with adverse effects consistent with current safety data. An additional 3 safety reports were identified from a published paper in relation to fertility in 3 children and young people using GnRH agonists assessed prior to starting cross -sex hormones: one patient was azoospermic and 2 had abnormal morphology and motility of sperm. EU periodic safety updates and FDA warnings identified a new safety signal for GnRH agonists in children in 2022. In 6 children (5 precocious puberty, one transgender for puberty suppression), the use of GnRH agonists was associated with the development of pseudotumour cerebri (idiopathic intracranial hypertension). Recent data suggest this signal is rare and may possibly be consistent with background rates (reference 4); however, clinicians are now advised to undertake periodic ophthalmologic examinations for children and young people on GnRH agonist therapy. This new safety signal highlights the need for ongoing safety assessment and reporting for GnRH agonists in this indication (FDA warning, July 2022 - reference 5).

Specific safety considerations for use of GnRH agonists to suppress puberty

20. In its licensed indication, GnRH agonists are used to suppress puberty in children and young people who have a disease causing them to enter puberty too early (precocious puberty). In children and young people with gender incongruence and/or gender dysphoria, GnRH agonists are used to inhibit a normal physiological process and its timing.

21. Safety is context dependent. The people in whom safety has been assessed to date within licensed indications are different (age and so on) from children and young people in the adolescent age range. Within the adolescent population age range to which this indication applies, additional safety concerns become considerations, particularly in relation to the age period encompassing puberty - that is, for the indication of puberty suppression in children and young people with gender incongruence and/or gender dysphoria. These include impacts related to maturational processes during puberty that may be delayed or disrupted by therapeutic puberty prevention with GnRH agonists.

Important safety considerations from toxicology studies

22. Animal models are used in medicine development to explore potential human risks. These risks may or may not be observed with medicines in clinical use.

23. GnRH agonists provided as medicines can cross from the blood to the brain, and thus long term GnRH agonist treatment may influence brain function and have cognitive and behavioural effects. In animal models studied in a developmental period relevant to puberty, GnRH agonists reduced spatial memory, increased anxiety and depressive behaviours in mice, and had an impact on nerve activity in an area of the brain called the hippocampus which is involved in stress, depression and cognition: GnRH agonists decreased reproductive organ weight with potential effects on reproduction. It is not known whether these animal observations may have corresponding clinical relevance in children and young people.

24. The risk of cancer development with long term use of GnRH agonists is theoretically possible but has limited reporting in people exposed (a full toxicology report with references is provided in appendix 1).

Clinical impact of GnRH agonists to suppress puberty in children and young people

25. The safety and clinical effects of GnRH agonists when used to suppress puberty within the pubertal age range in children and young people have been evaluated in 4 systematic reviews (references 8, 9 and 10) (Miroshnychenko 2024, in press), which are summarised in appendix 2. Two further reviews were identified but were not included in the summary as they overlapped with other reviews (references 11 and 12). All reviews agree that the data is poor or moderate quality and with a high risk of bias that may influence the results, providing insufficient confidence to draw conclusions.

26. It is widely accepted that there are detrimental impacts on bone mineralisation. The degree of impact and ability to recover post puberty suppression has a significant lack of data from large high-quality studies. CHM heard from experts that diet, exercise and vitamin use may be able to support bone health in individuals at risk of loss of bone mineral density. CHM found no data investigating the effect of these measures to offset bone mineralisation impacts when GnRH agonists are used during puberty.

27. Within systematic review data, mental health was generally stable or improved. These findings highlight the importance of the Endocrine Society guidelines recommendation that GnRH agonists should only be prescribed in individuals with stable mental health, and the importance of appropriate patient assessment and selection when using GnRH agonists to suppress puberty (reference 13). A report analysing UK -based subjects that was not included in systematic reviews identified a deterioration in mental health measures in 15% to 34% of those receiving GnRH agonists (reference 14). More data is required on mental health outcomes to inform the use of GnRH agonists in children and young people with gender incongruence and/or gender dysphoria. Other measures (growth, blood markers and so on) were variable across reviews. With the caveats as explained demonstrating widespread evidence gaps, overall the data does not identify significant evidence of short term harm.

28. CHM additionally identified specific and important missing data with regard to safety, including impacts on fertility and long term safety and outcomes, including neurodevelopmental, and gender and sexuality (reference 3) maturation (including cognition).

29. During representation, CHM was provided with valid hypotheses that cognition may be irreversibly impacted by the use of GnRH agonists in the adolescent age range (references 6 and 7). However, further evidence is required to explore this important human development and should be included in the future research agenda.

Specific safety consideration with regard to loss of fertility

30. The impact of GnRH agonists on future fertility is an important safety consideration when used in the pubertal age range. GnRH agonists applied pre or early puberty act to prevent the development of reproductive function in their birth registered sex. For many children and young people, the short term aim and gain of gender transition may override longer term consideration of fertility (reference 15), especially if that includes a delay to access of GnRH agonists or additional cost (CHM understands that some private providers charge for NHS fertility referrals).

31. Research in cis-adolescent boys with cystic fibrosis (who are infertile through sexual intercourse) demonstrate the complexity of these discussions at this age and the need to provide a period for reflection (reference 16). In Tanner stage 2 (approximate age 11 to 12 years, frequently identified as optimal time to suppress puberty), only 20% of cis-boys will have developed spermatogenesis,

increasing to 100% by Tanner stage 3 or 4 (approximate age 13 to 17), though sperm may be more mature in even later stages.

32. For transgender men, prepubertal cryopreservation of ovarian tissue is considered experimental, with oocyte preservation possible once perimenarchal (reference 15).

33. CHM could not identify any long term safety data on the impact of GnRH agonists on fertility in people with gender dysphoria. Given the complexities, probable finality and experimental nature of these considerations, Gillick competence would be more challenging to achieve than in many other therapeutic areas in paediatric practice. Provision of adequate consent in relation to fertility has been an identified issue raised by GMC with private practitioners providing gender services.

Age at which GnRH agonists are provided for puberty suppression

34. CHM has received representation advising that careful consideration should be given to the age or stage of puberty at which GnRH agonists might be prescribed, as this determines impacts on the development of secondary sexual characteristics.

35. Prescribing at an early stage of puberty - for example, the prevention of, or reduction in, breast development in young people assigned as female at birth - could reduce the requirement for chest surgery in adulthood.

36. In young people assigned as male at birth, CHM heard that early prescription of puberty blockers can prevent normal penis development. An underdeveloped penis can make it difficult to surgically create a vagina in adulthood, and young people who subsequently decide not to transition will likely have an underdeveloped penis throughout adulthood.

37. CHM was provided with testament during the representation and in published evidence that the use of GnRH agonists in children and young people can reduce or eliminate the need for future surgical procedures (and associated risks) (reference 15). Transgender adults who have not undergone puberty suppression can undergo:

- transwomen: facial feminisation surgery, chondrolaryngoplasty and laser hair removal

- transmen: mastectomy and liposuction (reference 12)

There is a surprisingly low volume and low quality of data on the ability of GnRH agonists to suppress secondary sexual characteristics that may later require a surgical procedure (appendix 2).

38. CHM heard representation that the safety of GnRH agonists to suppress or prevent the development of secondary sexual characteristics should be taken in

context with the safety of future surgical procedures to reverse secondary sexual characteristics in those who have not used GnRH agonists for puberty suppression.

39. CHM acknowledges this testament, but considers more data is required to understand the patient population who should be provided with GnRH agonists for puberty suppression. This is particularly important because it informs risk reduction for the proportion of gender dysphoric children and young people who, at any future timepoint, would not wish to progress to gender transition in the long term.

40. CHM heard representation that children and young people may exhibit flexible gender and sexuality during early adolescence. The impact of GnRH agonists to suppress puberty on this flexibility and final adult gender and sexuality has very limited evidence and is an important safety consideration that requires exploration.

Safe consent and prescribing of GnRH agonists for pubertal suppression

41. CHM was provided with examples of access to GnRH agonists for puberty suppression via alternative routes and jurisdictions, including the USA and Ireland. Access can be by supply to the UK or by children and young people travelling overseas for treatment. A UK based website offering private transgender care for children and young people in the UK provides information on accessing medicines to suppress puberty from non-UK organisations.

42. CHM heard representation from support organisations that parents and children and young people acknowledge the standard of healthcare provided by some private healthcare providers may not be consistent with a UK NHS level; however, parents and children and young people feel compelled by their perceived need to seek alternative routes.

43. CHM reviewed examples of private healthcare advertising, prescribing and communication with regard to consultation and prescription of GnRH agonists to transgender children and young people for the purposes of puberty suppression. CHM considers that these examples demonstrate poor medical and prescribing practice that would not be considered to have fulfilled Gillick competence, safe prescribing practice or GMC guidance.

44. CHM considered that should the temporary order not be made permanent, then off-label prescribing of GnRH agonists within private healthcare settings would require additional safety and minimum care standards to be put in place.

Point 2

The safety considerations that should be made if there is an interruption to supply of GnRH agonists for puberty suppression in under 18 years of age for those already on a course of treatment

45. The summary statements are as follows:

- an unanticipated interruption or stop to GnRH will see children and young people proceed with puberty aligned to their birth registered gender. For those who had already socially transitioned, CHM heard that this was an acutely traumatic experience for most
- it is not possible to calculate the total number at risk of any interruption to supply, but it may be reasonably estimated to be several hundred children and young people
- children and young people who have lost access to GnRH agonists because of the temporary ban would likely experience significant mental health strain. Additional systems should be put in place to enable patients receiving prescribed GnRH agonists at the time of the temporary ban coming into place to identify themselves and be prioritised for review by mental health services
- concern is raised by CHM that waiting times for mental health services, already under considerable clinical pressure, will add potential safety risk to children and young people on the waiting list for gender services

Number of children and young people impacted by the temporary order

46. CHM heard from NHS England that on 1 April 2024, a cohort of 206 children and young people had their care transferred from the Tavistock to endocrine clinics at University College London Hospitals NHS Foundation Trust (UCLH) and Leeds Teaching Hospital. Of the 206, 55 were waiting for a first appointment at the gender clinic or waiting for a consent appointment in advance of confirmation of prescribing of GnRH agonists. Data was not provided on how many of the 55 were waiting for a GnRH agonist consent appointment. The remaining 151 were either on GnRH agonists for puberty suppression or gender affirming hormones. Data on the proportion of the 151 receiving GnRH agonists was not provided.
47. CHM sought data from DHSC on prescribing and/or dispensing of GnRH agonists within the age range that would be consistent with use for puberty suppression. NHS England community dispensing data was analysed in the period September 2023 to August 2024 - that is, most data is prior to the first emergency temporary order coming into force.

48. The DHSC pharmacy team estimate that around 500 individual 10 to 17 year olds received GnRH agonists during this period. It is not known whether prescriptions were for licensed indications or off-label use; however, restricting to this age range should have largely filtered out those receiving medicines for precocious puberty. GnRH agonists do not have significant off-label use in this population apart from gender dysphoria and so the 500 most likely represents a close estimate of the population receiving these medicines through an NHS community prescription in England. CHM does not have corresponding dispensing data for Scotland, Wales or Northern Ireland.

49. No data is available on the number of children and young people who have been prescribed GnRH agonists through private prescribers in the UK or EEA. It is not currently possible for DHSC to provide data on dispensing of private prescriptions within the UK – for example, those issued through GenderGP. The assumption has been that much of the prescribing of GnRH agonists has been by private prescription.

50. Private prescription data is not available in the UK, which includes children and young people who had a private UK or EEA prescription of GnRH agonists for puberty suppression at the time of the temporary ban coming into place (3 June 2024). CHM was therefore unable to provide context as to what proportion of those individuals receiving GnRH agonists whose care was transferred from the Tavistock clinic represent the total number of children and young people receiving GnRH agonists for puberty suppression at the time of the temporary ban coming into place. While it is not possible to calculate the total number at risk of any interruption to supply, it may be reasonably estimated to be several hundred children and young people.

51. In those children and young people who had received GnRH agonists to suppress their puberty, but could no longer gain access, puberty will progress aligned to the birth registered gender. This may occur both as a result of the temporary ban (and any permanent order) and also where supply of a GnRH agonist is ceased by a private prescriber when a family can no longer afford private access.

52. The primary immediate safety concern where GnRH agonists have an unanticipated interruption or are stopped is on the mental health of those affected. CHM received testament from consultation responses and representations of significant mental anguish in parents and children and young people associated with the temporary ban. The LGBT Foundation reported a 14% increase in calls to their support service in relation to transition in the 6 months since the temporary ban was put in place. NHS England has made available a letter for parents in England (31 May 2024), explaining the temporary legislation and with advice to contact their GP or allocated mental health service for any associated distress.

53. In July 2024, there were 6,033 individuals on the national waiting list for NHS children and young people gender services.

54. CHM was provided with information from NHS England on current waiting times for mental health services in England for children and young people on the gender services waiting list. Invitations were issued to 5,275 individuals in April and May 2024; 37% (1,951) responded, of which:

- 114 (6%) were either seen or did not attend an appointment (CHM was informed that most of these attended)
- 875 (45%) have been offered an appointment to attend929 (48%) have indicated they would like an appointment and are waiting to be provided with an appointment

In September 2024, a further invitation was sent to those joining the waiting list since April and May 2024, of which 29% have responded.

55. NHS England provided an impact assessment reporting that 72% of children and young people are seen within one year of referral to mental health services, and that this is significantly shorter than the current more than 3-year median waiting time for children and young people gender services. The impact of these additional gender related referrals on waiting times in children and young people mental health service was not known.

56. CHM considered that children and young people who have lost access to GnRH agonists because of the temporary ban would likely experience significant mental health strain. Additional systems should be put in place to enable these patients to identify themselves and be prioritised for review by mental health services.

57. While CHM acknowledges the work performed to provide mental health appointments for children and young people on waiting list for gender services, CHM noted that the significant waiting times across both mental health and gender services cause a significant safety concern in this population. CHM was informed by many within the consultation and representation of the risk to mental health from children and young people on the waiting list for gender services. Concern is raised by CHM that waiting times for mental health services, already under considerable clinical pressure, will add potential safety risk to children and young people on the waiting list for gender services.

58. Another safety concern where there is acute unanticipated withdrawal is that the children and young people have been exposed to the risks of GnRH agonists without realising the benefits. Given NHS England clinical policy on prescribing GnRH agonists together with the described safety concerns, any children and young people regularly prescribed GnRH agonists for puberty suppression should be invited to contribute data to the safety studies outlined in this document.

Point 3

Any gaps the CHM can identify in support for those currently receiving GnRH agonists for puberty suppression, those who may have had treatment withdrawn, or removed as an option for their care who may have been expecting it

59. The summary statements are as follows:

- as outlined in point 2 (starting from paragraph 46), CHM was unable to determine the precise number of individuals who may have had their treatment withdrawn

- CHM considered it incongruous that children and young people can now only access GnRH through a specialist gender service, yet a GP is expected to act as the specialist gender service to those previously prescribed by an EEA private prescriber. NHS England has no data on how many children and young people have presented to GPs and requested continuation of care, and in how many this has not been agreed (that is, a withdrawal of GnRH agonists). CHM heard that the impact on the mental health of medicines withdrawal and pubertal progression, particularly in those who have socially transitioned, will likely be significant

- CHM considered that GPs should be able to provide direct referral to NHS specialist gender services for individuals who have evidence of prescribed use of GnRH agonists prior to the temporary ban coming into place. These individuals should be prioritised for mental health service access and could have ongoing needs assessed through specialist gender service rapid triage

- CHM considered that GPs should not be placed in the position of solely having to provide specialist gender services, unless they have expertise and experience in the area - that is, it would be wholly unacceptable that a GP be expected to take on continued care should a private prescriber no longer support the children and young people

- CHM noted that NHS England currently has no plans to make GnRH agonists available within NHS services outside the puberty suppressing hormone study until the study results are available (estimated as 2031). CHM identified a communication gap and considered that communication to children and young people and parents or carers setting out the work and timetable to resolve the issues that require a ban (if introduced) could help reduce mistrust, potentially reduce reliance on black or grey market medicines and enhance trial recruitment

Gaps for children and young people currently receiving GnRH agonists for puberty suppression

60. Consideration of impacts for those currently receiving GnRH agonists are addressed in point 1 (starting from paragraph 12) above.

Gaps for children and young people having GnRH agonists for puberty suppression withdrawn

61. CHM heard of concerns expressed through consultation and representation of the impact of the temporary and prospective permanent ban on children and young people who may have had treatment withdrawn or removed as an option. The groups affected included those who accessed GnRH agonists privately through an EEA prescriber prior to the temporary ban where a UK GP had declined to continue prescribing, and those who have come to an age where

puberty suppression would be a preferred choice to help align gender identity but who can no longer gain legal access.

62. CHM could not be provided with data on the number of individuals who had accessed GnRH agonists through a private EEA prescriber. Individuals in these circumstances are directed by NHS England information to discuss continued prescribing with their GP.

63. In a letter to GPs in England (22 August 2024), NHS England informed GPs that a child or young person could continue with a treatment course where they can demonstrate a UK or EEA prescription for GnRH agonists issued in the 6 months prior to 3 June 2024.

64. The Royal College of General Practitioners, in their submission, identify the unease which GPs would experience providing specialist gender care (through continued prescribing and monitoring of GnRH agonists where NHS England stipulates the GP has determined the need appropriate). In the consultation, we heard examples where GPs had declined to take on this responsibility, though we were not provided with evidence of the number of individuals impacted. CHM considered this group of individuals a safety risk, as it may be reasonably anticipated that withdrawal of a treatment (and late progression through puberty) would place greater mental health risk to these children and young people. CHM heard of a small number of individuals who had socially transitioned, where school withdrawal occurred where the child or young person entered puberty opposite to the gender they were identified with and so were ‘outed’ to those unaware of their change in gender.

65. Aligned with the perspective of the BMA in their consultation submission, CHM considered it incongruous that children and young people can now only access GnRH agonists through a specialist gender service, yet in the absence of a viable referral pathway into NHS secondary care beyond the phase of the application of the initial advice not to end treatment abruptly, a GP has been expected to act as the specialist gender service to those previously prescribed by an EEA private prescriber. CHM considered that from a safety perspective such individuals should be provided with access to specialist gender services to continue a course of treatment where appropriate, with referral by GPs when approached with evidence of EEA prescription prior to the temporary order being put in place.

Gaps for children and young people having GnRH agonists for puberty suppression made unavailable when they may have been expecting access

66. CHM also heard from consultation and representation that individuals who may have had GnRH agonists for puberty suppression removed as an option for care report feeling a great sense of marginalisation and being targeted by the current proposals. These children and young people consider they will ‘miss’ their opportunity. Enhanced appraisal and access for these individuals to mental health services while on the gender waiting list is warranted.

Safety impact of stopping or restricting access to GnRH agonists to suppress puberty, specifically risk of suicide

67. Concern about the mental health impact, in particular suicide risk, of a permanent ban on GnRH agonists for puberty suppression was raised frequently in representations and written consultation submissions. There was a strong belief expressed that GnRH agonists can reduce suicide risk (with online private suppliers identifying the medicines as 'life saving'). It is well documented that mental health issues in children and young people with gender incongruence and/or gender dysphoria, including suicidal ideation and deliberate self-harm, is higher than the background population at this age.

68. Data was available on the risk of suicide in children and young people with gender incongruence and/or gender dysphoria within 2 systematic reviews (references 17 and 18), the Appleby report of risk of suicide within the Tavistock clinic (reference 19) and 2024 papers from Finland and the USA (references 20 and 21).

69. The majority of data contributing to the knowledge base is of low quality with high risk of bias. The use of GnRH agonists to suppress puberty have no demonstrable adverse effects on mental health. Systematic reviews identify a possible reduction, but the data is at high risk of bias and data from Finland concludes that gender dysphoria does not appear to be predictive of suicide when psychiatric history is accounted for.

70. The question of the impact of the withdrawal of access of GnRH agonists to suppress puberty on risk of suicide is more complex. One report from the USA highlights the impact of "state level anti-transgender laws" and concludes that risk of suicide attempt was increased in the range 7% to 72% (reference 20). The manuscript reports that state laws in the USA encompass a range of issues including access to gender-affirming healthcare, but also impact on social transition including access to bathrooms or participating in sports or school activities aligned with gender identity.

71. CHM was therefore unable to conclude whether withdrawal or inability to access GnRH agonists to suppress puberty would be associated with an increased risk of suicide, though it seems probable that there will be a risk to wider mental health that should be addressed.

The need for supportive communication

72. During consultation and representation, criticism was made of communications and distribution strategy targeted to children and young people, and families and GPs. It was felt that the current communication lacks empathy and sets out in (problematic) clear language to parents or carers, GPs and pharmacists how the temporary order impacts them and the penalties for non-compliance.

73. Responses to the consultation and those provided by representation gave varied perspectives (as may be expected), but CHM observed a general view from a number of patient and professional organisations that a permanent ban may be counterproductive - that is, from their perspective, the aims of the Cass report could be better achieved without a permanent ban. CHM had varied views on this but agreed that communication could be more supportive to children and

young people and their parents or carers were the decision made to make the order permanent.

74. A communication strategy that rationally and logically explained the need for a permanent ban, how it may impact them as individuals but also as future trans children and young people, and a timetable to resolve these issues and a review date to provide more information will be important. If people can understand the strategy and timescale, it may help to:
    - reduce distrust in healthcare services
    - enhance trust in research studies to be part of any solution
    - potentially limit access to non-GnRH agonist puberty suppressors
    - potentially limit access to the grey or black healthcare market for pubertal suppression

.

Point 4

Any other factors CHM thinks the Secretary of State and Minister for Health should consider when making a decision on making permanent the existing order

75. The summary statements are as follows:

- CHM considers the planned puberty suppressing hormone study will provide important safety and efficacy data that will enable a better-informed discussion for off-label prescribing, but it is unlikely to be sufficient on its own to lead to a licensed indication
- CHM heard that NHS England does not plan to provide NHS access to GnRH agonists for puberty suppression until the results of the National Institute for Health and Care Research (NIHR) puberty suppressing hormone study are available (estimated 2031). As currently planned, the study will require, from a safety perspective, an ability to continue GnRH agonists for puberty suppression as children and young people exit the trial (as children and young people may not have reached 16 years of age and therefore be eligible for gender affirming hormones). Any gap in planning should be addressed rapidly as it is likely to reduce children's and young people's confidence in the study and may cause delays to final approvals from an ethical perspective and therefore in study start up
- CHM considered a permanent order risks children and young people seeking GnRH agonists through non-UK or EEA, possibly counterfeit, routes with clear risks for the quality and safety of the products from unregulated sources
- CHM was provided with data on alternative medicines that may act to impede puberty, with evidence suggesting these routes are already active and being used

- CHM is concerned that the criminalisation of access to GnRH agonists will drive health and social care avoidance by children and young people, with a clear safety risk to health

Availability of GnRH agonists for puberty suppression in the UK going forward from a decision to make permanent the existing order within the legal framework

76. CHM met with Professor Emily Simonoff, Professor of Child and Adolescent Psychiatry, King's College, London. Professor Simonoff is chief investigator of a puberty suppressing hormone study being considered for funding by NIHR. The aim of the trial is to provide more research data regarding the use of GnRH agonists to suppress puberty in children and young people (the Pathways Trial). As with all studies such as this, there will be a need for both Medicines and Healthcare products Regulatory Agency (MHRA) and ethical approvals. The study is currently planned as an open label randomised trial, where participants will remain in the trial for 24 months, with an anticipated report publication date of 2031. There are plans to obtain longer term safety data in the trial population beyond 24 months subject to consent and additional funding.

77. CHM heard from NHS England that GnRH agonists for pubertal suppression will only be prescribed within the trial and that future availability of GnRH agonists within an NHS service would not be considered until the results of the clinical trial are available.

78. CHM heard from DHSC that the permanent order can permit prescribing within the NHS, but that it is the clinical policy that has been instituted by NHS England that will prevent access to the medicines for gender incongruence and/or gender dysphoria. The other UK nations are currently following NHS England policy.

79. CHM is not requested to advise on the clinical trial but does consider the trial in the context of safety with regard to the impact of the permanent order. The trial as currently configured and with the restriction by NHS England on the provision of GnRH agonists outside the clinical trial setting raises a safety issue for participants. People prescribed GnRH agonists, in a majority of cases (92% currently) continue on to gender affirming hormones at the end of their GnRH agonist treatment. NHS England is to make gender affirming hormones available to those eligible around their 16th birthday. Therefore, individuals entering the trial before their 14th birthday would, as currently stands, have GnRH agonists removed from their care and enter puberty aligned to their birth registered sex. These children and young people would have been exposed to the safety risks of the intervention (GnRH agonists) without a corresponding benefit (suppression of puberty until potential transition to gender affirming hormones).

80. An exit strategy should therefore be in place for children completing the trial to ensure continued (off-label) prescribing of GnRH agonists by gender specialist service clinical teams where this is an agreed pathway with the patient and/or parents or carers. It was noted that were this in place, then clinicians would use their professional competence to prescribe GnRH agonists off label to some children outside the trial, but not to others.

Risk of use of GnRH agonists by alternate routes, use of alternative puberty suppressing medicines

81. CHM considers medicines for quality, safety and efficacy. In regulated services, the formulations being used have been licensed for other GnRH agonist indications and can be considered to be of appropriate quality. However, CHM cannot comment on products which are accessed via unregulated services on the internet, where there may be a risk of counterfeit products. CHM was provided with testament during consultation of an example of a counterfeit oestrogen product privately supplied for transgender healthcare.

82. The proposed legislation would make it illegal for a dispenser of medicines in the UK to sell or supply a GnRH agonist ordered on prescription for a patient under 18, if it is for puberty suppression, unless the prescriber is a UK practitioner, and the patient started a course of treatment with a GnRH agonist before the restrictions originally came into force. A number of organisations through the consultation and representations, representing both medical and patient support groups, reported a concern to CHM that individuals impacted are seeking GnRH agonists via alternative routes and jurisdictions.

83. Patient support organisations could not provide any estimate of how many children and young people are choosing or will choose alternative routes. Few patient support organisations had direct contact with children and young people with gender dysphoria. CHM met with representation from Mermaids, a charity to support trans children and young people and their families. Mermaids provided testament from a focus group of 5 transgender children and young people. Mermaids also reported to us that they provide support to 21 local groups across the UK, containing a range of 10 to 50 children and young people and parents in each. Across numerous representations, CHM was informed that due to the temporary legislation, few if any individuals would identify themselves for personal concern (acting illegally within the act) and to protect routes to access.

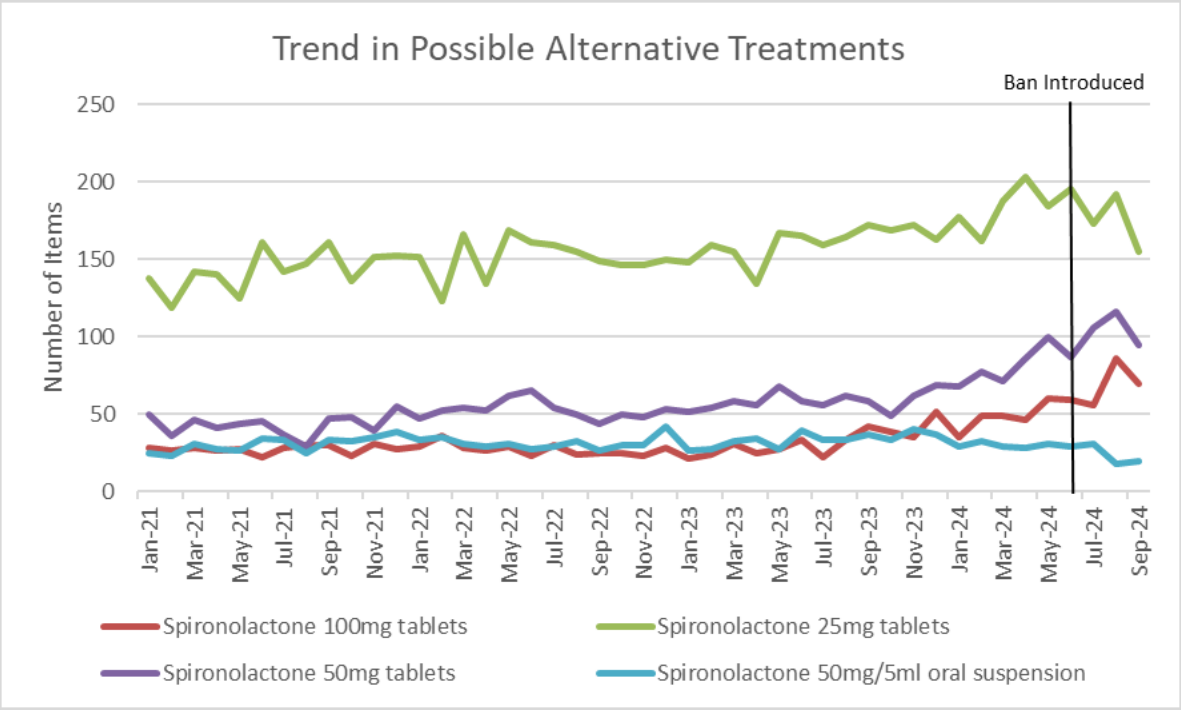
84. CHM received representation that children and young people may seek alternative therapies to GnRH agonists to suppress puberty that do not include those within the legislation. There are a range of medicines that can act to suppress puberty, with variable degrees of effectiveness. Private healthcare providers are now identifying alternatives to GnRH agonists for pubertal suppression. Due to the common usage of these medicines across a range of ages and conditions, CHM considered it would be impractical and problematical to place UK restrictions on the prescription of the products below.

85. For transgender girls, the anti-androgens spironolactone and cyproterone acetate represent an alternative therapy (recommended to be used combined within the Melbourne Children's Hospital Australian Standard of Care) (reference 22). Cyproterone has important liver side effects observed in about 10%. The anti- androgen bicalutamide, used for prostate cancer, has been reported as used in this group also.

86. For transgender boys, the anti-oestrogen SERMS (selective oestrogen receptor modifiers), which include raloxifene, clomiphene, toremifene and tamoxifen, and GnRH antagonists (ganirelix or cetrorelix), used to treat infertility, could also have a role in delaying puberty, but are not widely reported to date.

87. CHM was provided with data from DHSC detailing UK prescribing for spironolactone from January 2021 to September 2024 in children and young people aged 10 to 17 years (the data in the final 6 months is highly uncertain) for 4 forms of spironolactone (100mg, 50mg and 25mg tablets, and 50mg or 5ml solution). Figure 1 demonstrates a progressive increase in prescribing of tablet forms since January 2021. Spironolactone is prescribed for a range of paediatric conditions. A change in prescribing practice for cardiac and renal paediatric conditions seems unlikely to explain this change. CHM notes that spironolactone can also be used to treat acne, female pattern hair loss, hirsutism and polycystic ovary disease, all of which occur in adolescence. It has not been possible to determine any change in practice for these conditions within the time frame available to prepare this advice.

Figure 1: NHS spironolactone prescribing in England (January 2021 to September 2024)



Risk to children and young people from avoidance of health and social care services in those who access GnRH agonists from other jurisdictions

88. CHM received consultation responses and representation expressing concern at the criminalisation of parents, carers and potentially children and young people who access GnRH agonists for puberty suppression from alternative sources. The risk of transgender children and young people's healthcare and societal avoidance in this group seems high.

89. NHS England made clear in their letter to parents that it will be illegal to possess GnRH agonists for the purpose of puberty suppression and that a GP should consider safeguarding or child protection should they suspect use of GnRH agonists.

90. CHM received evidence on individual examples of healthcare avoidance by children and young people in this position. The GMC in their response to the consultation highlight their concern of the safety impact of the permanent order on the open dialogue between patient and doctor. The GMC example provided is where individuals may not declare medicines that are being taken (GnRH agonists, or possibly alternatives as above) to ensure medicine compatibility with any newly GP prescribed medicines.

91. CHM was also concerned that children and young people receiving GnRH agonists for puberty suppression may come to harm if they did not access healthcare for important adverse effects of treatment - for example, headache associated with benign intracranial hypertension (as detailed under point 1).

92. CHM was concerned that the impact of health and social care avoidance by even relatively few individuals poses significant concerns for the safety and wellbeing of these children and young people.

Impact of the temporary legislation on the use of GnRH agonists for licensed indications

93. CHM received representation that use of GnRH agonists for licensed indications was being impacted by the temporary legislation and this impact may be anticipated to continue with a permanent ban in place. The principal indications mentioned were for:
    - cancer treatment (prostate and breast)
    - gynaecological treatment (endometriosis and uterine fibroids)
    - obstetric use (pituitary desensitisation for in-vitro fertilisation)
    - psychiatric use (male hypersexuality with severe sexual deviation)

94. Impact information was sought by DHSC from relevant royal colleges and CHM via relevant expert advisory groups and their networks. No instances were reported of a licensed use of GnRH being impacted by the temporary legislation. CHM has no reason to consider legislation will impact licensed use of GnRH agonists.

Perspectives of clinical organisations who can present clinical perspectives and responded to the consultation

95. Those agreeing with the proposal to make the order permanent were:
    - NHS Greater Glasgow and Clyde
    - Belfast Health and Social Care Trust (adult services)

96. Those disagreeing with the proposal to make the order permanent were:

- children and young people gender service (North West), provided by Alder Hey Children's NHS Foundation Trust in partnership with Royal Manchester Children's Hospital (one of 2 first wave NHS England services)
- The Royal College of General Practitioners
- The British Medical Association
- The Royal College of Psychiatrists

Common themes across all consultation and representation responses

97. CHM would like to thank all those who provided consultation responses, and particularly those who made representation. The representation meetings were open, respectful and provided valuable perspectives and evidence.

98. There were common themes of understanding including:

    a. more resource is required to support children and young people with gender incongruence and/or dysphoria

    b. the mental health of children and young people with gender incongruence and/or dysphoria requires particular support

    c. research is required to improve knowledge of safe and effective care for children and young people with gender incongruence and/or dysphoria

    d. NHS delivered care is the preferred route for gender care in children and young people with gender incongruence and/or dysphoria

Point 5

Give a timeline for review of the permanent order and the conditions that must be satisfied

99. If the decision is to make the order permanent, CHM recommends that the permanent order is reviewed by April 2027 and, if required, at a later appropriate date, but no later than the end of the puberty suppressing hormone trial.

100. The following conditions should be satisfied for the order to either continue or be modified:

    a. there is a mechanism in place to prevent prescribers registered outside the UK from prescribing and dispensing GnRH agonists in the UK for children and young people under 18 years of age for the indication of gender incongruence and/or gender dysphoria

b. prescribers should complete a risk acknowledgment form with patients and parents or carers when prescribing GnRH agonists for puberty suppression in children and young people under 18 years of age. This form should be identical across the UK's 4 nations

c. it is important that a set of consistently audited common care standards for specialist gender services is developed for children and young people under 18 years of age, adopted and implemented for use in all parts of the UK by April 2027, in both public and private sectors, and adherence regularly assessed by the healthcare regulators

d. there is an absence of long term safety and efficacy data for this population. DHSC should facilitate the development of a funded strategy for capturing and reporting long term safety and efficacy data across all UK gender specialist services. All children and young people who were prescribed GnRH agonists at the time of the temporary ban coming into place should be given the opportunity to participate and co-design the studies

References

1. GMC. Prescribing unlicensed medicines 2024 (accessed 8 November 2024)

2. Olson KR, Raber GF and Gallagher NM. Levels of satisfaction and regret with gender-affirming medical care in adolescence. JAMA Pediatrics 2024

3. Biggs M. The Dutch protocol for juvenile transsexuals: origins and evidence. Journal of Sex and Marital Therapy 2023: volume 49(4), pages 348-68

4. Karamanis G, Frisell T, Holmberg M and others. Incidence of idiopathic intracranial hypertension in individuals with gonadotropin-releasing hormone analogue treatment for gender dysphoria in Sweden. JAMA Pediatrics 2023: volume 177(7), pages 726-7

5. FDA. Risk of pseudotumor cerebri added to labeling for gonadotropin-releasing hormone agonists (PDF, 146KB). 2022 (accessed 8 November 2024)

6. Larsen B and Luna B. Adolescence as a neurobiological critical period for the development of higher-order cognition. Neuroscience and Biobehavioral Reviews 2018: volume 94, pages 179-95

7. Goddings AL, Mills KL, Clasen LS, Giedd JN, Viner RM and Blakemore SJ. The influence of puberty on subcortical brain development. NeuroImage 2014: volume 88, pages 242-51

8. Ludvigsson JF, Adolfsson J, Hoistad M, Rydelius PA, Kristrom B and Landen M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. Acta Paediatrica 2023: volume 112(11), pages 2,279-92

9. Taylor J, Mitchell A, Hall R and others. Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: a systematic review. Archives of Disease in Childhood 2024: volume 109 (supplement 2), pages s33-s47

10. Thompson L, Sarovic D, Wilson P and others. A PRISMA systematic review of adolescent gender dysphoria literature: 3) treatment. PLOS Global Public Health 2023: volume 3(8) pages e0001478

11. Bragge P, Cong-Lem N, Delafosse V, Goldberg E, Temple-Smith M, Sanci L. Evidence check: evidence for effective interventions for children and young people with gender dysphoria - update (an evidence check rapid review brokered by the Sax Institute) 2024

12. Ramos GGF, Mengai ACS, Daltro CAT, Cutrim PT, Zlotnik E and Beck APA. Systematic review: puberty suppression with GnRH analogues in adolescents with gender incongruity. Journal of Endocrinological Investigation 2021: volume 44(6), pages 1,151-8

13. Hembree WC, Cohen-Kettenis PT, Gooren L and others. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 2017: volume 102(11), pages 3,869-903

14. McPherson S and Freedman DEP. Psychological outcomes of 12-15-year-olds with gender dysphoria receiving pubertal suppression in the UK: assessing reliable and clinically significant change. Journal of Sex and Marital Therapy 2024: volume 50(3), pages 315-25

15. Panagiotakopoulos L, Chulani V, Koyama A and others. The effect of early puberty suppression on treatment options and outcomes in transgender patients. Nature Reviews Urology 2020: volume 17(11), pages 626-36

16. Sawyer SM, Tully MA, Dovey ME and Colin AA. Reproductive health in males with cystic fibrosis: knowledge, attitudes, and experiences of patients and parents. Pediatric Pulmonology 1998: volume 25(4), pages 226-30

17. Christensen JA, Oh J, Linder K and others. Systematic review of interventions to reduce suicide risk in transgender and gender diverse youth. Child Psychiatry and Human Development 2023

18. Heathcote C, Taylor J, Hall R and others. Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: a systematic review. Archives of Disease in Childhood 2024: volume 109 (supplement 2), pages s19-s32

19. Appleby L. Review of suicides and gender dysphoria at the Tavistock and Portman NHS Foundation Trust: independent report. Department of Health and Social Care, 2024

20. Lee WY, Hobbs JN, Hobaica S, DeChants JP, Price MN and Nath R. State-level anti-transgender laws increase past-year suicide attempts among transgender and non-binary young people in the USA. Nature Human Behaviour 2024

21. Ruuska SM, Tuisku K, Holttinen T and Kaltiala R. All-cause and suicide mortalities among adolescents and young adults who contacted specialised gender

identity services in Finland in 1996-2019: a register study. BMJ Mental Health 2024: volume 27(1)

22. Telfer MM, Tollit MA, Pace CC and Pang KC. Australian standards of care and treatment guidelines for trans and gender diverse children and adolescents - version 1.3 (PDF, 1.1MB). Melbourne: The Royal Childrens Hospital, 2020

Appendix 1: toxicology of GnRH agonists in relation to use in puberty

Cognition and fertility

GnRH agonists are used therapeutically to down-regulate GnRH receptors within the pituitary gland and block reproductive axis activity. Exogenous GnRH has been shown to cross the blood brain barrier (Caraty and Skinner, 2008) and GnRH receptors are found in the hippocampus and amygdala areas of the brain. Chronic use of GnRH agonists may result in desensitisation of GnRH receptors in the pituitary gland (Ferguson and others, 1996; Armstrong and others, 2011) and suppress activity within the hypothalamic-pituitary-gonadal (HPG) axis. Thus, long term GnRH agonists treatment may also influence brain function and have cognitive and behavioural effects. A study by Hough and others (2017) investigated the risks involved in peripubertal GnRH agonists treatment in the development of spatial orientation, learning and memory in rams. While the study showed that rams improved spatial orientation and learning performance with age, the results did not support a role for GnRH agonists on these tests. GnRH agonists-treated animals did however take longer to traverse a familiar or novel maze, suggesting an effect on long term spatial memory.

Limbic brain regions involved in emotional and cognitive function express GnRH receptors and thus can be affected by GnRH agonists. In a study in 4 week old BALB/c male and female mice, chronic leuprolide exposure after the onset of puberty (20mg daily subcutaneous for 6 weeks) increased locomotion and cortisone response and altered social preference in male mice. On the other hand, leuprolide increased hyponeophagia and despair-like behaviour and increased neural activity in the dentate gyrus in female mice. Leuprolide did decrease reproductive organ weight in both male and female mice suggesting possible effects on reproduction. The agent did not impact avoidance behaviour or contextual fear discrimination learning in female or male mice. Leuprolide did affect female behaviours in mice that are commonly interpreted as depression-like, as well as on neural activity in the hippocampus, which is involved in stress, depression and cognition (Anacker and others, 2021).

Cancer risk

With long term exposure to GnRH agonists, there is the potential for an increased risk of cancer. In transgender females, 2 cases of testicular cancer have been reported, though background rates and any link to sex steroid changes is not known (Chandhoke, 2018). Neither testosterone suppression nor oestrogen elevation has been linked to risk of testicular cancer. Similarly, a low incidence of prostate cancer (0.04%) was reported in the Amsterdam study (Crowley, 2022). There are no cases to date of breast or uterine cancer reported in transgender men who have had puberty suppression (Panagiotakopoulos and others, 2020).

References

Anacker C, Sydnor E, Chen BK, LaGamma CC, McGowan JC, Mastrodonato A, Hunsberger HC, Shores R and others. Behavioral and neurobiological effects of GnRH agonist treatment in mice - potential implications for puberty suppression in

transgender individuals. *Neuropsychopharmacology* 2021: volume **46**, pages 882-890

Armstrong, SP, Caunt, CJ, Finch, AR, and McArdle, CA. Using automated imaging to interrogate gonadotrophin-releasing hormone receptor trafficking and function. *Molecular and Cellular Endocrinology* 2011: volume **331**, pages 194-204

Caraty, A and Skinner, DC. Gonadotropin-releasing hormone in third ventricular cerebrospinal fluid: endogenous distribution and exogenous uptake. *Endocrinology* 2008: volume **149**, pages 5,227-5,234

Chandhoke G, Shayegan B and Hotte SJ. Exogenous estrogen therapy, testicular cancer, and the male to female transgender population: a case report. *Journal of Medical Case Reports* 2018: volume **12**, article number 373

Crowley F, Mihalopoulos M, Gaglani S, Tewari AK, Tsao CK, Djordjevic M, Kyprianou N, Purohit RS and Lundon DJ. Prostate cancer in transgender women: considerations for screening, diagnosis and management. British Journal of Cancer 2022: volume128, pages 177-189

Ferguson, SSG, Barak, LS, Zhang, J, and Caron, MG. G-protein-coupled receptor regulation: role of G-protein-coupled receptor kinases and arrestins. *Canadian Journal of Physiology and Pharmacology* 1996: volume **174**, pages 1,095-1,110

Hough D, Bellingham M, Haraldsen IRH and others. Spatial memory is impaired by peripubertal GnRH agonist treatment and testosterone replacement in sheep. *Psychoneuroendocrinology* 2017: volume **75**, pages 173-82

Panagiotakopoulos L, Chulani V, Koyama A, Childress K, Forcier M, Grimsby G and Greenberg K. The effect of early puberty suppression on treatment options and outcomes in transgender patients. *Nature* Reviews *Urology* 2020: volume **17**, pages 626-636

Appendix 2: summary of systematic reviews

The safety and clinical effects of GnRH agonists when used to suppress puberty within the pubertal age range in children and young people have been evaluated in 4 systematic reviews, summarised in the table below.

None of the reviews included evidence sufficient to draw conclusions (as determined by authors).

Ludvigsson 2023

Data up to November 2021

Population: children aged less than 18 years with reported gender dysphoria

Extent of evidence: 21 observational studies of GnRH agonists

Thompson 2023

Data up to October 2020

Population: gender dysphoria or transgenderism where data collected on adolescents aged 12 to 17 inclusive

Extent of evidence: 14 observational studies of GnRH agonists

Taylor 2024

In discussion of the CHM Core Group with Professor Hewitt from the University of York team we were informed that by usual standards the impacts identified as moderate quality evidence would usually be consistent with poor quality evidence, but were placed in this category as the overall quality was so poor they considered a need to provide some differentiation.

Data up to April 2022

Population: children and/or adolescents aged 0 to 18 with gender dysphoria, gender incongruence or referral to gender identity service

Extent of evidence: 39 observational studies of GnRH agonists

Miroshnychenko 2024

Data up to September 2023

Population: individuals aged under 26 with gender dysphoria, gender identify disorder, gender incongruence, or who were transgender or non-binary. [No subgroup analyses of those aged under 18 presented]

Extent of evidence: 10 observational studies of GnRH agonists

Bragge 2024

A rapid evidence synthesis was also identified (Bragge P, Cong-Lem, N, Delafosse V, Goldberg E, Temple-Smith M, Sanci L. 'Evidence check: evidence for effective interventions for children and young people with gender dysphoria – update' (an evidence check rapid review brokered by the Sax Institute).

Ramos 2021

A further systematic review was identified (Ramos 2021) which did not provide evidence tables and changed criteria for inclusion (4 papers were identified for bone maturation, but only the most recent 3 were included for reasons that are unclear). This data is not reported as its inclusion period (2009 to 2019) will have been captured by other systematic reviews presented.

Table 1: clinical outcomes identified by the reviews

	Ludvigsson 2023	Thompson 2023	Taylor 2024	Miroshnychenko 2024	Bragge 2024	Ramos 2021
Bone Density	Delay to bone mineralisation and bone mineral density gain. Partial recovery, in hip but not lumbar spine, by 22 years (6 studies)	Decreased bone mineral density (1 study) and bone mineral apparent density z-scores (3 studies) Bone mineral density values stable during longer treatment but z-scores reduced.	Increased absolute bone mineral density (1 study), bone mineral density constant (2 studies), bone mineral density decreased (1 study). Z-scores decreased for both bone mineral apparent density, bone mineral density (5 studies)	May be lower at 12-36 months (hip (2 studies), lumbar (5 studies), femur neck (2 studies)).		
Suicide Ideation	No change (1 study)	Not assessed	Less in treated (similar to no gender dysphoria) (1 Study). No change (1 study).	Not assessed		
Gender Dysphoria	No change (2 studies)	No change (1 study)	No change (2 studies)	Suggestion of lowering at 23-36 months (2 studies) but considerable uncertainty		
Depression	No change (2 studies)	Decrease (2 studies)	Decrease (1 study)	May be lower at 23 months (1 study).		
Anxiety	No change (2 studies)	Decrease (1 study)	No change (1 study)	Not assessed		

Internalising problems	Not assessed	Improvement (1 study); no change (1 study)	Fewer problems /small improvement (2 studies). No change (1 study)	Not assessed		
Externalising problems	Not assessed	Not assessed	Small improvement (1 study). No change (2 studies)	Not assessed		
Psychopathology	Not assessed	Not assessed	Small improvement (1 study). No change (1 study)	Not assessed		
Psychological functioning over time	Not assessed	Not assessed	Improved at 18 months (1 study) No change over time (2 studies)	Not assessed		
Global Function	Improved Children's Global Assessment Scale (4 studies)	Improved Children's Global Assessment Scale (3 studies)	Improved Children's Global Assessment Scale (1 study); no change (2 studies)	Higher at 12 months (2 before-after studies). May be higher at 23-36 months (2 studies). No improvement at 6 months (1 study).		
Quality of Life	Some Improvement (2 studies)	Normal mental and physical QoL post-treatment (1 study)	No change (1 study)	Not assessed		
Cognitive outcomes	No change (1 small matched-control study)		No change (2 studies)	Not assessed		

Arthropometric measures	Increase in weight and body mass index (1 study)	Mixed findings (7 studies) Increases generally in line with normal development	No change in body mass index (10 studies). Increase in 2 studies (1 for birth registered males but not birth registered females; the other for early-treated individuals but not later-treated)	Not assessed		
Body Composition	Decrease lean body mass (3 studies)	Not assessed	Lean mass decreased (2 studies) Body fat increased (1 study)	Not assessed		
Lipids	No change (2 studies)	Significant increase in total cholesterol, low density lipoprotein and high density lipoprotein (1 study). No change (1 study)	Decrease high density lipoprotein and triglycerides (1 study). Decrease in high density lipoprotein and increased low density lipoprotein (1 study). No change (1 study)	Not assessed		
Blood Pressure	Limited data identified (1 study)	Increase diastolic blood pressure 3 studies). systolic blood pressure 3 increased (2 studies) and decreased (1 study).	Increase in diastolic blood pressure (1 study). No change in systolic blood pressure (3 studies).	Not assessed		
Growth	Reduced growth velocity (1 study)	Not assessed	Similar to comparator (1 study)	Not assessed		

Glucose metabolism	Decreased insulin sensitivity (2 studies)	No change glucose or insulin. (1 study)	No change glucose or haemoglobin A1c. (2 studies)	Not assessed		
Liver Enzymes	Not assessed	Mixed results: Increase in alkaline phosphatase (1 study). No change alanine aminotransferase, aspartate aminotransferase (2 studies) or gamma glutamyl transferase (1 study). Increase in alanine aminotransferase, aspartate aminotransferase (1 study)	Decrease in alkaline phosphatase (both sexes) and creatinine (birth registered females only) (1 study) Unchanged alkaline phosphatase, creatinine (1 study)	Not assessed		
Haemoglobin	Not assessed	No change (3 studies)	Not assessed	Not assessed		
QTc	Not assessed	Not assessed	No change in mean QTc (1 study)	Not assessed		
Side Effects	Not assessed	Not assessed	Common: Headache, hot flushes (2 studies) Less common: Mood swings/ emotional (2 studies) Fatigue (2 studies)	Not assessed		

			Frequency unknown: Acne (1 study)			
Pubertal progression	Not assessed	Not assessed	**See note 1**	Not assessed		
Progression to cross sex hormones	Not assessed	21% prescribed cross sex hormones by 16yrs (1 study)	Not assessed	69% at 12 months (1 study) 92% by 36 months (2 studies)		
Long term follow up	Not assessed	Not assessed	Not assessed	Not assessed		

Colour coding

Red Evidence insufficient to draw conclusions (as determined by authors)
Amber Moderate quality evidence
Green Evidence sufficient to draw conclusions (as determined by authors)

Note 1: Taylor and others review. On pubertal progression (4 studies - 2 cohort, 2 pre-post):

a. clinical pubertal escape was reported in 2 out of 21 participants (breast enlargement in one case and in another case testicular enlargement and voice change)
b. Tanner stage 2 or 3 treatment resulted in smaller breast size in birth-registered females and lower average penile length and fewer testes descended in birth-registered males, comparing Tanner stage 4 or 5 with Tanner stage 2 or 3 or no GnRH agonists
c. Tanner stage 2 or 3 treatment resulted in need for fewer and less burdensome mastectomies in birth-registered females, but more genital surgery in birth-registered males, compared with Tanner stage 4 or 5 or no treatment
d. in birth-registered males, testicular volume decreased for 43 out of 49 participants during GnRH agonists treatment. Results were unclear for breast development in birth-registered females, most of whom started treatment in Tanner stage 4 or 5 less than 50% birth-registered males reported decreased facial shaving. Some reported decreased spontaneous erections (numbers not reported). Breast development was noted in around 30% of birth-registered females

Appendix 3: membership of CHM

Chair

Professor Sir Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP (Edin) FBPhS, FFPM (Hon) FMedSci
David Weatherall Chair of Medicine, University of Liverpool, NHS Chair of Pharmacogenetics, Director of the Wolfson Centre for Personalised Medicine, Director of the Centre for Drug Safety Science

Vice Chair

Professor Steven Cunningham MBChB PhD FRCPCH FRCP
Professor of Paediatric Respiratory Medicine, University of Edinburgh and Honorary Consultant, Royal Hospital for Children and Young People, NHS Lothian, Edinburgh

Members

Professor Amanda Adler MD PhD FRCP
Professor of Diabetic Medicine and Health Policy, University of Oxford

Professor Jamie Coleman MD MA (Med Ed) FRCP FBPhS
Consultant Physician, University Hospitals Birmingham NHS Foundation Trust and Honorary Professor in Clinical Pharmacology and Medical Education, University of Birmingham

Mrs Julia Cons
Lay Representative

Mr David Crundwell
Lay Representative

Professor Paul Dargan MB BS FRCP Edin FACMT FRCP ERT FAACT FEAPCCT FBPhS MAE
Consultant Physician and Professor of Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust, London and Professor of Clinical Toxicology, King's College London

Professor David Dockrell MB BCh MD FRCPI FRCP (Glas) FACP
Professor of Infection Medicine, University of Edinburgh

Professor David Hunt MB BChir FRCP PhD
Consultant Neurologist, NHS Lothian and Professor of Neuroinflammatory Medicine, University of Edinburgh

Professor David Moore MBChB MD MSc DTM&H
Professor of Infectious Diseases and Tropical Medicine, London School of Hygiene and Tropical Medicine and Consultant in Infectious Diseases and Tropical Medicine, Hospital for Tropical Diseases, University College London Hospital

Dr Gerri Mortimore PhD; MSc Advanced Practice; PgCert (IPPE); Ba(Hons) Health Studies; iLM. RGN; NMP; FHEA - Associate Professor in Advanced Clinical Practice; NICE Nurse Expert Advisor

Professor Sandosh Padmanabhan MBBS MD PhD FRCP(Glasg) FRCP(Edin) FBPhS FBIHS
Professor of Cardiovascular Genomics and Therapeutics, University of Glasgow

Professor Poulam Patel PhD, MBBS, FRCP
Professor of Clinical Oncology, University of Nottingham

Professor Yvonne Perrie BSc Hons MRPharmS FAPS FSB PhD
Chair in Drug Delivery, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland

Professor Rui Providencia MD PhD
Institute of Health Informatics Research, University College London
Consultant Cardiologist and Cardiac Electrophysiologist, Barts Health NHS Trust

Professor Vanessa Raymont MBChB MSc MRCPsych
Associate Professor, University of Oxford and Honorary Consultant Psychiatrist, Oxford Health NHS Foundation Trust

Professor Marc Turner MB ChB PhD MBA FRCP FRCPath FRSE
Professor of Cellular Therapy; Director Scottish National Blood Transfusion Service (SNBTS)

Professor Heather M Wallace PhD FRCPath FRSC FRSB FBTS FBPhS ERT
Professor Emerita of Biochemical Pharmacology and Toxicology, University of Aberdeen

Professor Anthony Williams BSc MSc MRCP, FRCPath, PhD
Professor of Translational Medicine and Honorary Consultant in Clinical Immunology and Allergy, University of Southampton and University Hospital Southampton NHS Trust

Professor Christopher Weir BSc (Hons) PhD MSc FRSS C.Stat
Personal Chair in Medical Statistics and Clinical Trials, Usher Institute, University of Edinburgh

Dr Martin Wilson MB ChB, MPhil (Glasgow), FRCP(Edin)
Consultant Physician in Care of the Elderly, Raigmore Hospital, Inverness

Co-opted member

Dr Jamie Fraser BSc (Hons) MBChB MRCGP
GP Partner, Southside Surgery, Inverness