Gender-affirming hormone treatment for young people with gender dysphoria: where do we go from here?

Alison Clayton

Child and adolescent gender medicine is currently one of the most heatedly debated fields in medicine. The recent Cass Review,[1] underpinned by a comprehensive research programme from the University of York, has corroborated growing worldwide concern regarding the use of puberty blockers (PBs) and gender-affirming hormone treatment (GAHT) for young people with gender dysphoria (GD). The review has contributed to an important professional debate about the future of these treatments—a debate which, at times, has been marred by serious misrepresentations of Cass's processes, findings and recommendations.[2–4]

Given the growing debate, the newest systematic review and meta-analysis (SR/MA)[5] evaluating psychosocial and physical outcomes of GAHT for young people (under 26 years of age) with GD is a welcome and important addition to the literature. Researchers from the department of health research at McMaster University followed the highest methodological standards for SRs. They undertook risk-of-bias assessments, performed meta-analyses and used the Grading of Recommendations, Assessment, Development, and Evaluations approach to evaluate the certainty of the evidence. They concluded that the evidence about the effects of GAHT in individuals under the age of 26 is very uncertain, the possibility of benefits and harms cannot be excluded, and more rigorous prospective studies are required to produce higher certainty evidence.

Importantly, this SR/MA highlights that it is not, as some have suggested,[2 3 6] just the absence of randomised controlled trials (RCTs) that results in the evidence being mostly rated as very-low certainty. Rather, it is the absence of reliable studies across all study designs; indeed, a poor-quality RCT would do little to improve the certainty of evidence. Another salient feature of the McMaster's SR is the inclusion of studies of individuals up until age 25. This demonstrates the lack of evidence of benefits of GAHT, not only in adolescents (less than 18 years of age) but also in the young adult population. This finding lends support to Cass's recommendations that National Health Service England urgently initiate a review of the adult services operations and model of care (p227).[1]

A limitation of the McMaster's SR is that it did not evaluate some important potential physical harms, for example, fertility or cancer risks. It also did not examine outcomes related to regret and detransition. Furthermore, the McMaster's review, like previous SRs of GAHT in adolescence, did not evaluate studies of harms found in older adults. Adolescents will soon become older adults, and GAHT is, mostly, expected to be a lifelong treatment. Thus, any evidence of harms at any age is important. Yes, there are risks of extrapolating findings in older adults to the adolescent population, but disregarding such evidence seems to pose a greater risk (somewhat analogous to if we ignored evidence of harms of smoking in adults when advising against adolescents smoking). Also relevant to this, and cause for serious concern, are the recent reports that the World Professional Association for Transgender Health's (WPATH) leadership were involved in restricting the publication of SRs evaluating the physical risks of GAHT.[2] This suggests that there is significant publication bias in gender medicine, which raises further questions about the certainty and integrity of the evidence in this field.

There are now multiple SRs reporting on GAHT in adolescents. These have been undertaken by different research groups in different countries and using a variety of rating instruments to assess various outcomes. All cohere in concluding that the evidence is weak and that there are significant knowledge gaps.[3–5]

What are the implications of this—where to from here? The McMaster's team highlight the need for more methodologically rigorous prospective studies. They also emphasise that it is crucial for decision makers, including young people, caregivers and clinicians, to comprehensively understand the uncertain evidence and knowledge gaps, which should, along with several other factors, inform a shared clinical decision-making process.

However, as the current debates raging in this field indicate, there is a foremost issue which needs to be decided by health regulatory bodies. Given the predominantly very low-certainty evidence for psychosocial benefits and given the potential serious harms of GAHT, should health authorities classify GAHT for adolescents as experimental and stipulate it to be only available as part of ethics committee approved clinical trials? Alternatively, should it remain available as part of routine treatment while further evidence is gathered? Or are the risks for adolescents too high and should GAHT only be available to adults, who have better capacity to give informed consent for treatments that pose serious risk of harm, especially to sexual and reproductive function? In this latter scenario, the main treatment option available for adolescents with GD would be holistic psychosocial care. I will not provide answers to these complex questions but will make a few observations relevant to both PBs and GAHT for GD.

It is helpful to consider the recently revised Declaration of Helsinki (DoH).[7] Due to concerns that some clinicians were misusing the previous version to support the continuous use of unproven interventions in clinical practice, paragraph 37 was revised to include a clear warning against such behaviour and, also, against clinicians compromising or evading research that would advance knowledge, for example, by not undertaking clinical trials or not recording or sharing data.[7 8] A further revision is the requirement that research must have a "scientifically sound and rigorous design to avoid research waste" (paragraph 21). This is a requirement because exposing research participants to risks without any prospect of valid knowledge generation is unacceptable.[8]

Considering these DoH revisions, Cass's recommendations that PBs should only be available as part of a high-quality clinical trial as the best way to generate reliable evidence (appendix 6)[1] seem sound. Although much will hinge on the trial's design (that is, its capacity to generate relaible evidence) and the ethical considerations inherent in experimenting in minors. Furthermore, the DoH revisions and the McMaster's SR's findings lend support to those arguing that GAHT for adolescents should similarly be restricted to clinical trial conditions. This is a position already taken by Swedish health authorities.[9]

The University of Melbourne, Melbourne, Victoria, Australia

Correspondence to Dr Alison Clayton; alclayton@student.unimelb.edu.au

The DoH revisions are also highly pertinent to some other observations made by Cass.[1] She observed that there was a concerning 'creep of unproven approaches into clinical practice' and an excessive permissiveness with 'off-label' prescribing (which is the case for both PBs and GAHT for GD) (pp74, 231). Cass also reported on a long delay in the publication of a study that had not found any evidence of beneficial outcomes (p25) and described the lack of cooperation from adult gender service clinicians with her attempts to obtain important long-term outcome information (appendix 4). These seem clear examples of the problematic clinician and researcher behaviour (as does the earlier mentioned behaviour of WPATH's leadership in restricting publication of SRs) that the revised DoH warns against.

It is also notable that, in response to the increasingly hard to dispute 'evidence of lack of evidence', some advocating for the use of PBs and GAHT in adolescents are now shifting the goalposts. For example, over the past two decades, narratives have focused on improved mental health outcomes as the *raison d'être* of PBs and/or GAHT in youth with GD.[6] However, some now suggest moving away from mental health outcomes as the yardstick of these treatments' effectiveness; instead, they posit that PBs and GAHT could be provided based on personal desire and autonomy to achieve embodiment goals irrespective of mental health and well-being impacts.[6] These shifting rationales are, in themselves, indicative of youth gender medicine's serious problems.

Moreover, we should hold grave concerns about this new rationale, which misunderstands the place of autonomy in clinical decision-making and is unbalanced with respect to the important ethical principles of beneficence and non-maleficence.[10] For example, consider the following clinical scenario. A young person, identifying as non-binary, requests ongoing PBs. This intelligent young person has read an article advocating in principle support for such a treatment approach, primarily because of the principle of autonomy.[11] It later emerges that this young person has unwanted homosexual (same sex) desires and fantasies. They report a strong and persistent preference to have no or diminished sexual desire—to be an asexual non-binary person rather than be a same-sex attracted sexual person. In effect, they are asking for PBs as chemical castration. (Similar scenarios of transgender identification and GAHT use because of internalised homophobia have been reported.) As a clinician, I would consider it unethical to acquiesce to such requests. However, those arguing for PBs and GAHT to be made available according to personal desire and an individual's life goals would appear to be required, if they are going to be consistent, to give in principle agreement to such requests. In doing so, although unwittingly, they resurrect the spectre of medical conversion practices for homosexual people—indeed, there are clinician and detransitioner accounts indicating this is already occurring.

As this example shows, medicine enters dangerous territory when its usual research, clinical and ethical standards are abandoned. The Cass Review, with its underpinning York SRs, and the McMaster's SR/MA are to be commended as part of the growing move for youth gender medicine to return to these important standards, which are in place to help ensure medicine benefits patients rather than harms them.

Funding No funding was received for the writing of this paper. Open access fees were provided by the Society for Evidence-Based Gender Medicine.

Competing interests AC is affiliated with the Society for Evidence-Based Gender Medicine.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Clayton A. *Arch Dis Child* 2025;**110**:415–416.
Accepted 25 February 2025
Published Online First 12 March 2025

Linked

► https://doi.org/10.1136/archdischild-2024-327909
► https://doi.org/10.1136/archdischild-2024-327921

Arch Dis Child 2025;**110**:415–416.
doi:10.1136/archdischild-2025-328478

ORCID iD
Alison Clayton http://orcid.org/0000-0002-3634-234X

REFERENCES

1 Cass H. Independent review of gender identity services for children and young people: final report. 2024. Available: https://cass.independent-review.uk/?page_id=936
2 Cheung CR, Abbruzzese E, Lockhart E, *et al*. Gender medicine and the Cass Review: why medicine and the law make poor bedfellows. *Arch Dis Child* 2025;110:251–5.
3 Clayton A, Amos AJ, Spencer J, *et al*. Implications of the Cass Review for health policy governing gender medicine for Australian minors. *Australas Psychiatry* 2025;33:89–95.
4 McDeavitt K, Cohn J, Levine SB. Critiques of the Cass Review: Fact-Checking the Peer-Reviewed and Grey Literature. *J Sex Marital Ther* 2025;51:175–99.
5 Miroshnychenko A, Ibrahim S, Roldan Y, *et al*. Gender affirming hormone therapy for individuals with gender dysphoria aged <26 years: a systematic review and meta-analysis. *Arch Dis Child* 2025;110:437–45.
6 Oosthoek ED, Stanwich S, Gerritse K, *et al*. Gender-affirming medical treatment for adolescents: a critical reflection on "effective" treatment outcomes. *BMC Med Ethics* 2024;25:154.
7 Resneck JS Jr. Revisions to the Declaration of Helsinki on Its 60th Anniversary: A Modernized Set of Ethical Principles to Promote and Ensure Respect for Participants in a Rapidly Innovating Medical Research Ecosystem. *JAMA* 2025;333:15–7.
8 Reis AA, Upshur R, Moodley K. Future-Proofing Research Ethics-Key Revisions of the Declaration of Helsinki 2024. *JAMA* 2025;333:20–1.
9 Socialstyrelsen [National Board of Health and Welfare]. Care of children and adolescents with gender dysphoria – summary. 2022. Available: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2023-1-8330.pdf [accessed 13 Jan 2024]
10 Gorin M. What Is the Aim of Pediatric "Gender-Affirming" Care? *Hastings Cent Rep* 2024;54:35–50.
11 Notini L, Earp BD, Gillam L, *et al*. Forever young? The ethics of ongoing puberty suppression for non-binary adults. *J Med Ethics* 2020;46:743–52.