



Received: 6 June 2022 | Accepted: 7 June 2022

DOI: 10.1002/jac5.1691

## LETTER TO THE EDITOR



## Puberty blockers for gender dysphoric youth: A lack of sound science

Dear Editor,

The medical transition of children and adolescents with gender dysphoria remains highly debated and there is significant divergence in policy internationally.<sup>1-7</sup> Mills and colleagues' review the interventions that comprise the "gender-affirmative" care pathway, an approach currently promoted by many medical organizations in North America.<sup>6-8</sup> We strongly agree with the authors that pharmacists have a responsibility to "understand the evidence," and "place the well-being of the patient over any personal cultural beliefs."<sup>8</sup> However, we think the use of evidence to support the authors' claim that gonadotropin releasing hormone (GnRH)-analogs are fully reversible and have been shown to improve mental health, requires critical appraisal.

GnRH-analogs have been used for decades to successfully delay the *early* onset of puberty in children with precocious puberty.<sup>9</sup> While generally considered safe for this indication, recent concern about impacts on polycystic ovarian disease, metabolic syndrome, and future bone density, have been raised.<sup>10</sup> Even less is known about the use of GnRH-analogs to halt *normally* timed puberty in youth with gender dysphoria; no long-term, longitudinal studies of GnRH-analogs for this indication exist.

Puberty-related hormones have wide ranging effects on brain structure, function, and connectivity.<sup>11</sup> Concerns have been raised that hormonal suppression of puberty may permanently alter neurodevelopment.<sup>2,11-13</sup> The possible impact of puberty blockade on a young person's cognition has important implications for the decision to initiate exogenous cross-sex hormones and the capacity to give informed consent.<sup>14</sup> Moreover, it has been suggested that pubertal suppression may alter the course of gender identity development, essentially "locking in" a gender identity that may have reconciled with biological sex during the natural course of puberty.<sup>13</sup> Over 95% of youth treated with GnRH-analogs go on to receive cross-sex hormones.<sup>15</sup> By contrast, 61-98% of those managed with psychological support alone reconcile their gender identity with their biological sex during puberty.<sup>16-18</sup> This lack of evidence to support the durability of a transgender identification is conceptually consistent with significant psychosocial determinants of cross-sex identity, while the belief in immutable biological influences can best be described as a "current hypothesis."<sup>19</sup>

There are also concerns that GnRH-analogs may have irreversible effects on sexual function and bone development. In some youth

pubertal blockade at Tanner stage 2 followed by exogenous cross-sex hormones has resulted in a complete absence of adult sexual function.<sup>20</sup> Profound effects on future sexual function may even occur when puberty is paused and later allowed to proceed, since the precise timing of hormone exposure during the peripubertal window is a determinative factor in adult sexual function.<sup>21</sup> Finally, several studies have found that the expected pattern of bone mass accrual during adolescence does not occur when puberty is halted.<sup>22-25</sup> The long-term clinical consequences of failure to accrue normal bone mass are unknown.

Uncertainties about long-term risks of medical transition are often overshadowed by the most potent argument provided by advocates of the affirmative model: failure to affirm a young person's transgender identity may result in suicide. Suicidal ideation and self-harming behaviors have been found to be higher than age-matched peers, but comparable to nongender dysphoric youth referred for management of other mental health diagnoses.<sup>26</sup> However, the relevant question is whether affirmative care reduces suicide risk. Mills and colleagues' assertion that GnRH-analogs have been shown to decrease lifetime suicidal ideation stems from a nonrepresentative, low-quality survey of transgender adults that has been thoroughly critiqued by others.<sup>27,28</sup> Moreover, their claim that these drugs are effective for other mental health outcomes is at odds with recent systematic reviews that concluded there is little change from baseline to follow-up in depression, anxiety, body image, gender dysphoria, or psychosocial functioning.<sup>2,12,29</sup> A seminal Dutch case-series of children with early-onset gender dysphoria is cited to support the assertion that GnRH-analogs improve psychological functioning.<sup>15</sup> The magnitude of posttreatment improvement in mental health outcomes in this study was small and of questionable clinical significance. Furthermore, the applicability of results to the most common demographic presenting today, that is, adolescent females with pre-existing mental health problems or neurodevelopmental conditions and no prior history of gender dysphoria, is questionable.<sup>4,30</sup> A recent attempt to replicate the results of the Dutch study in the United Kingdom found no psychological benefit with GnRH-analogs, but treatment was associated with adverse effects on bone development.<sup>31</sup>

Multiple European countries that were pioneers in youth medical transition are now adopting a more cautious approach to the use of

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. JACCP: *Journal of the American College of Clinical Pharmacy* published by Wiley Periodicals LLC on behalf of Pharmacotherapy Publications, Inc.

Doe Pls' Trial Ex.

123

GnRH-analogs and cross-sex hormones after their own evidence reviews failed to show mental health benefits and highlighted a profound lack of knowledge about harms. The UK's Cass review emphasized the paucity of data in their interim report stating, "it is important that it is not assumed that outcomes for, and side effects in, children treated for precocious puberty will necessarily be the same in children or young people with gender dysphoria."<sup>13</sup> The NHS updated guidance on treatment of gender dysphoria removed statements about the reversibility of GnRH-analogs and now states, "little is known about the long-term side effects of hormone or puberty blockers in children with gender dysphoria."<sup>4</sup> The Swedish Health Authority no longer offers GnRH-analogs to minors except in exceptional cases stating, "the risks of puberty suppressing treatment with GnRH-analogues and gender affirming hormonal treatment currently outweigh the possible benefits."<sup>3</sup> Finland has severely restricted their use and now recommend psychotherapy as first-line treatment for gender-dysphoric youth.<sup>2</sup> Lastly, the French Académie Nationale de Médecine recently issued a press release stating, "great medical caution must be taken in children and adolescents, given the vulnerability, particularly psychological, of this population and the many undesirable effects, and even serious complications, that some of the available therapies can cause."<sup>5</sup> Although puberty-blockers and cross-sex hormones will still be available, the Académie emphasized, "the greatest reserve is required in their use, given side effects such as impact on growth, bone fragility, risk of sterility, emotional and intellectual consequences and, for girls, symptoms reminiscent of menopause."<sup>5</sup>

In summary, we believe the authors' review does not present a balanced assessment of the evidence and betrays a bias toward uncritically promoting medical transition. The widespread methodological weaknesses in the research coupled with the lack of certainty that benefits outweigh harms, should raise questions about affirmation being positioned as the "standard of care" in the United States and Canada.<sup>29</sup> Patients and their families rely on pharmacists to resist ideological influence and communicate transparently. To this end, we call on Mills and colleagues to revisit their important review and provide a more nuanced discussion of the evidentiary basis for gender-affirming care.

#### ACKNOWLEDGEMENTS

The Society for Evidence Based Gender Medicine paid the open access fee.

#### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

#### FUNDING INFORMATION

There was no external funding for this research.

Sarah C. J. Jorgensen Pharm.D., MPH<sup>1</sup> 

Patrick K. Hunter M.D., M.Sc. Bioethics<sup>2</sup>

Lori Regenstreif M.D., M.Sc.<sup>3</sup>

Joanne Sinai M.D., M.Ed.<sup>4</sup>

William J. Malone M.D.<sup>5</sup>

<sup>1</sup>Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

<sup>2</sup>Department of Medicine, Florida State University College of Medicine, Tallahassee, Florida, USA

<sup>3</sup>Department of Family Medicine, McMaster University, Hamilton, Ontario, Canada

<sup>4</sup>Department of Psychiatry, University of British Columbia, Victoria, British Columbia, Canada

<sup>5</sup>Department of Medicine, Idaho College of Osteopathic Medicine, Boise, Idaho, USA

#### Correspondence

Sarah C. J. Jorgensen, Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, 1 King's College Circle, Toronto, Ontario M5S 1A8, Canada.  
 Email: [sarah.jorgensen@utoronto.ca](mailto:sarah.jorgensen@utoronto.ca)

#### ORCID

Sarah C. J. Jorgensen  <https://orcid.org/0000-0003-1333-0378>

#### REFERENCES

1. The World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. 7th version; [https://www.wpath.org/media/cms/Documents/SOC%20v7/SOC%20V7\\_English.pdf](https://www.wpath.org/media/cms/Documents/SOC%20v7/SOC%20V7_English.pdf)
2. Recommendation of the Council for Choices in Health Care in Finland (PALKO/COHERE Finland) Medical Treatment Methods for Dysphoria Related to Gender Variance in Minors. 2020. Society for evidence based gender medicine unofficial translation. [https://segm.org/sites/default/files/Finnish\\_Guidelines\\_2020\\_Minors\\_Unofficial%20Translation.pdf](https://segm.org/sites/default/files/Finnish_Guidelines_2020_Minors_Unofficial%20Translation.pdf)
3. SOCIALSTYRELSEN. The National Board of Health and Welfare (NBHW). Care of children and adolescents with gender dysphoria. 2022. <https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-3-7799.pdf>
4. National Health Service (NHS). Treatment—Gender dysphoria; 2020. <https://www.nhs.uk/conditions/gender-dysphoria/treatment/#:~:text=Puberty%20blockers%20and%20cross%2Dsex%20hormones&text=Little%20is%20known%20about%20the,the%20psychological%20effects%20may%20be>
5. Académie Nationale de Médecine. Communiqué. La médecine face à la transidentité de genre chez les enfants et les adolescents; 2022. [https://www.academie-medecine.fr/la-medecine-face-a-la-transidentite-de-genre-chez-les-enfants-et-les-adolescents/?lang=en#\\_ftn1](https://www.academie-medecine.fr/la-medecine-face-a-la-transidentite-de-genre-chez-les-enfants-et-les-adolescents/?lang=en#_ftn1)
6. Office of Population Affairs. Gender-affirming care and young people. <https://opa.hhs.gov/sites/default/files/2022-03/gender-affirming-care-young-people-march-2022.pdf>
7. Bonifacio JH, Maser C, Stadelman K, Palmert M. Management of gender dysphoria in adolescents in primary care. *CMAJ*. 2019;3:E69–E75.
8. Mills AR, Astle K, Frazier CC. "Affirming" journey: Narrative review and practice considerations on gender affirming care. *JACCP: Journal of the American College of Clinical Pharmacy*. 2022;5:697–706.
9. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, ESPE-LWPES GnRH Analogs Consensus Conference Group. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;4:e752–e762.
10. De Sanctis V, Soliman AT, Di Maio S, Soliman N, Elsedfy H. Long-term effects and significant adverse drug reactions (ADRs) associated with the use of gonadotropin-releasing hormone analogs (GnRHs) for central precocious puberty: A brief review of literature. *Acta Biomed*. 2019;3:345–359.

11. Chen D, Strang JF, Kolbuck VD, et al. Consensus parameter: Research methodologies to evaluate neurodevelopmental effects of pubertal suppression in transgender youth. *Transgend Health*. 2020;4:246–257.
12. National Institute for Health and Care Excellence (NICE). Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria; 2020.
13. Cass Review. Independent review of gender identity services for children and young people. Interim report; 2022 <https://cass.independent-review.uk/publications/interim-report/>
14. Levine SB, Abbruzzese E, Mason JW. Reconsidering informed consent for trans-identified children, adolescents, and young adults. *J Sex Marital Ther*. 2022;1–22. <https://doi.org/10.1080/0092623X.2022.2046221>
15. de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *J Sex Med*. 2011;8:2276–2283.
16. Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ. A follow-up study of girls with gender identity disorder. *Dev Psychol*. 2008;1:34–45.
17. Ristori J, Steensma TD. Gender dysphoria in childhood. *Int Rev Psychiatry*. 2016;1:13–20.
18. Singh D, Bradley SJ, Zucker KJ. A follow-up study of boys with gender identity disorder. *Front Psychiatry*. 2021;12:632784.
19. Saraswat A, Weinand JD, Safer JD. Evidence supporting the biologic nature of gender identity. *Endocr Pract*. 2015;2:199–204.
20. Blum B. Would you give up an orgasm? Opinion. The Jerusalem Post. June 2, 2022. <https://www.jpost.com/opinion/article-708397> Video recording from Women's Voices <https://twitter.com/WomenReadWomen/status/1521692875242688512>.
21. Shirazi TN, Self H, Dawood K, et al. Pubertal timing predicts adult psychosexuality: Evidence from typically developing adults and adults with isolated GnRH deficiency. *Psychoneuroendocrinology*. 2020;104733:104733.
22. Biggs M. Revisiting the effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria. *J Pediatr Endocrinol Metab*. 2021;7:937–939.
23. Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: Findings from a large national cohort. *J Pediatr Endocrinol Metab*. 2019;10:1077–1081.
24. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab*. 2015;2:E270–E275.
25. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone*. 2017;95:11–19.
26. Zucker KJ. Adolescents with gender dysphoria: Reflections on some contemporary clinical and research issues. *Arch Sex Behav*. 2019;7:1983–1992.
27. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal suppression for transgender youth and risk of suicidal ideation. *Pediatrics*. 2020;145:e20191725.
28. Biggs M. Puberty blockers and suicidality in adolescents suffering from gender dysphoria. *Arch Sex Behav*. 2020;7:2227–2229.
29. Brignardello-Peterson R, Wiercioch W. Effects of gender affirming therapies in people with gender dysphoria: Evaluation of the best available evidence. May 16, 2022. [https://ahca.myflorida.com/letkidsbekids/docs/AHCA\\_GAPMS\\_June\\_2022\\_Attachment\\_C.pdf](https://ahca.myflorida.com/letkidsbekids/docs/AHCA_GAPMS_June_2022_Attachment_C.pdf)
30. Strang JF, Meagher H, Kenworthy L, et al. Initial clinical guidelines for co-occurring autism spectrum disorder and gender dysphoria or incongruence in adolescents. *J Clin Child Adolesc Psychol*. 2018;1:105–115.
31. Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. *PLoS One*. 2021;2:e0243894.