



# Pubertal Blockade and Subsequent Gender-Affirming Therapy

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For youth who identify as transgender or are unsure and wish to explore possibilities before the development of permanent secondary sex characteristics, use of a gonadotropin-releasing hormone analogue (GnRHa) is a key medical option. Sometimes colloquially called “puberty blockers,” they have been used safely for decades in children with precocious puberty<sup>1</sup> and endometriosis,<sup>2</sup> among other medical indications. Multiple professional societies now endorse pubertal blockade for youth with gender dysphoria.<sup>3,4</sup> Recently, the use of GnRHa has received attention because of legislated concerns regarding the medical and surgical treatment of transgender youth, including criminalizing the provision of this care in some states.<sup>5</sup> Without evidence, the assumption has been made that GnRHa treatment leads to increased ultimate use of gender-affirming therapy (GAT) in transgender youth and that prescription of a GnRHa inappropriately advances the decision to start GAT. The article by Nos et al<sup>6</sup> provides data to the contrary—that this therapy can be offered both for mental health and cosmetic benefits without the concern of increasing the subsequent use of GAT.

An understanding of the medical management of a transgender child or adolescent is needed to appreciate the issues at hand.<sup>3,4,7</sup> A GnRHa is more potent than native GnRH and produces initial stimulation of pituitary gonadotrophs, with increased secretion of follicle-stimulating hormone, luteinizing hormone, and gonadal hormones, followed by downregulation of the pituitary-gonadal axis. As sex steroid secretion is inhibited, the development of pubertal changes ceases. Pubertal blockade with a GnRHa buys time for a child or adolescent, pausing puberty and allowing for the exploration of gender identity. Initiated early in puberty, the GnRHa delays the development of irreversible pubertal changes and, in some cases, eliminates the need for subsequent surgery. GnRHa therapy is reversible; discontinuation leads to prompt resumption of the pituitary-gonadal axis. Although pubertal blockade and GAT are often prescribed as complementary approaches, they are separate phases in transgender treatment.<sup>3</sup>

Through a retrospective cohort study of billing and pharmacy records, Nos and colleagues<sup>6</sup> explored the timely question of whether GnRHa use was associated with subsequent use of GAT among transgender and gender-diverse adolescents. They reviewed data between 2009 and 2018 from the US Military Healthcare System. Participants had at least 2 transgender-related encounters, with the first occurring between ages 10 and 17 years, and at least 1 encounter after the participant’s 14th birthday (the earliest a clinician would start GAT according to current guidelines).<sup>3,4,7</sup> The sample included 434 adolescents, with 71.9% assigned female at birth and 69.1% having an enlisted insurance sponsor. Younger patients (aged 10-13 years) were more likely to start GnRHa therapy than older (aged 14-17 years) patients: 57.1% vs 10.1%. Patients who were assigned male at birth were more likely to receive GnRHa than those assigned female but were not more likely to be prescribed gender-affirming hormones. In fact, patients who were prescribed GnRHa were less likely to start GAT within 6 years of the first encounter than those who were not (hazard ratio, 0.52; 95% CI, 0.37-0.71). For clinicians, the salient point is that the prescription of a GnRHa did not imply the ensured subsequent use of GAT. The findings suggest that clinicians can offer GnRHa therapy without the concern of influencing the future use of GAT. The decision to initiate GnRHa therapy represents an independent therapeutic decision for a clinician, ideally working in concert with a multidisciplinary team of both medical and mental health clinicians.<sup>5</sup>

Limitations of the study of Nos and colleagues<sup>6</sup> merit discussion. They included younger children compared with earlier studies, which is a strength of the study, but as younger age was associated with higher GnRHa discontinuation rates, this could explain the finding. However, overall,

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few patients discontinued treatment. Data were also extracted from an administrative database that did not afford information on the reasons why a clinician initiated therapy or not, and why patients chose to continue or discontinue the treatment. Patients could have obtained prescriptions outside of the Military Healthcare System that were not captured. However, the high costs out of pocket or through private insurance make this possibility unlikely. Lack of official approval for GAT coverage before 2016 may have influenced the decisions of patients or clinicians. Finally, there may be inherent biases among military medical personnel regarding gender identity and potential reluctance to provide treatment. The reasons could be personal ones or related to a lack of expertise. Replication of these results in a different study setting will be important to expand the generalizability of the current findings.

A question that arises in the course of transgender care is whether GnRHa therapy has long-term adverse medical consequences, including effects on bone health. More than one-half of an individual's bone density is acquired during adolescence, and transgender youth assigned male at birth are known to be at higher risk for low bone density even before GnRHa therapy.<sup>7</sup> Understanding whether GnRHa use is associated with fracture risk will be the critical long-term question that must be answered in future studies. In pediatrics, we are often left needing to weigh risks vs benefits, with limited available evidence, and needing to prescribe medications off-label. For the adolescent who goes on to receive GAT, theoretically and anecdotally, reintroduction of sex steroids appears to mediate skeletal gains, especially for transgender male individuals. In considering bone health and other health outcomes, optimizing bone density must be balanced with the known benefits of GnRHa for gender dysphoria, including decreased suicidal ideation.<sup>6</sup> Concerns about skeletal losses become less significant in an adolescent with active suicidal ideations. Although the significance of the risks may be unclear, there is strong evidence regarding the benefits of GnRHa in transgender youth: it can be a life-changing and lifesaving treatment for a vulnerable population who is at high risk for anxiety, depression, and suicide.<sup>4,5,7</sup>

The treatment decisions for transgender youth can be complex, with many factors that need to be considered. The novel findings provided by the study of Nos and colleagues<sup>6</sup> add to the growing body of work demonstrating that GnRHa therapy is a safe and necessary component of transgender care, especially for children or adolescents with gender dysphoria. Their results emphasize that use of GnRHa and subsequent GAT are different phases of treatment, and their use should be guided by independent decisions that a clinician makes separately. From a cosmetic standpoint, it is much easier to treat a patient if pubertal changes have only just begun to develop, and gender dysphoria subsides as the worry of continued development of secondary sex characteristics comes to a halt. We hope that an enhanced understanding of transgender medical management, including the separate phases of therapy, and how a GnRHa works therapeutically, will help to dispel myths. The study by Nos and colleagues<sup>6</sup> is hopefully one step forward in that direction. One phase of transgender treatment does not and should not dictate the next phase, thereby enabling clinicians to individualize care. Perhaps, even moving away from the term "puberty blocker" and instead describing mechanistically and clinically how these agents work will help return the focus of gender care to what matters most: the health and wellness of the child or adolescent.

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#### ARTICLE INFORMATION

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