

# Ethical dilemmas of gonadotropin-releasing hormone analogs for the treatment of gender dysphoria

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Gender dysphoria (GD) is a condition of distress due to the incongruence between gender identity and gender assigned at birth. The discomfort tends to start during childhood and increases at times of puberty; however, the condition may emerge directly at puberty or adulthood. GD's prevalence is higher than that of clinic-referred sample of adults only, highlighting the increasing pensiveness among youths, with a percentage between 0.5 and 1.3 recently being reported among children, adolescents, and adults.<sup>1</sup> Due to this significant rise, several specialized clinics have opened in many countries, with the most widely used approach being the “Dutch protocol.”<sup>2</sup> Health care providers' role consists of assessing gender diverse children and adolescents and supporting them in exploring and expressing their experienced gender, while psychiatric assessment is an unnecessary step.<sup>3</sup>

Blocking treatment with gonadotropin-releasing hormone analogs (GnRHa) plays a pivotal but still debatable role. When it comes to its use, the ethical considerations concern the principles of beneficence, non-maleficence, autonomy, justice, proportionality, integrity, and economic resources assignment.<sup>4</sup>

GnRHa can significantly reduce personal distress due to the mismatch between the gender

assigned at birth and the experienced gender, and the development of unwanted secondary sex characteristics.<sup>5, 6</sup> GD induces stressful experiences in social situations and is associated with an impairment in multiple daily functioning areas. The suppression of puberty seems to be an essential and protective step for the psychosocial wellbeing of gender-nonconforming youth as it reduces depression, anxiety, and suicidality associated with pubertal bodily changes.<sup>7-9</sup>

Overall, research has shown an improvement in psychological functioning during pubertal suppression and a reduction (or disappearance) of GD distress.<sup>10</sup> The use of GnRHa for those who will persist in their transgender identities is beneficial as it allows less invasive procedures in the future, promoting damage reduction.<sup>4</sup> While previous data before GnRHa treatment availability showed that the majority of patients were “desisters,” recent evidence shows that up to 100% of treated patients will eventually opt for a transgender identity.<sup>11</sup> Finally, some studies have reported increasingly harmful behavior when blockers are not used, and this is important when speaking of the principle of non-maleficence.<sup>12</sup> This last point is also relevant for the economic resources' assignment principle. The treatment with GnRHa appears to be cost ben-

efit compared to the cost of treatments related to self-harmful behaviors potentially associated with non-treatment. The same discourse that has been advanced for the principles of beneficence and non-maleficence could be applied to the potential advantages of treatment for the principles of justice, proportionality, and integrity.

Arguments against the use of GnRHa are related to the unknown long-term metabolic and endocrine effects and the psychological and developmental dimensions.

GnRHa could reduce bone mineral density (BMD) and increase the risk of osteoporosis in later life. However, studies have shown that even though a decline in age-related Z scores has been reported, there is no actual BMD change in transgender adolescents on long-term GnRHa therapy. Furthermore, adverse effects on bone mineralization can be reversed once gender-affirming hormones are started.<sup>13, 14</sup>

Puberty represents a critical period in terms of neurocognitive development, with evidence showing that estrogen and testosterone play an active role in brain maturation.<sup>15</sup> However, functional magnetic resonance imaging studies in adolescents with GD undergoing GnRHa show that GnRHa therapy does not affect executive functions' tasks; the long-term use of GnRHa does not result in long-term effects on cognition, self-perception, and behavior.<sup>16</sup>

Finally, puberty's suppression may distort the relationship to time in young persons. This may have both social and developmental implications as gender-nonconforming youth taking puberty blockers are "out of sync" compared with their same-aged peers, who continue into puberty while they remain in the prepubescent stage.<sup>14</sup>

Fertility concerns have also been raised, as the treatment with GnRHa during the early phase of puberty suspends germ cell maturation. The issue of fertility is a delicate one within the ethical debate as individuals on puberty suppression may have a desire for offspring, but at the same time, they may not want to advance into the wrong puberty with the gender assigned at birth. In this context, prepubertal cryopreservation is a good option but is still in the experimental phase.<sup>16</sup>

Even though guidelines exist, the complexity of the disease and its ethical and moral dilem-

mas still leave room for uncertainty. In this perspective, a recent court decision in the UK stated that clinicians must first seek court authorization to administer under 16s adolescents with GD on puberty blockers. This is a very relevant issue because of the particular implications in the domain of gender-affirming care. Patients seek this type of care at an increasingly young age, and they may not always agree with their family members with regards to the optimal course of treatment.<sup>4</sup>

Due to all the above considerations, while it appears mandatory that the presence of a pervasive and persistent GD pattern should be confirmed in highly specialized settings,<sup>12</sup> it is worth mentioning that GnRHa effects are primarily reversible overall. Since strong evidence show that a great deal of distress accompanies GD, providing no-treatment might be more harmful. In this perspective, GnRHa treatments present minor ethical challenges compared to the other non-reversible treatment steps, such as hormonal sex change or surgery, that may be considered at a later stage.<sup>17</sup>

Studies have highlighted the higher risk of suffering from mental health problems due to minority stress and discrimination due in part to the level of tolerance/acceptance of gender-variant behaviors in different cultures.<sup>18</sup> Specifically, the Italian context presents high levels of homo/transphobia, and Italian transgender and nonconforming people seem to experience one of the highest rates of transphobic verbal comments in Europe.<sup>19</sup> As far as treatment goes, Italian guidelines for GD adolescents are available.<sup>20</sup> It is possible to prescribe GnRHa to adolescents diagnosed with GD under specific conditions strictly defined by the Italian Medicines Agency in specialized centers. Unfortunately, the distribution of these centers on Italian territory is not even, leaving a significant proportion of patients without adequate access.

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*Conflicts of interest.*—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

*Authors' contributions.*—Ludovica Barbi and Gianluca Tornese have given substantial contributions to manuscript writing and revision. Both authors read and approved the final version of the manuscript.

*Acknowledgements.*—The authors acknowledge Atila Ratib for the English revision of the manuscript.

(Cite this article as: Barbi L, Tornese G. Ethical dilemmas of gonadotropin-releasing hormone analogs for the treatment of gender dysphoria. *Minerva Endocrinol* 2023;48:1-3. DOI: 10.23736/S2724-6507.21.03452-7)