Long-term Puberty Suppression for a Nonbinary Teenager

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Many transgender and gender-diverse people have a gender identity that does not conform to the binary categories of male or female; they have a nonbinary gender. Some nonbinary individuals are most comfortable with an androgynous gender expression. For those who have not yet fully progressed through puberty, puberty suppression with gonadotrophin-releasing hormone agonists can support an androgynous appearance. Although such treatment is shown to ameliorate the gender dysphoria and serious mental health issues commonly seen in transgender and gender-diverse young people, long-term use of puberty-suppressing medications carries physical health risks and raises various ethical dilemmas. In this Ethics Rounds, we analyze a case that raised issues about prolonged pubertal suppression for a patient with a nonbinary gender.

Referrals of transgender and gender-diverse (TGD) children and adolescents to gender clinics worldwide have grown dramatically in the past decade as societal awareness of gender diversity has increased and relevant clinical services have become available.[1,2] At the same time, it has become apparent that many TGD young people have a gender identity that does not conform to the binary categories of male or female; that is, they have a nonbinary gender identity.[3–5] Some nonbinary individuals are most comfortable with an androgynous gender expression. For those who have yet to fully progress through puberty, puberty suppression with gonadotrophin-releasing hormone agonists (GnRHa) can support an androgynous appearance. Although such treatment is shown to ameliorate the gender dysphoria and serious mental health issues commonly seen in TGD young people, long-term use of puberty-suppressing medications also carries physical health risks and raises various ethical dilemmas. In this Ethics Rounds, we present a case that combines features of several real cases that raised issues about prolonged pubertal suppression for a patient with a nonbinary gender. We then ask clinicians and experts in bioethics from The Royal Children's Hospital in Melbourne, Australia; the Uehiro Centre for Practical Ethics at Oxford University in the United Kingdom; and The University of British Columbia to comment on the case.

THE CASE

EF is a physically well, academically bright 15-year-old. EF was assigned male at birth but has for many years had a nonbinary gender identity and preferred the use of gender-neutral "they" and "them" pronouns.

As a preschooler, EF displayed gender-diverse behaviors and struggled to identify with being exclusively male or female. At primary school, they initially presented as male, but this did not feel

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right. During this time, with parental support, they identified and dressed as a girl at home. This did not feel right either. EF became increasingly unhappy, prompting a referral to their local gender service, where they received a diagnosis of gender dysphoria and have had ongoing psychiatric and pediatric support.

Soon after attending the gender service, EF began to identify as agender (ie, they saw themselves as neither male nor female). With the support of their family, friends, and the school community, they have lived full-time as such ever since, although with their long hair and tendency to wear dresses, they are often regarded as female by strangers. EF's mental health had been good with only minor discomfort associated with their male genitalia.

The onset of puberty at age 11 was associated with worsening gender dysphoria and increased anxiety about possible voice deepening and facial and body hair growth. EF regarded these masculinizing changes as inconsistent with their agender identity and was therefore keen to commence GnRHa to suppress further pubertal development. Relevant counseling with their pediatrician and psychiatrist included discussion of the possible benefits and harms of commencing GnRHa therapy. Eventually, both EF and their parents provided assent and consent to commence GnRHa. Treatment was started at age 12 while EF was at Tanner stage 2.

At age 15, EF remains on regular GnRHa treatment. The dysphoria and anxiety have diminished. Annual dual-energy radiograph absorption scan monitoring has shown that their bone mineral density has regularly fallen and is now in the lowest 2.5 percentile, although there have been no fractures. EF, whose desire for biological children in the future remains unclear, wishes to continue puberty suppression until they are at least 18 years old under the care of their gender service. Their clinicians contact the clinical ethics consultation team to ask, "Is that appropriate?"

Lauren Notini, PhD, Rosalind McDougall, PhD, and Lynn Gillam, PhD, Comment

The key question in this case is whether it is ethically justifiable for clinicians to offer puberty blockers long-term to EF.

In many health care situations involving young people, questions of capacity arise. The issue of whether EF has the capacity to consent to puberty blockers on their own behalf is 1 element of this case. However, in our view, it is not the most ethically important nor the most ethically complex aspect of this situation. The capacity question is relevant only insofar as it determines who can provide consent to the intervention. The more ethically complex aspect of this case is whether the intervention should be provided even with the consent of EF or their parents. We will therefore assume that EF's parents will consent to long-term blockers if EF is not capable of providing their own consent. We focus, then, on the question of whether offering blockers long-term is justified.

In this case, there is the range of possible pathways for EF's care with substantial uncertainty about the risks and benefits of each approach. There is currently a lack of evidence about the impact of using puberty blockers long-term. But we can speculate.

If EF does use blockers long-term, there seem to be 2 main risks: impaired fertility in the future and low bone density. There is 1 primary benefit: treatment could continue to alleviate EF's gender dysphoria and anxiety. How that should be weighed against the risks depends on the magnitude and seriousness of the harms that could result.

EF's bone density has already fallen to the lowest 2.5 percentile. It can be expected to continue falling. Although EF is at increased risk of fractures, this needs to be put into perspective. According to 1 calculator, a 50-year-old birth-assigned male with a bone density in the lowest 2.5 percentile has a 0.2% to 0.3% risk of sustaining a hip fracture and a 1% to 2% risk of other fractures in the next 5 to 10 years compared with a control with normal bone density (0% risk of hip fracture and 0.7%–1% risk of other fractures in the next 5–10 years).[1] This calculator is based on data from older adults who have gone through puberty; hence, how low bone density affects EF's actual risk of fractures is unknown. Nevertheless, even if EF's risk of fractures is higher than these statistics, EF and/or their parents may still decide that these risks are outweighed by the potential psychosocial benefits of EF having a body that fits their nonbinary identity.

Alternatively, EF could discontinue blockers and recommence male puberty. Or they could begin estrogen and a transition to a female phenotype. These options could address the bone density concerns described above to some degree. Although adolescents who have received puberty suppression experience an increase in bone density after estrogen or testosterone therapy, their bone density is still below that of age-matched peers.[2] It is not known whether their bone density catches up later. An ethical problem with this approach is that EF would develop unwanted secondary sexual characteristics. Their gender dysphoria and anxiety will likely return, potentially increasing their risk of self-harm or suicide.[3] The trade-off here is thus between EF maintaining normal bone density with increasing gender dysphoria and EF using medication to relieve gender dysphoria but increasing the risk of bone fractures.

A third option is that EF could remain on blockers for another year or 2 only to give EF more time to consider their gender identity and future options. This presents less risk to bone density than if EF remained on blockers long-term and so would be more ethically justifiable. However, it may not resolve the issue. EF may continue to identify as nonbinary and not be willing to discontinue blockers at a later stage.

There is another option that appears to avoid the trade-off between bone health and psychological well-being. EF could remain on blockers long-term while receiving medication known as selective estrogen receptor modulators (SERMs). Because SERMs have estrogenlike actions in certain tissues (eg, bone) but not others (eg, breasts),[4] they could theoretically promote improved bone density while preventing the development of unwanted secondary sexual characteristics, allowing EF to continue to psychosocially benefit from blockers. On the other hand, SERMs are typically only used in much older patients to treat breast cancer, osteoporosis, and menopausal symptoms, although they have been occasionally used to treat boys who develop gynecomastia during puberty.[5] They have not been used in conjunction with puberty blockers in young patients such as EF. SERMs are also associated with side effects of their own, including hot flashes and increased risk of blood clots.[4] There is also some evidence that tamoxifen, a type of SERM, can be associated with cognitive impairment in women being treated for breast cancer.[6] This risk could potentially be exacerbated in the developing adolescent brain.

Notwithstanding these potential risks, the possibility of using SERMs to achieve the body shape that EF wants, while avoiding the problem with bone density, is attractive. It seems to have mostly ethical pros and minimal ethical cons, according to the terms in which we have framed the ethical issue.

Dealing with the straightforward concern about bone density allows other, deeper ethical questions to emerge. Is it ethically justifiable to use medical interventions to support nonbinary gender identity on a permanent basis? Or is there some ethically significant difference between nonbinary gender identity and binary transgender identity? For example, critics might argue that nonbinary bodily appearance in adults is just too different from what is "natural" and that creating such an appearance does not fall within the proper goals of medicine. In contrast, on this view, binary transgender identity does involve a desire for a "natural" bodily appearance (albeit not the 1 that matches the bodily appearance at birth) and so can be regarded as consistent with the proper goals of medicine. We do not find this argument convincing, but we do see that there is as important question to answer. But that question is beyond the scope of this essay.

Overall, then, using SERMs to support EF in their nonbinary gender identity long-term looks to be the most ethically justifiable option, although it is not without its own ethical complications.

Julian Savulescu, PhD, and Dominic Wilkinson, FRACP, PhD, Comment

The basic ethical principle of medical ethics is that doctors should offer patients treatments that are in their best interest. Best interest clearly includes not just the treatment of disease but the psychosocial well-being of the person. Doctors are not under an ethical or legal obligation to offer interventions that are not in the best interest of the patient. So, the central ethical question in this case is whether continued hormonal suppression of puberty for EF, with an increasing risk of osteoporosis and fractures, is in their best interest. Biologically, it is not. Continuing puberty suppression poses some significant health risks. The issue is whether the psychosocial benefits outweigh the biological harms. This requires a deep exploration of the patient's psychology, conscious and unconscious motivations, values, capacity for psychological change and adaptation, and the nature of their social relationships.

Philosophy can contribute to the analysis of such a case through theories of the meaning of well-being. There are 3 main theories of well-being: hedonistic, desire fulfillment, and objective list. According to hedonistic theories, what matters is happiness and pleasure. For desire fulfillment, the good of a person lies in that person satisfying their deepest and strongest desires. According to objective list theories or perfectionistic theories, what is good for a human being is to be engaged in certain meaningful activities, like deep personal relationships, having and raising children, being creative, or being morally good.

A person's psychology places certain boundaries on what can be good for them. For example, if a person deeply does not wish to be a parent, then having children could be bad for that person and their children. For another person, having children could be good.

However, it is not merely present psychology and a person's occurrent wishes that determine their well-being. Psychological development may open new possibilities for greater well-being. In this regard, extensive psychological analysis and counseling is necessary. Lemma[7] notes that some transgender cases represent deep conflicts about identity and other unconscious conflicts. A psychological assessment can assist in identifying whether transitioning to another gender or, in this case, delaying puberty is best for this patient.

In many cases, it will not be clear what is in the best interest of the patient.[8] Because of pluralism in value and different valuing of risk, it can be ambiguous as to which course of action is best. The second principle of medical ethics is that patients should make their own autonomous decisions about the medical treatments offered to them. When it is uncertain whether a course of action is in the interest of the patient, doctors should defer to the autonomous evaluations of the patient.

Autonomy is self-determination. It is about forming one's own values and choosing from a range of options what one believes will make one's own life best (or acting morally). It is not mere choice: many of our choices do not promote our values. Values are what we rationally endorse: what we believe is valuable when we have all the facts, are thinking logically, and are vividly imagining the alternatives. Importantly, autonomy requires a concept and understanding of the self, the being whom choice will affect. Autonomy involves the matching of the world to that self.

EF is 15 years old, and it is not clear what their level of cognitive development is. Moreover, full autonomy, even for adults, requires a deep understanding of both conscious and unconscious desires and motivations. It requires not only understanding of the world (in this case, the medical options and their consequences) but of oneself. The importance of psychological analysis is again central to such cases.

Just as it may not be clear whether a choice is in the best interest of the patient, it may not be clear whether that choice is fully autonomous. In such cases, we should defer to the desires of a competent patient or, if they are incompetent, their competent surrogate (in this case, the parents).

Where does that leave us? In cases like EF's, we suggest that there is deep uncertainty around the question of whether continued puberty suppression is in their best interest and whether their desire for this is autonomous. What should we do then? When either the implications of a medical intervention for well-being are unclear or the extent of the autonomy of the patient is not fully determined, we contend that there is a moral obligation to scientifically study such interventions to determine their impact on well-being or the degree of autonomy. That is, the intervention should be as rigorously studied as possible.

The gold standard for scientific research is the randomized placebo-controlled trial. A controlled trial would be preferable to either uniformly providing or denying this treatment. It would promote the interests of young people with gender dysphoria, both now and in the future, through generating evidence about the benefits and harms of treatment. But such trials are not always feasible. If EF did not wish to enter a trial, a case-control design might be employed. Research would reduce uncertainties about whether such interventions are in the best interest of the patient. Without good outcome data, we leave EF's fate to guesswork. This approach would almost certainly result in harm to some patients, now and in the future.

Some people analyze dilemmas such as this by relying on a distinction between "treatment" and "enhancement." We reject that approach. Even if gender dysphoria is not a disease in the strict medical sense, the use of puberty blockers might be an instance of an enhancement that promotes well-being.[9]

Beth A. Clark, PhD, HEC-C, RCC, and Johanna Olson-Kennedy, MD, Comment

We provide an analysis using a clinical ethical decision-making framework to identify a path forward for EF, their family, and their care team.[10]

Step 1: Identify ethical concerns. Continuation of pubertal suppression, although beneficial for alleviating distress, preventing secondary sex characteristic development, and providing time for decision-making about fertility and family creation, may be inappropriate because of diminishing bone density.

Step 2: Gather relevant information. EF has received care consistent with current guidelines, including assessment of needs and pubertal suppression. This has improved their quality of life, and EF's stated preference is to continue pubertal suppression. Discontinuing puberty blockers without other interventions would result in the development of a testosterone-directed puberty (eg, lower voice, facial hair, and larger stature) that is either permanent or would require surgical intervention to change. It is well understood that the development of secondary sex characteristics that are not aligned with gender identity causes suffering for many transgender individuals.[11] Potential effects of long-term pubertal suppression monotherapy on bone density are unclear; however, with shorter-term use (2 years), bone density increases significantly once sex hormones are introduced.[12] Some clinicians recommend limiting suppression to 2 years to promote optimal bone density.[13] Although the benefits of pubertal suppression are clearly established,[14] EF will need to experience sex hormones at some point.

Autonomy is supported through timely access to information that is necessary for informed decision-making.[15] EF likely has the capacity to make decisions regarding their care and should be supported in this by their parents and care team. It is

unknown whether EF and their parents have received adequate information regarding known and unknown implications of extended pubertal suppression and the temporary nature of this intervention and whether they have been engaged in fertility and family-creation counseling.[1,13,16,17]

Decisions about EF's care are being made in a societal context of increasing affirmation of transgender experiences and availability of gender-affirming care. However, gender-affirming care remains largely focused on binary experiences, contributing to excessive barriers and health inequities for nonbinary (including agender) youth.[15,18] Decision-making may be impacted by a lack of information regarding gender-affirming care options for nonbinary people. Care planning that validates nonbinary experiences and explores a range of options, including not taking exogenous hormones (known as "noho") and low-dose hormone regimes (known as "loho"), is essential for promoting justice.

It is vitally important to respect EF's experience of gender and goals of care because only EF can know their own gender. However, although patients generally have a negative right to refuse unwanted interventions, they do not have a positive right to demand unreasonable treatment.[19] EF's clinicians must consider whether the request to continue pubertal suppression as a monotherapy is medically reasonable and balance this with their fiduciary duty to EF. The path forward should epitomize an ethic of care to avoid harm to relationships and/or fostering distrust of health care providers through perceived abandonment.

Step 3: Identify options. We have identified 3 potential courses of action: (1) immediately stop pubertal suppression, (2) continue pubertal suppression monotherapy until age 18, or (3) make a decision about sex hormones now.

Step 4: Consider consequences. First, a unilateral decision by the team to immediately halt pubertal suppression without a clear and imminent health risk carries potential for both triggering a mental health crisis and neglect of fiduciary duties. We also find the second option, continuation of pubertal suppression as a monotherapy until age 18, insupportable because "kicking the can down the road" (ie, delaying inevitable decision-making) is likely to have detrimental effects and may not yield significant long-term benefits. Third, making a decision about sex hormones in the short-term could result in benefits for bone density, access to decisional support from family and familiar care providers, minimization of harms, and promotion of fidelity.

Step 5: Make, implement, and evaluate a choice. We support a gender-affirmative approach with a care plan that involves the following: creating space to explore the complexities of gender and the full range of appropriate medical and nonmedical options, making a decision about sex hormones (ie, endogenous or exogenous; alone or in combination with pubertal suppression), and ceasing pubertal suppression as a monotherapy in a supportive manner. Via an ethic of care, the team can communicate that they trust EF to decide what will help them live most comfortably, but long-term pubertal suppression is not possible because of negative health effects. They can work with EF to clarify specific goals around primary and secondary sex characteristics and provide supportive counseling related to hormones options, fertility, family creation, pubertal changes, and/or potential distress. Taking a narrative ethics approach, EF can be supported in envisioning a range of possibilities and feeling empowered to author their unique gender journey.[20]

John D. Lantos, MD, Comments

The case and comments illustrate the complexity of providing medical care in the absence of a strong scientific evidence base for making choices. Ideally, we would know the long-term physical and psychological consequences of various interventions and their corresponding noninterventions. Then, at least, we could base a risk-benefit assessment based on facts. In this case, uncertainties abound. Experts must make recommendations on the basis of speculation and extrapolation. Furthermore, the nature of treatment options in cases like this are such that randomized trials are likely infeasible. All we can hope for are cautious clinical judgments, shared decision-making, and careful evaluation and reporting of outcomes after different choices are made.

ABBREVIATIONS

GnRHa: gonadotrophin-releasing hormone agonists
SERM: selective estrogen receptor modulators
TGD: transgender and gender diverse

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