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Review

Gender-affirming endocrine care for youth with a nonbinary gender identity

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***Abstract*:** Nonbinary individuals, or those who identify outside of the traditional gender binary, are currently present in up to 9% of the general population of youth or up to 55% of gender-diverse youth. Despite the high numbers of nonbinary individuals, this population continues to experience barriers to healthcare due to providers' inability to see beyond the transgender binary and lack of competence in providing nonbinary care. In this narrative review, we discuss using embodiment goals to individualize care of nonbinary individuals, and review hormonal and nonhormonal treatment options for gender affirmation. Hormonal treatments include those often used in binary transgender individuals, such as testosterone, estradiol, and anti-androgens, but with adjustments to dosing or timeline to best meet a nonbinary individual's embodiment goals. Less commonly used medications such as selective estrogen receptor antagonists are also discussed. For nonhormonal options, alterations in gender expression such as chest binding, tucking and packing genitalia, and voice training may be beneficial, as well as gender-affirming surgeries. Many of these treatments lack research specific to nonbinary individuals and especially nonbinary youth, and future research is needed to ensure safety and efficacy of gender-affirming care in this population.

Keywords: adolescent gender care, hormone replacement, nonbinary gender identity hormone replacement

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Introduction

Nonbinary is a term that describes someone who identifies outside of the traditional gender binary.[1] There are several other terms used, such as genderqueer, genderfluid, agender, two-spirit, often from non-Western societies with centuries-old practice of nonbinary persons being present in their societies.[2] For the purposes of this review, we use nonbinary to encompass all identities outside of the binary but recognize that this term may not be accurate for all.

Prevalence

The prevalence of nonbinary youth depends upon the base population studied. In addition, it depends upon how people were asked about their gender, such as whether only binary choices were given or whether there was a space provided to identify outside the binary. Table 1 shows studies of youth between school age and 25 years that specifically provided an option to identify other than cisgender or transgender. When surveying a general population, the prevalence of self-reported nonbinary identity in this age group is between 1% and 9%.[3–5] However, one study showing a 9% prevalence recruited from lesbian, gay, bisexual, transgender, queer or questioning (LGBTQ)-friendly websites which may have led to selection bias.[5]

Within a surveyed population of gender-diverse youth, between 40% and 55% self-identify as nonbinary.[6,7] Within a population of youth seeking care at a gender clinic, <15% of them self-identify as nonbinary.[8,9] The reasons underlying the discrepancy between the prevalence of nonbinary youth seen at a gender clinic compared with the community are not known. Potential reasons may be barriers to care in clinics catered for a transgender population, or that some nonbinary persons may not feel that medical treatment is needed to affirm their gender identity.

Table 1. Prevalence of nonbinary youth.

Study	Country	Year	Recruited population	*N*	Age (years)	Prevalence of self-reported nonbinary (%)
Base population = All youth						
Kidd *et al.*	USA	2018	Urban school	3168	14–18	2.9
Hughes *et al.*	Scotland	2017	National school sample	1195	12–24	1
Aparicio-Garcia *et al.*	Spain	2018	Community	782	14–25	9
Base population = Gender-diverse youth						
Clark *et al.*	Canada	2013–2014	National sample	839	14–25	41
Rimes *et al.*	UK	2012–2013	National sample	677	16–25	53.4
Base population = Youth receiving care in gender clinics						
Handler *et al.*	USA	2015–2018	Referral to gender clinic	417	4–17	13
Twist *et al.*	UK	2016–2017	Pts at gender clinic	251	12–18	12

Similar studies in adults show slightly lower prevalence than nonbinary youth, with results showing 0.18–4% self-identified nonbinary adults in the general population,[10–13] 9–35% in a population of gender-diverse adults,[14,15] and 29% in a population seeking care at a gender clinic.[16]

These studies indicate that the prevalence of nonbinary youth has increased over the last several years. It is unknown whether the increase in prevalence noted by these studies is due to improvement in identifying persons with a nonbinary identity or a true increase in numbers of people with nonbinary identity.[3,8]

Mental health

There have been several studies evaluating mental health in gender-diverse youth; two studies have evaluated nonbinary youth comparing with binary transgender youth. One study evaluated adolescents and young adults aged 16–25 referred to the UK national transgender health services.[17] The participants completed scales assessing anxiety, depression, self-esteem, and perceived social support. Compared with those with binary gender identities, nonbinary persons scored higher in anxiety and depression, lower in self-esteem, and similarly in social support.[17]

Another study included youth aged 12–24 who sought services from the Trevor Project, a national gender and sexual minority crisis prevention service.[18] Of the 589 youth recruited, 261 were gender-diverse, with roughly one half of that group nonbinary identified. When using cisgender as the reference, the nonbinary and binary transgender youth had an odds ratio more than 2 for reporting a prior suicide attempt.[18]

Healthcare experiences

Nonbinary youth also may experience transgender dedicated healthcare differently than binary transgender youth. A qualitative study of young adults accessing transgender targeted health services found that nonbinary youth noted providers' inability to see beyond the transgender binary, lack of competence in providing nonbinary care, use of the transgender label, and inadequacy of gender care services altogether.[19] These experiences are in addition to the barriers to healthcare faced by gender diverse youth as a whole, including few pediatric providers trained in gender-affirming care,

uncoordinated care, and delayed access to care.[20] Due to these barriers, one study found that nonbinary youth were less likely than binary transgender youth to have a primary care provider who knows they are gender diverse, less likely to take hormone therapy, and more likely to forgo healthcare in young adulthood.[6]

Embodiment goals

Hormone treatment is an important intervention to improve gender dysphoria and affirm sense of self for many but not all gender-diverse persons. Some studies indicate that nonbinary identifying individuals experience less gender and body-specific dysphoria and therefore do not seek gender-affirming hormonal treatment,[21] while other studies suggest that the binary framework of gender-affirming care deters nonbinary persons from seeking potentially affirming care.[21,22] Nonbinary adults who seek care in gender-affirming centers have similar motives for desiring gender-affirming hormonal treatment as transgender adults and express negative mental health consequences if the gender-affirming treatment is not fulfilled.[23] Nonbinary adults are more likely to state that a medical or surgical treatment is not pursued because treatment would not be affirming, while transgender adults are more likely to state that treatment is not pursued because of cost or potential adverse effects.

In providing respectful healthcare for nonbinary persons, we as providers must adjust our language to avoid the binary delineation of gender, in addition to using chosen pronouns and names. Terminology has changed significantly over the last several years. Previously, common terms such as 'gender nonconforming' implied that gender should conform to our binary constructs of gender. Similarly, terms such as 'transition' and 'cross-sex hormones' are rooted in the idea that a person journeys from one binary gender to another, without leaving space for those who do not fall into those binary categories. Newer terms such as 'gender diverse' and 'gender-affirming' are more inclusive without having binary connotations.

In discussions of potential affirming hormonal therapies in individuals with gender incongruence and the physical changes that occur, phrases such as masculinizing and feminizing are often used, but these phrases are binary and nonspecific. What is feminine and masculine may have different meanings to each individual. Instead, using language that is specific to body parts and physical changes is more accurate, descriptive, and inclusive. In this way, providers can ask questions about what specific changes to specific body parts would be affirming, for example, asking about 'embodiment goals'. Gender embodiment has been defined as the shape, feeling, and behavior of one's body.[24] A Gender Embodiment Scale has been developed to help assess and discuss embodiment goals, which can then be used to guide hormonal and nonhormonal treatments, if desired.[24] The Gender Embodiment Scale asks patients to rate both importance and satisfaction in up to 42 items, such as 'a drop in my voice', 'fertility status', 'being consistently read by strangers as a cis man', 'being read by strangers as trans and/or gender diverse'.[24] Asking questions in this manner can help to discuss affirming features, rather than using phrases like transition which implies a binary identity.

Hormonal treatment options

Gender dysphoria upon puberty onset is associated with a persistence into adulthood which is the basis for medical intervention in adolescents to relieve the experienced gender dysphoria and associated mental health consequences.[25,26] Medical treatment of gender-diverse adolescents can be considered after the diagnosis of gender dysphoria is made by a qualified professional and according to WPATH and Endocrine Society guidelines.[25,26] Treatment of nonbinary adolescents requires specific knowledge of their embodiment goals and discussion with the adolescent of feasible goals that can be reached with hormone treatment. One of the major challenges of achieving one's gender embodiment goals is that each person may have a different physical response to a hormonal treatment, as we often see different levels of hormones among individuals on the same formulation of a medication at the same dose.[26–30] In addition, there is a differential tissue response to hormone levels due to different hormone receptor activities in the case of estrogen, limiting ability to isolate and target certain areas of the body for specific hormone responses.[31] Topical application of hormones to a specific organ still results in systemic absorption leading to systemic changes. Counseling of individuals should occur to discuss these limitations upon developing a

plan for an individual to help attain their gender embodiment goals, with close follow-up to discuss physical changes, gender dysphoria, and mental health and adjust the treatment plan accordingly.

Multiple resources outline recommendations for gender-affirming hormone therapy using gonadotropin-releasing hormone agonists (GnRHa) as puberty blockers, testosterone for transmasculine persons, and estradiol and anti-androgens for transfeminine persons.[25,26,32] These guidelines provide target hormone doses and levels meant for those desiring full effects of estrogen or testosterone on the body. There are no published protocols or data on body and mental health outcomes in persons who do not elect full hormone replacement. In this section, we review treatment options that have been used alone or in combination in treatment of nonbinary persons.[33] Because treatment is individualized, many of these treatments lack high-quality evidence for use in gender-affirming care. However, with an understanding of the physiology or the hormonal effects and pharmacology of the medications, tailored treatment regimens can be attained.

Gender-affirming hormones

For nonbinary individuals assigned female at birth, testosterone remains a common choice for gender affirmation. Some may desire full effects of testosterone with levels in typical adult ranges, similar to treatment frequently used in transgender males,[26] many nonbinary individuals may want only some of these effects. This can sometimes be achieved by using low doses of testosterone or only using testosterone for a short time to achieve some permanent physical changes such as voice deepening. Using low doses is often called microdosing in the gender-diverse community, but there is no clear definition of what dosing constitutes this. Many providers use subcutaneous testosterone 20 mg once a week as a low dose for starting testosterone, which could be considered a microdose.[32] While some adolescents taking testosterone may start on this dose and increase over time, some may choose to maintain this dose for microdosing. Because it is difficult to predict the changes that will happen at any given dose or duration of treatment, it is important to review all the potential effects of testosterone and that any of those changes may occur with treatment. Moreover, there are no long-term data on potential side effects of maintaining low levels of sex steroids rather than adult levels, particularly in regard to bone health. For individuals who are taking GnRHa or who have had gonadectomy, there are no data to show the lowest dose needed to maintain bone health. There are no guidelines recommending a minimum dose for gender-diverse individuals or cisgender individuals with hypogonadism.

For nonbinary individuals assigned male at birth, similar strategies for using estradiol at lower doses or for short term can be tried, though the same challenges with variable effects apply. Breast development is the main permanent physical effect from estradiol, and even this breast tissue may decrease a little bit if estradiol is discontinued, so a short course of estradiol is likely less beneficial unless some breast development is the primary goal.[32] An estradiol dose of 0.5–1 mg oral or 12.5–25 μg/24 h transdermal patch may be considered a microdose in youth.[32] There are similar concerns about long-term effects on bone health for individuals using low-dose estradiol, especially those who are on GnRHa or who have had gonadectomy. In postmenopausal cisgender women, a low estradiol dose of 25 μg/24 h transdermal patch has been shown to increase bone mineral density and decrease bone turnover, but this has not been studied in younger individuals or in gender-diverse populations.[34,35] In premenopausal cisgender women with anorexia, 100 μg/24 h transdermal estradiol for 1 year improves bone mineral density to the same degree as nonhypoestrogenic ciswomen, but lower doses have not been studied.[36]

GnRHa

GnRHa are frequently used to pause endogenous puberty progression in pubertal gender-diverse youth to prevent physical changes of puberty that do not align with gender identity, and to allow additional time for gender exploration if needed.[26,37,38] GnRHa have benefits in gender-diverse youth including improved psychosocial functioning and lower rated of lifetime suicidal ideation.[39–41] However, GnRHa are generally used as a temporary treatment when used alone. GnRHa use in gender-diverse adolescents has been shown to decrease bone mineral density,[42,43] and sex steroids are needed to improve bone health long term.

Some nonbinary individuals may have goals for an androgynous physical appearance, and may not want the effects of testosterone or estradiol. Pang

et al. explored the unknowns and the ethics of this situation in two thoughtful articles.[44,45] The first article explored this scenario in a person over 18 years, and reviewed potential harms (decreased bone density, impaired fertility and sexual function, possible metabolic effects, possible psychosocial and cognitive effects) and benefits (preventing irreversible puberty changes, preventing need for future surgeries, improving overall psychosocial functioning).[44] The second article asked the co-authors to provide opinion on what they would do in this situation and discuss the ethics surrounding the decision-making.[45] The views varied from recommending selective estrogen receptor modulators (SERM) to promote bone health with lesser chance of breast development, develop a research paradigm to study cases such as this prospectively, state that humans experience puberty, present possible options, and proceed with a therapeutic plan that lowers bone health risk and minimizes body changes.[45] Ultimately, the authors agreed that long-term use of GnRHa was not a reasonable choice, and that the nonbinary individual could be supported with a number of other treatment options that could be individualized to their embodiment goals.[45]

Menstrual suppression

Menses can be a source of distress for gender-diverse youth, and several hormonal medications are frequently used for menstrual suppression.[46] These medications include progesterone-only oral pills (norethindrone, norethindrone acetate), injections (depot medroxyprogesterone acetate), or implants such as intrauterine devices. Intrauterine devices can be placed at any age after menarche occurs and have been studied in adolescents as young as 13 years.[47] Combined oral contraceptive pills are also effective for menstrual suppression when used continuously, skipping the placebo week. Some nonbinary youth assigned female at birth may choose menstrual suppression alone or in combination with other options. While these medications are generally safe and effective, there are some concerns for low bone density in long-term use of depot medroxyprogesterone acetate injections,[48] which should be considered if menstrual suppression alone is being used long term.

Anti-androgens

Anti-androgens such as spironolactone, finasteride, and bicalutamide are typically used in conjunction with estradiol for feminizing therapy to decrease androgen action, as estradiol alone does not sufficiently suppress testosterone production at physiologic levels.[32,49] In nonbinary individuals assigned male at birth, anti-androgens may also be beneficial to use in conjunction with low-dose estradiol to decrease facial hair and body hair or to use alone, though there are little data to support the efficacy of this. Some of these medications may induce breast development even when used alone due to increasing testosterone levels and aromatization to estradiol, especially bicalutamide due to potency.[50] This should be discussed as a potential effect in relation to the individuals' embodiment goals.

SERM

Another medication group with potential therapeutic utility is SERMs. SERMs bind estrogen receptor alpha and beta with different affinities and can have estrogen agonistic effects and antagonistic effects in different tissues. The majority of the research available on SERMs is from their use in cisgender women with breast cancer or osteoporosis,[51] with little research available for use of SERMs in gender-affirming care.[52] The three available SERMs are tamoxifen, most often used for breast cancer treatment, and raloxifene and lasofoxifene which are used for treatment of osteoporosis.[52] All of these SERMs are antagonistic in breast tissue, agonistic or neutral on bone health and fat distribution, and variable on skin effects.[51,52] One of the main side effect considerations of SERMs is an increased risk of deep vein thrombosis, but this has only been evaluated in cisgender women.[51,52]

In gender-affirming care for nonbinary individuals, SERMs may be beneficial for someone AMAB who desires estrogen-induced changes in skin and body fat redistribution, but does not desire any breast development. Raloxifene has estrogen agonist effects in skin and fat distribution and can be tried alone for these effects, but data are lacking on the degree of physical results that may occur.[52] SERMs can also be in combination with estradiol for more effects on skin and fat distribution, with the antagonistic effect on breast tissue to theoretically decrease in breast development that would typically occur with estradiol. Again, there is no available research in the use of SERMs in this population, and potential risks (known and unknown) must be considered.

Another use of SERMs in gender-affirming care could be in nonbinary youth AFAB who do not

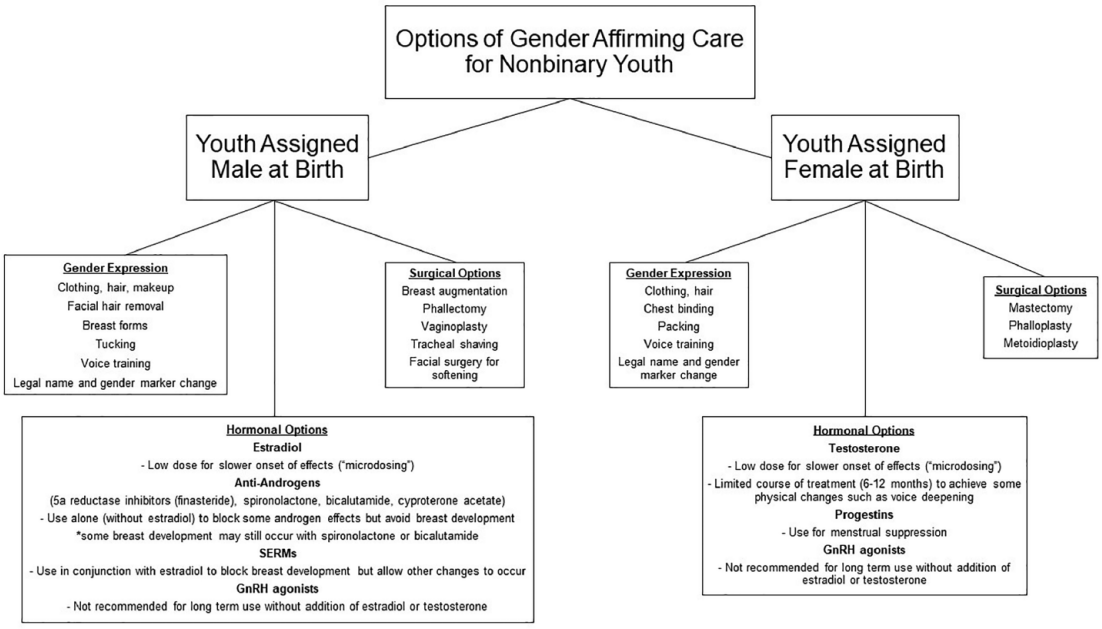

Figure 1. Medical and nonmedical treatment options for nonbinary youth.

desire effects of estrogen or testosterone. For someone who has begun treatment with a GnRHa and does not desire to discontinue treatment or start testosterone, the addition of an SERM may be a temporary solution to provide estrogen agonist effects on bones without leading to breast development.[45,52] It is unclear whether SERMs alone would be sufficient to prevent breast development in a pubertal youth AFAB.[52] Data on use of SERMs in this context are also lacking, and it is unclear the degree to which this would improve bone density and the length of time this may be a reasonable treatment option.

Nonhormonal treatment options

There are several nonhormonal options to affirm gender identity, including outward gender expression involving clothing and hair, and practices such as binding chests, tucking and packing genitalia, hair removal, and voice training.[53] These nonhormonal options can be used alone or in conjunction with hormonal options for nonbinary individuals.

Legal gender affirmation, such as name change and gender marker change, can also be a way to affirm gender identity. The gender marker 'X' which may be most representative of nonbinary persons is available on US passports as of April 2022, in addition to driver's licenses and birth certificates in many states.[54,55]

Surgical gender affirmation is used by many gender-diverse individuals, including those who are nonbinary. Some nonbinary persons may opt for surgical treatment with or without hormonal intervention. Gender-affirming surgeries are associated with improved mental health outcomes in gender-diverse adults, including nonbinary individuals.[56] Previously, guidelines recommended gender-affirming surgery only after a patient received gender-affirming hormone therapy for a certain time period. Recent guidelines made an exception for those individuals who do not desire the effects of gender-affirming hormones because they are not consistent with the patient's goals or gender identity, proving more options for care for nonbinary individuals.[25] It is important to note that any gender-affirming surgery that includes removal of gonads would require sex hormone replacement to prevent the negative effects of prolonged hypogonadism on bone health. The age and timing of surgical gender affirmation is an individual decision informed by local or national laws that regulate surgery directly affecting future fertility.

Future needs

The classic guidance for treatment of nonbinary persons is to individualize the treatment based on the person's embodiment goals (Figure 1). While this is true of any gender-diverse individual, there are very few studies of effects and safety of

gender-affirming hormone therapy at lower doses that may be desired by nonbinary individuals, giving uncertainty to the safety of these treatments. Any outcome data on hormonal replacement for cisgender or transgender adolescents currently inform care for nonbinary persons, but specific research on nonbinary outcomes is needed. Heterogeneity of nonbinary population may preclude these studies, and variability in testosterone and estradiol lab assays also make this challenging. As the prevalence of nonbinary individuals is increasing, we are hopeful that more research will be possible to guide sage and effective care for this population.

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Juanita K. Hodax: Conceptualization; Writing – original draft; Writing – review & editing.

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