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## Psychopharmacological Considerations for Gender-Affirming Hormone Therapy

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### Abstract

The field of transgender health has grown exponentially since the early 2010s. While this increased visibility has not been without controversy, there is growing acknowledgement of the needs of transgender, nonbinary, and gender expansive (TNG) patients and the health disparities they experience compared to the cisgender population. There is also increased interest among clinicians and trainees in providing gender-affirming care in all medical specialties. This is particularly relevant in psychiatry as mental health disparities in TNG patients have been well-documented. TNG patients experience significant minority stress and higher rates of psychiatric illness, self-harm, suicidality, and psychiatric hospitalization compared to their cisgender peers. In this review, we will cover potential interactions and side effects relevant to psychiatric medication management for the three most common medication classes prescribed as part of gender-affirming hormone therapy (GAHT): gonadotropin-releasing hormone receptor agonists, estradiol, and testosterone. Although no studies directly examining the efficacy of psychiatric medications or their interactions with GAHT for TNG patients have been published yet, we have synthesized the existing literature from both cisgender and TNG patients to shed light on health care disparities seen in TNG patients. Since clinicians' lack of comfort and familiarity with gender-affirming care contributes significantly to these disparities, we hope this narrative review will help psychiatric prescribers provide TNG patients with the same quality of gender-affirming care that cisgender patients receive.

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## Keywords

transgender; gender-affirming hormone therapy; LGBTQIA+; psychopharmacology

## INTRODUCTION

Transgender, nonbinary, and/or gender expansive (TNG) people experience higher rates of psychiatric comorbidities compared to their cisgender counterparts. These include psychiatric problems often directly related to marginalization and discrimination, such as generalized anxiety, social anxiety and panic attacks,<sup>1</sup> depression,<sup>2,3</sup> posttraumatic stress,<sup>4</sup> substance use disorders,<sup>5,6</sup> prescription drug misuse,<sup>7</sup> non-suicidal self-injury,<sup>8</sup> and suicidality.<sup>3</sup> TNG people also experience higher rates of bipolar disorder, schizophrenia, obsessive-compulsive disorder,<sup>9</sup> attention-deficit hyperactivity disorder (ADHD) and autism.<sup>9,10</sup> Although there is noted heterogeneity in outcomes (e.g., when comparing binary vs. nonbinary TNG people, or trans women vs. trans men), a trend of increased risk for negative health outcomes holds true for the TNG population overall.<sup>2,11</sup> Although the process of gender affirmation can be long, nonlinear, and increasingly difficult to access with recent legislative actions in the United States, access to gender-affirming care is consistently associated with improvement in many aspects of overall well-being and mental health of TNG people.<sup>12</sup> Patients receiving gender-affirming care experience decreased depressive symptoms and perceived stress, and improved psychological adjustment, quality of life, body satisfaction, and self-esteem.<sup>12</sup>

Proposed explanations of gender diversity range from psychoanalytic<sup>13</sup> to neurobiological to genetic.<sup>14</sup> Like any facet of human identity, gender identity is complex and likely influenced by biological, cultural, psychological, and social factors. While specific terms like transgender and nonbinary may be relatively new, the existence of diverse gender experiences is not.<sup>15</sup>

Conceptualization of gender identities, roles, and expressions has varied throughout history and specific cultural contexts, implying that the binary gender paradigm is neither innately human nor a universal construct.<sup>15</sup> We should understand gender diversity as part of human diversity, and acknowledge that variations outside of the binary construct are not inherently bound to psychopathology.

The health disparities experienced by TNG people are understood through the minority stress model,<sup>16,17,18</sup> which offers a paradigm for how social norms generate stressors that affect the overall health and well-being of minoritized populations.<sup>18</sup> Such risk factors for stress and resilience are compounded in complex, rather than simply additive, ways along multiple axes of identity, such as for TNG people of color.<sup>19</sup> Transgender students experience high rates of victimization in school settings.<sup>20</sup> Half of the transgender respondents in the 2015 United States (US) Transgender Survey reported being verbally harassed, physically attacked, or denied equal treatment for their gender identity.<sup>21</sup> Proximal and distal stressors are well-documented in TNG populations and interact to create health inequities.<sup>22</sup>

While health disparities experienced by TNG patients largely stem from numerous socioeconomic factors, clinician-level issues cannot be ignored. Lack of clinician familiarity with gender-affirming care is a commonly cited concern for TNG patients—one in four respondents to the 2015 US Transgender Survey reported having to educate their clinicians about some aspect of transgender health, and more than half were unsure how much their clinicians knew about transgender health.<sup>21</sup> Patients also commonly reported discrimination and poor treatment, and nearly a quarter of all respondents said they delayed or avoided medical care because of concerns about being mistreated.<sup>21</sup> Such discrimination in health care settings has been associated with prescription drug misuse,<sup>7</sup> depression, and suicidal thoughts<sup>23</sup> in TNG patients. Supportive, affirming interactions with health care workers are associated with less psychological distress and decreased likelihood of suicide attempts;<sup>24</sup> having a more knowledgeable primary care clinician correlates with better overall health.<sup>25</sup> For clinicians, ambivalence about caring for TNG patients has been associated with lack of education and exposure.<sup>26</sup> Institutional investment in providing TNG-inclusive and transgender health education and training can be integral to addressing the health care disparities of TNG patients.

Little research to date has studied the efficacy of standard pharmacological or psychological treatments for TNG populations, or how to best adapt such therapies for TNG patients. Nevertheless, we hope to provide a starting point for clinicians working with TNG patients who experience psychiatric problems.

## METHODS

For this narrative review, we conducted an initial background search in Medline (via PubMed) for keywords and headings related to the most commonly prescribed psychiatric medications (antidepressants, anxiolytics, antipsychotics, mood stabilizers, stimulants, and a list of psychiatric medications that are most commonly prescribed in the United States<sup>27</sup>), gender-affirming hormones (estradiol, estrogen, testosterone, gonadotropin-releasing hormone agonists, leuporelin, histrelin, goserelin, triptorelin, spironolactone), transgender health, medication interactions, and adverse effects. Of these, we reviewed articles for major recurring adverse effects, drug-drug interactions, and hepatic Cytochrome P450 (CYP) enzyme interactions that could be clinically relevant. Additionally, we used the newly released list of potentially increased risks associated with GAHT from the World Professional Association for Transgender Health (WPATH) Standards of Care 8 (SOC 8)<sup>28</sup> guidelines. These risks—venous thrombosis, weight gain, hypertriglyceridemia/dyslipidemia, hypertension, low bone mass/osteoporosis, cardiovascular disease, and acne—served as a guide for additional targeted searches on the occurrence of these side effects from psychiatric medications. We excluded articles on interactions involving nonpsychiatric medications (e.g., nonsteroidal anti-inflammatory drugs and HIV medications) and hormones not used in GAHT (e.g., oxytocin), nonpsychiatric conditions (e.g., aging, pregnancy, and perimenopause), and non-human animal studies. As specific regimens for GAHT often vary regionally, we have focused on the three main medication classes most consistently used in GAHT: gonadotropin-releasing hormone agonists (GnRHAs), estradiol, and testosterone.

Although our discussion focuses on potential side effects and risks, particularly as they overlap with commonly prescribed psychiatric medications and GAHT, the benefits of GAHT for TNG patients cannot be overstated. For most patients, gender-affirming treatments are safe; severe side effects are rare.<sup>29,30</sup> Patients who had access to timely GAHT in adolescence compared to those who had to delay care until adulthood, despite desiring GAHT, were significantly less likely to experience suicidal ideation, problematic substance use, and severe psychological distress.<sup>31</sup> GAHT is consistently linked to numerous positive outcomes, such as improved psychological functioning, better quality of life, and decreased depression,<sup>32</sup> as are gender-affirming surgeries.<sup>33</sup>

## RESULTS

### Puberty Suppressants (GnRHAs)

GnRHAs, known as pubertal suppressants, or colloquially as puberty blockers, have been used since the 1980s for treatment of central precocious puberty. GnRHAs are equally effective for preventing physical changes associated with puberty for both TNG patients and patients with central precocious puberty. GnRHAs are also used during in vitro fertilization for ovarian stimulation, and for treatment of prostate cancer.<sup>34,35</sup> In endogenous puberty, pulsatile release of gonadotropin-releasing hormone (GnRH) causes release of luteinizing hormone (LH) and follicular stimulating hormone (FSH), which act on ovaries to produce estrogen or on testes to produce testosterone. In turn, these hormones act on tissues to produce secondary sex characteristic changes. Continuous levels of GnRH or GnRHA cause desensitization of GnRH receptors and lead to suppression of LH and FSH, which suppresses estrogen or testosterone levels and halts puberty.<sup>34</sup>

GnRHAs are typically used for pubertal suppression at Tanner Stage 2 to allow children experiencing gender dysphoria to delay distressing changes brought on by puberty. This allows patients time to weigh whether to discontinue GnRHAs and allow endogenous puberty to proceed, or to initiate GAHT. As part of GAHT, GnRHAs may also be used for adults as an anti-androgen, and may be more effective than cyproterone acetate<sup>36</sup> or spironolactone.<sup>37</sup>

GnRHAs are well tolerated with few side effects.<sup>38,39</sup> Aside from injection or surgical site-related reactions, specific side effects include hot flashes and mood swings at the beginning of treatment, as we would expect with a significant change in endogenous hormone production.<sup>40</sup> Use of GnRHAs are linked with many positive outcomes<sup>41</sup>—reducing psychiatric symptoms, behavioral dysregulation,<sup>42</sup> suicidal ideation, psychological distress, and substance use<sup>43</sup> in TNG children and adolescents—regardless of gender/sex assignment. Use of GnRHAs may help reduce the need for future interventions. Adolescents who receive GnRHAs at younger ages may need lower doses of GAHT.<sup>44</sup> Use of GnRHAs in early puberty may also be more effective in achieving desired physical changes, such as waist-to-hip ratios closer to those of cisgender peers.<sup>45</sup> Pubertal suppression may completely obviate the need for surgical affirmation, such as chest reconstruction surgery, or allow for less invasive techniques.<sup>46</sup>

## Metabolic Side Effects

Weight gain is a noted side effect for both TNG youth<sup>44</sup> and children with central precocious puberty receiving GnRHAs.<sup>47</sup> Compared with their cisgender peers, transgender girls undergoing treatment with GnRHAs followed by GAHT experience a greater increase in body fat percentage than cisgender girls, with the greatest increase during monotherapy with GnRHAs.<sup>45</sup> Transgender boys experience a decrease in body fat percentage compared to cisgender boys whose body fat percentage generally remains stable through puberty.<sup>45</sup> This effect may not be solely attributable to the effects of GnRHAs themselves, but rather to the differences in baseline body composition of TNG youth compared to their cisgender peers of the same affirmed gender prior to puberty; children assigned female at birth tend to have more body fat than children assigned male at birth.<sup>45</sup> Prescribing clinicians should be mindful of potential overlap in metabolic side effects from psychiatric medications.

## QT Prolongation

Leuprolide carries a warning for prolonged QT interval, which is defined as a rate-corrected QT (QTc) interval on electrocardiography above the 99<sup>th</sup> percentile, or 480ms for cisgender women and 470ms for cisgender men, with QTc interval greater than 440ms considered borderline.<sup>48</sup> A QT interval greater than 500ms has been linked with increased risk of torsades de pointes, with at least one documented case associated with leuprolide.<sup>48,49</sup> QT prolongation is also a potential side effect of numerous psychiatric medications, such as stimulants, antidepressants, and antipsychotics (e.g., haloperidol, thioridazine, and ziprasidone). Depending on a patient's risk factors for arrhythmias, routine monitoring may be beneficial if there are unavoidable risk factors and multiple medications.<sup>50</sup>

## Seizures

There are reports of patients on GnRHAs having convulsions, including patients without other risk factors for seizures, such as a history of prior seizures, other neurological disorders, cerebrovascular disorders, or other medications known to lower seizure threshold.<sup>40</sup> Although an uncommon side effect, clinicians should be aware of other medications with potential to lower seizure threshold. Among psychiatric medications, bupropion and tricyclic antidepressants (TCAs) are most notable for lowering the seizure threshold, though varying degrees of risk exist for most antidepressants and antipsychotics.<sup>51</sup>

## Bone Health

Puberty and adolescence are key periods in bone mass development and linear growth, with the majority of adult bone mass accrued by age 20.<sup>52</sup> During puberty, sex hormones play a critical role in building bone mass, and later in regulating bone homeostasis.<sup>53</sup> Bone mass peaks around age 30 and gradually decreases thereafter.<sup>52</sup> In the general population, lower bone mineral density (BMD) is predictive of increased risk of osteoporosis.

Lower BMD Z-scores have been described in pediatric TNG patients of all genders and adult trans feminine patients.<sup>53,54,55</sup> Bone mass accrual, BMD, and overall bone health are linked to several modifiable and non-modifiable risk factors, such as genetics, malabsorptive disorders, smoking status, dietary intake, physical exercise, and hormonal milieu, which may

account for discrepancies observed in TNG patients compared to cisgender peers.<sup>55</sup> This is of particular concern for youth, given the importance of early-life bone mass accrual. Trans feminine patients seem to be at higher risk of lower Z-scores<sup>54,56</sup> in both pediatric and adult populations.<sup>53</sup> One study found that those initiating pubertal suppression at an older age were more likely to have lower BMD Z-scores. This suggests that factors negatively influencing bone health were present prior to initiation of GnRHAs, and lower Z-scores in patients receiving GnRHAs are likely not wholly attributable to the effects of GnRHAs.<sup>56</sup>

Although lower BMD is predictive of increased osteoporosis risk later in life, it is unclear whether the statistically significant differences in measures of bone health found among TNG patients correlate to a clinically meaningful difference in long-term rates of osteoporosis, fractures, or other negative outcomes.<sup>53</sup> Regardless, clinicians should be aware of this potential impact of GnRHAs, particularly for trans feminine youth, and how this may overlap with effects of other psychiatric medications commonly prescribed during this critical period for bone development. While studies have not characterized patterns of psychiatric medication prescribing for TNG youth, given the increased rates of psychiatric comorbidities, polypharmacy may be more common in this population.

In terms of psychiatric medications, selective serotonin reuptake inhibitors (SSRIs), stimulants, benzodiazepines, anti-epileptic drugs (AEDs), and antipsychotics have been linked to various changes in bone health; the strongest correlation is noted in geriatric patients.<sup>52</sup> The effect of SSRIs on developing bones is less known, and there are few published data on other antidepressant categories.<sup>52</sup> SSRIs may have a negative impact on BMD for pediatric eating disorder patients, or for patients on long-term SSRI treatment (>24 months).<sup>57</sup> This is of particular concern for TNG youth, given their greater risk of disordered eating, anxiety, and depression. The potential additive impact of GnRHAs and SSRIs on bone health may be balanced by improvement of depressive or anxiety symptoms, which may in turn increase health-promoting behaviors that improve BMD.<sup>52</sup> TNG patients receiving AEDs (whether for seizure or mood disorders), may experience effects on bone health in numerous ways. Enzyme-inducing AEDs, such as carbamazepine, increase metabolism of vitamin D, thereby reducing calcium absorption and leading to secondary hyperparathyroidism.<sup>58</sup> Valproic acid causes depletion of carnitine,<sup>59</sup> a crucial compound for bone formation and slowing bone loss, and it has been linked to decreased linear growth and decreased BMD in children.<sup>52</sup> Carbamazepine, oxcarbazepine, gabapentin, and topiramate have all been linked to decreased Z-scores in patients, while lamotrigine appears to have a neutral effect.<sup>52</sup> Vitamin D monitoring and universal vitamin D supplementation are recommended for all pediatric patients on AEDs<sup>52</sup> and may be particularly important if patients are also on GnRHAs and other medications that can negatively affect bone health and mass accrual. Of the mood stabilizers, lithium has a potentially positive effect on osteogenesis.<sup>60</sup>

SOC 8 references neurodivergence, particularly autism and autistic traits, in TNG adolescents,<sup>28</sup> and additional research explores the occurrence of ADHD in TNG patients.<sup>61</sup> Stimulant medications, which can be used in patients with autism and ADHD, have a clear negative impact on growth velocity, particularly early in treatment.<sup>52</sup> Children on stimulants for more than three months had lower BMD than those without stimulant treatment.<sup>62</sup>

Due to their appetite-suppressing effects and resulting potential for weight loss, stimulants decrease nutritional intake and negatively affect bone mass accrual.<sup>63</sup> Children on stimulants also had lower weights than controls, and lower weight for their ages.<sup>62</sup> Stimulants may also increase osteoclast activity by enhancing sympathetic tone.<sup>57</sup> While there are no specific guidelines or recommendations for direct measurement of bone health among children on stimulants, clinicians should monitor for poor appetite and excessive weight loss, track overall growth, and counsel families on mitigating modifiable risk factors for bone health.

Antipsychotics have also been linked to bone loss in adults and may be of concern for TNG adults on GnRHAs as an anti-androgen. As with depression and antidepressant use, this relationship is complicated because schizophrenia is also linked to negative bone outcomes, independent of antipsychotic use.<sup>52</sup> Potent dopamine antagonists, such as risperidone, affect bone health through hyperprolactinemia, which causes hypogonadism leading to bone loss.<sup>64</sup> Prolactin has an inhibitory effect on osteoblasts.<sup>65</sup> Compared to cisgender adults, it is less clear for TNG patients already on GnRHAs or GAHT how much this specific mechanism may contribute to bone loss. Antipsychotics may indirectly contribute to bone loss through sedation and decreased activity.<sup>66</sup> While potent D2 receptor antagonists (e.g., risperidone and haloperidol) are most likely to cause hyperprolactinemia, the medications quetiapine, ziprasidone, and clozapine are usually prolactin-sparing.<sup>67</sup> Switching from olanzapine or risperidone to aripiprazole may reduce prolactin levels.<sup>68</sup> Adjunctive aripiprazole may also help reduce side effects related to elevated prolactin levels.<sup>69</sup>

All medications carry potential risks and benefits. It is not feasible or safe to avoid the use of GnRHAs or psychotropic medications entirely in many patients; however, clinicians should be aware of modifiable risks. TNG patients are also less likely to meet daily requirements for calcium and vitamin D as well as exercise,<sup>56</sup> and are more likely to exhibit disordered eating<sup>70,71</sup> and substance use.<sup>72</sup> While not all risk factors may be mitigated, clinicians should work with patients and families to address these whenever possible.

## ESTROGEN

Estrogen, whether naturally extracted or laboratory-synthesized, has been in therapeutic use for hundreds of years.<sup>73</sup> Several case studies for treatment of menopausal symptoms or sexual dysfunction with bovine or porcine ovarian extracts were published in the late 1800s.<sup>73</sup> Estrogen was first extracted in its purified form in 1923 and first used as part of GAHT in the United States in the 1950s. Since its purification and commodification, estrogen has been used for oral contraception, menopausal hormone replacement therapy, hypogonadism, and chemotherapy for prostate and breast cancer.

TNG patients initiating GAHT are counseled on numerous potential risks of estrogen. Unfortunately, existing findings on the health risks of estrogen are heterogeneous. Many studies specific to TNG populations focus on adults and the use of estrogen in patients who have already undergone androgenic puberty, and whose risk profiles may differ from those of young adults or adolescents starting estrogen after pubertal blockade. Outside of literature specific to TNG patients, clinicians often extrapolate based on the historical use

of conjugated or synthetic estrogens. Since these medications are no longer commonly used in hormone regimens for TNG patients, such extrapolation adds an additional layer of complexity.<sup>74</sup>

Currently, 17 $\beta$ -estradiol is the most commonly used bioidentical estrogen for oral, sublingual, and transdermal formulations. All estrogens exert physiological effects by binding nuclear estrogen receptors, ER $\alpha$  and ER $\beta$ .<sup>75</sup> Different effects of estrogen in various tissues and organs are mediated by the differential distribution of estrogen receptor subtypes and relative binding affinity between different estrogens and receptors.<sup>75</sup>

## Estrogen Metabolism

Estrogens are primarily metabolized by CYP enzymes. Outside of the liver, estradiol is metabolized into various other metabolites with differing levels of estrogenic activity.<sup>75</sup> Genetic and external factors, such as diet, alcohol intake, substance use, smoking, and physical activity levels affect estrogen metabolism.

Of the CYP enzymes, CYP1A2 and 3A4 play the most notable roles;<sup>76</sup> therefore, medications that inhibit or induce CYP1A2 or 3A4 may either increase or decrease estradiol levels. Notable psychiatric medications<sup>77</sup> are listed in Table 2. Enzyme-inducing AEDs increase the hepatic metabolism of estradiol and may lead to lower levels of serum estradiol.<sup>78</sup> Induction of the CYP system with enzyme-inducing AEDs leads to increase in serum sex hormone binding globulin (SHBG),<sup>79</sup> which binds estradiol with the greatest specificity and affinity.<sup>80</sup> This increase in SHBG may decrease the proportion of bioactive free estradiol<sup>79, 81</sup> and thereby diminish the efficacy of GAHT.

Estrogens, including 17 $\beta$ -estradiol, increase hepatic glucuronidation, and can significantly decrease serum lamotrigine levels.<sup>78,82</sup> Of the mood stabilizers, lithium bypasses hepatic metabolism entirely and may allow for more consistent therapeutic levels than AEDs, which can have significant adverse impacts on hepatic metabolism. Close monitoring of AED serum levels and estradiol may be necessary, particularly with dose changes.<sup>83</sup>

## SIDE EFFECTS OF ESTROGEN

### Cardiovascular/Metabolic Risks

In cisgender women, the primary risks of estrogen therapy noted in the literature are its cardiovascular and cerebrovascular effects, due to its known pro-thrombotic properties. The thrombotic risk of estrogen therapy is determined by the specific compound's estrogenicity, and individual genetic or acquired susceptibility to coagulation, anti-coagulation, and fibrinolytic pathway abnormalities.<sup>84</sup>

For TNG patients, the actual risk is harder to discern<sup>30</sup> due to numerous confounding factors (e.g., smoking). Historical changes and existing variability in GAHT regimens, whether self-administered or medically monitored, also prevent easy generalization.<sup>30</sup> Based on Behavioral Risk Factor Survey data (2014–2017), transgender women have a two-fold increase in odds of experiencing a myocardial infarction compared to cisgender women—but not compared to cisgender men—when controlling for other factors.<sup>85</sup> In a 2021

study of 183 TNG patients ages 15–20 initiating estrogen therapy, there were no incidental occurrences of venous thromboembolism (VTE), even for patients with individual risk factors such as obesity, smoking status, history of thrombosis, and known thrombophilia.<sup>74</sup> A 2021 meta-analysis showed that the pooled prevalence estimate for a VTE was 0% for patients under 37 years old, while an analysis restricted to those above 37.5 years of age showed a pooled prevalence estimate of 2% with high heterogeneity.<sup>86</sup>

A 2010 meta-analysis on the metabolic impacts of estrogen showed that GAHT may be correlated with “unfavorable changes in lipid profiles.”<sup>87</sup> An updated meta-analysis showed a slightly higher degree of evidence for increased triglyceride (TG) levels but no other changes, such as elevated or lowered high-density lipoprotein (HDL).<sup>88</sup> Estrogen is associated with increased body fat, increased BMI, increased overall body weight, and decreased lean body mass.<sup>89</sup> Despite statistically significant changes in TG levels at 24 months, and aforementioned changes in body composition, serious events such as myocardial infarction, stroke, VTE, and death were rare, indicative of the overall safety of medically monitored estrogen.<sup>88</sup>

Although serious events, such as stroke or myocardial infarction, may be rare, clinicians should be aware of multiple potential overlaps in side effects with psychiatric medications. Antipsychotics are known for their significant adverse metabolic effects, such as weight gain and dyslipidemia.<sup>90</sup> Of additional concern for TNG patients taking estrogen, antipsychotics are also associated with an increased risk for VTE.<sup>91</sup> Additionally, dopamine antagonism carries the risk of hyperprolactinemia. While this is a potential side effect of both antipsychotics and estradiol,<sup>89</sup> it is much more commonly seen with antipsychotics<sup>92</sup> than with estradiol-based GAHT.<sup>83</sup> Unfortunately, prolactin-sparing antipsychotics, such as quetiapine and clozapine, also carry a higher risk of potential weight gain.<sup>90</sup>

While most antidepressants are weight neutral, there is a higher risk of weight gain with amitriptyline, mirtazapine, and paroxetine.<sup>93</sup> Fluoxetine and bupropion are more likely to cause weight loss.<sup>93,94</sup> Among the mood stabilizers, carbamazepine and lamotrigine have a lower risk of weight gain,<sup>95</sup> whereas lithium and valproic acid have been linked with weight gain.<sup>95,96</sup>

## TESTOSTERONE

For hundreds of years, testosterone, via organotherapy, has been used for various indications, such as “rejuvenation” and virility.<sup>97</sup> Testosterone was isolated and purified in 1935.<sup>98</sup> Aside from its use in primary or secondary hypogonadism, its use for sexual dysfunction, osteoporosis prevention, and psychological symptoms such as depression is controversial in cisgender patients without low testosterone levels.<sup>99</sup>

Testosterone diffuses into cells to bind to the androgen receptor. Testosterone is converted to 5 $\alpha$ -dihydrotestosterone (DHT) by 5 $\alpha$ -hydroxylase in certain tissues, such as skin and hair follicles.<sup>100</sup> This is a much more potent androgen than testosterone, which binds the androgen receptor with a greater affinity, while aromatase is responsible for the peripheral conversion of testosterone to estradiol.<sup>98</sup> Estradiol and DHT, the differential expression

of androgen-responsive genes and varying levels of testosterone, lead to the physiological effects of testosterone at different target organs.<sup>98</sup> Some concern has been expressed about the potential peripheral conversion of testosterone to estrogen, leading some patients and clinicians to consider the use of aromatase inhibitors;<sup>101,102</sup> at least one study with trans masculine patients, however, showed that their estradiol levels are within the reference range for cisgender men.<sup>102</sup>

### Testosterone Metabolism

As with estrogen, testosterone undergoes hepatic metabolism, with the majority of testosterone metabolized by CYP3A4,<sup>103</sup> and minor contributions by CYP2C19, CYP2C9, and CYP2D6.<sup>104</sup> Psychiatric medications with notable CYP interactions<sup>77</sup> are listed in Table 3. In the serum, testosterone is also highly protein-bound by albumin, corticosteroid binding hormone, and SHBG. Typically, only 1–2% of total testosterone is free in the serum.<sup>105</sup> Among epilepsy patients taking enzyme-inducing AEDs (e.g., carbamazepine and phenobarbital), an increase in serum SHBG concentration leads to decreased bioavailable fraction of testosterone.<sup>79</sup>

While valproic acid is not an enzyme-inducing AED, it can also produce neuroendocrine disruptions, which may be of concern for TNG patients depending on their specific gender embodiment goals (particularly in relation to body and facial hair). For cisgender women with epilepsy, valproic acid is associated with hyperandrogenic conditions, such as polycystic ovarian syndrome (PCOS), menstrual disorders, and reproductive endocrine disorders, while valproic acid treatment in cisgender men with epilepsy is associated with decreased FSH and testosterone.<sup>79</sup>

## SIDE EFFECTS OF TESTOSTERONE

Testosterone, when prescribed as part of medically monitored GAHT, appears to be overwhelmingly safe and beneficial for TNG patients, with serious side effects exceedingly rare.<sup>29</sup>

### Mood and Aggression

Historically, the WPATH Standards of Care, Version 7<sup>106</sup> listed potential destabilization of psychiatric disorders (bipolar disorder, schizoaffective disorder, and other affective disorders, which may include manic or psychotic symptoms) as a potential side effect of testosterone. Studies of TNG patients, however, consistently show testosterone is associated with significant improvements in global functioning and psychopathology,<sup>12</sup> depression and anxiety,<sup>107</sup> internalizing symptoms, body satisfaction,<sup>108</sup> general well-being, and suicidality.<sup>109</sup> As such, destabilization of psychiatric disorders by testosterone was removed from the WPATH SOC 8; nevertheless, prescribers still commonly express reticence about prescribing testosterone for GAHT based on this unsubstantiated myth.

Sex steroids, such as testosterone, have a complex role in brain development and regulation of mood and cognition.<sup>110</sup> GAHT has been shown to correlate with gender-specific changes in the brain.<sup>111</sup> Testosterone replacement therapy in cisgender men with hypogonadism improves cognition, mood, and sleep, and reduces irritability and anger.<sup>112</sup> There does not

seem to be a consistent correlation between serum testosterone levels in TNG patients and expressions of anger; however, self-rated intensity of anger (state-level anger) was associated with overall negative affect, lower quality of life,<sup>113,114</sup> and persistent menstrual bleeding.<sup>114</sup> Intensity of anger after initiation of testosterone was not associated with a prior psychiatric diagnosis either.<sup>113</sup>

Part of the concern about a possible link between testosterone and mood changes originates from cases of exogenous testosterone administration, often involving anabolic steroid regimens of multiple testosterone derivatives at 10 to 100 times the physiologic dose.<sup>112</sup> TNG patients and hypogonadal patients are prescribed testosterone doses within physiological range.<sup>107</sup> A 2004 review by the Norwegian Knowledge Centre for the Health Services found that “there is good evidence that low doping doses influence the level of aggressiveness only slightly or not at all.”<sup>115</sup>

The relationship between testosterone and mood is complex, mediated by both individual factors and societal perceptions. Based on the abundant literature on the positive effects of GAHT, psychiatric conditions should not be considered a general contraindication for initiating or continuing testosterone. Mood changes, irritability, and changes in anger levels, if present at all, may be most noticeable at the beginning of GAHT<sup>107</sup> and decrease after gender-affirming surgery.<sup>116</sup> Dose adjustments, changes in injection intervals, or changes in formulation may also be helpful.<sup>107</sup>

### Metabolic/Cardiovascular Risks

Patients typically experience an increase in total body weight, redistribution of body fat, and increase in lean body mass with testosterone. A 2017 systematic review showed only two patients taking testosterone developed clinically significant hypertension, and no severe adverse effects were reported among any of the patients.<sup>117</sup> TNG patients on testosterone should be counseled on any potential overlapping metabolic risks with psychiatric medications and have metabolic parameters monitored regularly.

### Hepatotoxicity

Serious hepatotoxicity for most commercially available testosterone preparations in the United States appears rare with appropriate monitoring; though transient, nonsignificant elevations in liver enzymes are observed.<sup>117</sup> Additional caution may be needed for TNG patients on both testosterone and psychiatric medications. For patients taking psychiatric medications, serious hepatotoxicity is idiosyncratic, rare, and difficult to predict.<sup>118</sup> With the exception of nefazodone, which carries a well-known risk of hepatotoxicity, antidepressants generally appear to be safe, aside from idiosyncratic hepatotoxicity.<sup>119</sup> Monoamine oxidase inhibitors (MAOIs) and TCAs have a slightly higher risk of potential hepatotoxicity than SSRIs.<sup>118</sup> Antipsychotics are often associated with a transient, benign elevation in liver enzymes, though rarely associated with clinically significant hepatotoxicity.<sup>119</sup> Up to 20% of patients taking phenothiazines can experience a benign elevation in liver enzymes, with clinically significant hepatotoxicity occurring in less than 1% of patients.<sup>118</sup> For clozapine and risperidone, up to 50% of patients may experience similar elevation in liver enzymes.<sup>118</sup>

Many commonly used mood stabilizers, such as carbamazepine, valproic acid, and lamotrigine, are associated with hepatic concerns, ranging from benign liver enzyme elevations to hyperammonemia to fulminant liver failure.<sup>118,120</sup> Oxcarbazepine seems to have fewer concerns related to liver pathology.<sup>118</sup>

For TNG patients with multiple risk factors, like those with type 2 diabetes, or patients on multiple potentially hepatotoxic agents, such as those with bipolar disorder who require both an antipsychotic and a mood stabilizer, routine monitoring of liver enzymes may be beneficial.<sup>119,120</sup>

### **Hematological Abnormalities: Erythrocytosis, VTE**

Erythrocytosis is another common side effect of testosterone.<sup>121</sup> Unlike pathological erythrocytosis in myeloproliferative disorders, erythrocytosis associated with GAHT is not typically associated with increases in clinically significant events like thromboembolism.<sup>122</sup> Clinicians should, however, be aware of potentially compounding risk when multiple aggravating factors are present, such as history of prior VTE, strong familial history, clotting disorders, or treatment with antipsychotics.<sup>91,123</sup> Treatment with antipsychotics is a predictor of recurrent VTE,<sup>124</sup> even when controlling for other risk factors.<sup>125</sup> TNG patients with increased risk factors who present with new neurological symptoms may require further assessment.

### **Integumentary Changes**

Testosterone causes characteristic changes in the skin, such as increased sebum production, infundibular keratinization, and sebocyte growth, all of which increase the risk of acne.<sup>126,127</sup> Lithium can also cause acne through a non-androgen-dependent pathway.<sup>128</sup> Acne is an uncommon potential side effect of TCAs, SSRIs, and quetiapine.<sup>129</sup> Although typical hormonal treatments for testosterone-induced acne, estrogen or spironolactone are usually undesirable for TNG patients; topical retinoids are often the initial treatment of choice.<sup>129</sup> Hormonal treatments may be an option for TNG patients who have likely reached maximal testosterone effects—after two years of continuous GAHT<sup>126</sup>—while monitoring for worsening dysphoria during treatment. Isotretinoin is a possible alternative option for patients with severe acne in the absence of additional risks for hepatotoxicity.<sup>126</sup> Testosterone should not be used as contraception, and all patients initiating isotretinoin should receive appropriate counseling regarding teratogenicity and effective contraceptive options.<sup>130</sup> For TNG patients with psychiatric morbidities, the association between isotretinoin and depression may be a notable concern; the current literature, however, is not reflective of such an increased risk. Many TNG patients experience distress related to body image and skin concerns, which may be effectively relieved with acne medications.

## **DISCUSSION**

The field of TNG health research has grown exponentially in recent years; however, there are currently no published studies evaluating the risks or efficacy of psychiatric medications for TNG patients on GAHT. Such studies would better elucidate potential compounding side effects or risks. Thus, our review extrapolates from the existing general

literature on psychiatric medications, GnRHAs, and exogenous testosterone and estradiol, not necessarily on their use among TNG people. As noted, studies of GAHT for adults may not be fully applicable for adolescents; regardless, we have strived to provide a review of GAHT most relevant for the psychiatric prescriber, and potential considerations for concurrent use of psychiatric medications and GAHT. Many TNG patients experience significant improvement in their mental health with initiation of GAHT; TNG patients may have psychiatric morbidities that must be addressed, especially when the psychiatric illness impairs the patient's ability to provide informed consent to initiate or safely continue GAHT. Additionally, we hope this review spurs further direct investigations on the effects of psychiatric polypharmacy and GAHT.

While individual behaviors and risk factors for cardiovascular disease, stroke, and other negative health outcomes are undoubtedly important, these are also influenced by structural and political determinants of health.<sup>131</sup> The disparities in health outcomes seen among TNG populations, as with other minoritized populations,<sup>132</sup> compared to cisgender peers, are unlikely wholly attributable to GAHT, but rather to economic and public health policies that have disproportionately negative effects on marginalized populations.<sup>131</sup> With recent waves of legislation targeting gender-affirming health care, there are concerns around the potentially chilling impact on clinicians. This could reduce access to gender-affirming care and increase unsupervised GAHT, thereby exacerbating health inequities for TNG patients.<sup>133</sup> Legislation and social climate affect the overall health of lesbian, gay, and bisexual (LGB) adults, even when not directly limiting health care services.<sup>134</sup> Regardless of whether proposed legislation or government actions become codified into law, they can increase symptoms of anxiety and depression.<sup>135</sup> A 2009 study found that LGB adults living in states without antidiscrimination protections had over four times the odds of a psychiatric comorbidity than LGB adults living in states with such legal protections.<sup>136</sup> TNG people often experience discrimination in public settings, such as gyms with gendered changing facilities or showers,<sup>137</sup> that can precipitate downstream effects on health. As the field matures, we will continue accruing more comprehensive and nuanced knowledge of longitudinal effects, particularly regarding rare outcomes, and more specific understanding of different subgroups (such as those who undergo gender affirmation in adulthood vs. in adolescence); however, the benefits of gender-affirming health care for improving the overall well-being and quality of life of TNG patients is well-established. Its importance for the health and safety of TNG patients cannot be overstated.

Although medical or surgical interventions are not the be-all and end-all of TNG health, an accurate understanding of basic gender-affirming care and its relevance to psychiatry should be within the purview of any psychiatric prescriber. TNG people are historically reported to represent 0.35–0.5% of the general population,<sup>138</sup> and up to 5% of young adults under 30 years of age, depending on the survey. This proportion may be even higher in psychiatry, as TNG youth are more likely to experience psychiatric hospitalization than their cisgender peers.<sup>139</sup> Thus, continuing to frame psychiatric care of TNG patients as requiring a trained subspecialist will exacerbate existing disparities.

With appropriate resources and institutional support, all clinicians, including psychiatric practitioners, are capable of providing gender-affirming care for TNG patients, just as they

provide gender-affirming care for cisgender patients. As of the 2023 legislative session, over 350 bills opposing transgender people's participation in society and/or limiting gender-affirming care were introduced in forty-three US states.<sup>140</sup> In such a hostile climate, it is all the more crucial for every clinician to offer gender-affirming care.

## Grants:

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**Table 1:**  
Main Classes of medications used in Gender Affirming Hormone Therapy regimens

| Main Sex Steroids         | Pubertal Suppressants, i.e., Gonadotropin-Releasing Hormone Agonists (GnRHAs)                                | Anti-androgens                                                     | Other                                                                                                           |
|---------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Estradiol<br>Testosterone | Leuprolide (Lupron, Eligard)<br>Triptorelin (Decapeptyl)<br>Histerelin (Supprelin LA)<br>Goserelin (Zoladex) | Spirolactone<br>GnRHAs<br>Cyproterone acetate<br>(internationally) | Progesterone (often in conjunction with estradiol)<br>Norethindrone, norethisterone (for menstrual suppression) |

Table 2:

CYP and drug-drug interactions for Estradiol

| Medications that May Increase Estradiol Levels                                                           | Medications that May Decrease Estradiol Levels                                                                                                                                                                      | Medication Levels that Estradiol May Decrease |
|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>CYP3A4 Inhibitors</b><br>Fluvoxamine, Nefazodone, Suboxone<br><b>CYP1A2 Inhibitors</b><br>Fluvoxamine | <b>CYP3A4 Inducers</b><br>Modafinil, St. John’s Wort, Tobacco, Topiramate<br><b>CYP1A2 Inducers</b><br>Modafinil, Tobacco<br><b>Enzyme-inducing AEDs</b><br>Carbamazepine, oxcarbazepine, topiramate, phenobarbital | Lamotrigine                                   |

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Table 3:

CYP and drug-drug interactions for Testosterone

| Medications that May Increase Testosterone Levels                                                                                                                                                                                 | Medications that May Decrease Testosterone Levels                                                                                                                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CYP3A4 Inhibitors</b><br>Fluvoxamine, Nefazodone, Suboxone<br><b>CYP2C19 Inhibitors</b><br>Progesterone, Fluvoxamine<br><b>CYP2C9 Inhibitor</b><br>Fluoxetine<br><b>CYP2C6 Inhibitors</b><br>Bupropion, fluoxetine, paroxetine | <b>CYP3A4 Inducers</b><br>Modafinil, St. John’s Wort, Tobacco, Topiramate<br><b>CYP2C19 inducer</b><br>Carbamazepine<br><b>CYP2C9 inducer</b><br>Carbamazepine<br><b>Enzyme-inducing AEDs</b><br>Carbamazepine, oxcarbazepine, topiramate, phenobarbital |

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