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Gender-Affirming Hormone Use in Transgender Individuals: Impact on Behavioral Health and Cognition

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Abstract

Purpose of Review—With increasing numbers of transgender and gender non-binary individuals presenting for care, knowing how to elucidate the mental health and cognitive outcomes of gender-affirming hormone therapy (GAHT) is necessary. This article reviews the present literature covering GAHT effects on mood, behavioral health, and cognition in these individuals and offers research priorities to address knowledge gaps.

Recent Findings—Although there are some conflicting data, GAHT overwhelmingly seems to have positive psychological effects in both adolescents and adults. Research tends to support that GAHT reduces symptoms of anxiety and depression, lowers perceived and social distress, and improves quality of life and self-esteem in both male-to-female and female-to-male transgender individuals.

Summary—Clinically, prescribing GAHT can help with gender dysphoria-related mental distress. Thus, timely hormonal intervention represents a crucial tool for improving behavioral wellness in transgender individuals, though effects on cognitive processes fundamental for daily living are unknown. Future research should prioritize better understanding of how GAHT may affect executive functioning.

Keywords

Transgender; Gender; Sex; Gender-affirming hormone therapy; Mood; Behavioral health; Cognition

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Conflict of Interest Hillary B. Nguyen, Alexis M. Chavez, Emily Lipner, Liisa Hantsoo, Sara L. Kornfield, Robert D. Davies, and C. Neill Epperson declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Background

Although people tend to use the terms *sex* and *gender* interchangeably, each has a distinct meaning. A newborn is typically designated a *sex*—either male or female—based on the appearance of their genitalia. *Natal sex* and *sex assigned at birth* are used interchangeably in this article to refer to this same concept. On the other hand, the term *gender identity* refers to an internal sense of self, which can be man, woman, a mix of both, or neither. For many, their sex assigned at birth is in accordance with their gender identity. These people are *cisgender* (abbreviated *cis*). *Transgender* (abbreviated *trans*) is an umbrella term that describes those who do not have a gender identity, gender expression (i.e., the way one presents their gender to others), and/or behavior (i.e., how the person expresses their gender identity through actions) that matches their sex assigned at birth, as defined by the norms of a given culture [1•, 2].

Most societies look at sex through a binary lens with two rigidly fixed options: male or female. Similarly, gender is viewed as a dichotomy between boy/man and girl/woman. As a result, most biomedical research has either neglected transgender individuals altogether or focused on the binary conception of the transgender experience: trans woman or trans man. Trans women (often labeled by the medical community as male-to-female or MTF) were assigned male at birth but identify as women. On the other hand, trans men (often labeled by the medical community as female-to-male or FTM) were assigned female at birth but identify as men. However, gender and sex are on a spectrum with many possibilities. Focusing on the two ends of the gender spectrum leaves out identities which lie outside of the male-female binary.

The transgender experience has previously been coded by the American Psychiatric Association as a pathological condition called gender identity disorder (GID) in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) third and fourth editions [3, 4]. In 2013, GID was reclassified in the DSM-5 as gender dysphoria (GD), which is characterized by “significant distress or problems functioning” associated with incongruence between a person’s assigned sex at birth and experienced or expressed gender [5]. Prevalence rates of GD are estimated by the DSM-5 to be 0.005–0.014% for natal males and 0.002–0.003% for natal females [5]. However, due to variation in diagnosis, presentation, and cultural acceptability across different nations and societies and associated stigma with trans identification, these numbers likely underestimate the true prevalence. Most recent estimates based on state- and national-level population-based surveys approximate between 0.3–0.6% of the U.S.A.—or approximately 1 million U.S. adults—are transgender, although this still may be a low estimate [6, 7]. Today, not all transgender individuals experience sufficient symptoms of gender dysphoria to meet criteria for the diagnosis. Nonetheless, over the past two decades, increasing numbers of people have been identifying as transgender, seeking help with transition, and/or receiving the GID/GD diagnosis [8].

Mosaic Brain

Corroborating the idea of a spectrum of gender and sex is a recent hypothesis of the brain as a mosaic with respect to “sexing” of the central nervous system. In utero, the male fetal brain responds to the androgen testosterone and its aromatization to estradiol to develop a more masculine phenotype across the lifespan [9, 10]. The female fetus acquires a more feminine brain phenotype due to the estrogen-binding activity of alpha-fetoprotein and absence of fetal androgen production [11]. However, the dichotomy between the female and male brain is not always clear-cut. Brain regions are programmed by androgens and estrogens to various degrees leading to a gradient of masculinization and feminization across the brain during prenatal development. This “mosaic” of maleness and femaleness is present in all individuals, including both transgender and cisgender individuals [12•]. During puberty, gonadal steroids, life experiences, and genetics all influence the programmed brain to form a phenotype somewhere along the sex continuum and an identity somewhere along the gender continuum [1•, 2, 13, 14].

Gender-Affirming Hormone Therapy

Transgender individuals who choose to transition can take medical and/or non-medical steps. Social transition includes actions such as changing one’s appearance (e.g., hair, clothing) or pronouns. A legal transition includes a change in name and new legal documents to reflect this. Medical transition (if desired) may include procedures such as gender-affirming hormone therapy (GAHT) and gender-affirming surgery (e.g., breast augmentation, phalloplasty) to develop or modify desired sex characteristics.

According to the National Transgender Discrimination Survey Report on Health and Health Care, at least 80% of transgender people have either taken GAHT or want to take GAHT at some point [15]. MTFs typically take estradiol and androgen blockers to feminize their bodies, while FTMs typically take testosterone to masculinize their bodies. Gender non-binary or gender non-conforming individuals who do not identify as transgender may choose to take hormones to develop more masculine or feminine sexual secondary characteristics. These populations have been absent from research in the effects of GAHT on behavioral health and cognition, which thus far has focused on FTMs and MTFs.

Early neuroscience research in the transgender population focused primarily on determining the etiology of GD and the transgender identity, particularly whether the brain of transgender individuals is more like that of their natal sex or their gender identity. Empirical evidence in cisgender participants suggests differences between the sexes with respect to cognition. Specifically, there is a sex distinction between spatial intelligence and verbal intelligence, although both cisgender males and females have similar overall IQ. Males tend to outperform females in spatial rotation tasks, and females outperform males in tasks requiring verbal fluency [16, 17]. In transgender individuals naive to GAHT, most cross-sectional neuroimaging research indicates that brain morphology, performance on cognitive tasks, and activation patterns at rest and during cognitive tasks are more congruent with gender identity than natal sex [1•, 18, 19•, 20–22, 23•, 24–29].

Based on the literature in cisgender populations, it is known that estradiol, testosterone, and progesterone—as well as its neurosteroid metabolite allopregnanolone (Allo)—have strong influence on neurotransmitter levels and receptors, as well as neuronal and glial architecture and function in presumably cisgender individuals [14, 30, 31]. Since changes in these gonadal and adrenal steroid levels can profoundly affect cognition and mood [14, 32], exogenous hormone administration by GAHT must further be studied to better inform patients about potential changes in executive functioning and behavioral health. Only a few studies have prioritized brain health as a function of exogenous hormone administration, which is the focus of this review. Our purpose is to provide the clinician with a comprehensive review of these recent studies so that they can approach their transgender patients with greater understanding of the potential behavioral health impact of GAHT.

Methods

Both cross-sectional and longitudinal studies within the last 5 years investigating GAHT effects on mood and behavioral/psychological/mental health were prioritized, though we present a brief summary of the limited literature on cognition as the latter certainly impacts day-to-day well-being and function. Using Google Scholar and PubMed, we searched for studies relevant to the topic and published in English using the terms “transgender,” “gender dysphoria,” “gender identity,” “hormone,” “mood,” “behavior,” and “cognition.” All studies were eligible regardless of sample size, but they required data from comparison groups: either from non-GAHT users in crosssectional studies or from the same individuals prior to their GAHT administration in longitudinal studies. Single case reports, review articles, commentaries, and studies that did not contain original data were excluded. Adolescents and children taking only puberty blockers were not considered in this review; interventions were restricted to either feminizing or masculinizing hormone therapy. Due to the large range of doses and types of GAHT, all styles of hormone administration, dosing levels, dose frequency, and types were included.

Results

Overall, GAHT has been found to influence both mood and cognition in transgender adults. The most recent studies (since 2013) are discussed below and organized by type of behavioral health parameters measured. Eleven of these were longitudinal studies [33•, 34, 35•, 36•, 37, 38•, 39,40, 41•, 42•, 43], while the rest were cross-sectional studies. We highlight these 11 longitudinal studies in Table 1, since by design they provide more reliable data about GAHT effects on behavioral health as a function of time.

Effect of GAHT on Depression

Depression and related mood states are extensively studied behavioral health-related parameters in transgender and gender dysphoric individuals undergoing GAHT. To the best of our knowledge, all cross-sectional and longitudinal studies over the last 5 years assessing depression—nine in total—reported lower depressive symptoms in both MTF and FTM transgender individuals receiving GAHT, most using self-report questionnaires [33•, 34, 35•, 44, 45, 46•, 47–49]. Three of these studies utilized a longitudinal design (Table 1), evaluating the same 118 patients over 12 months [33•], the same 57 people over 3–6 months

[34], and the same 54 people over 24 months [35•] pre- and post-GAHT. A limitation of these investigations is that none of the three documented hormone blood levels before or after GAHT. Additionally, subjects received varying levels of hormones. Future research questions lie in considering the significance of doses, route of administration, and dosing schedules in GAHT.

Effect of GAHT on Anxiety, Stress, and Social Functioning

As opposed to depression, anxiety has been investigated only recently. Both cross-sectional and longitudinal studies (Table 1) consistently report a reduction in symptoms of anxiety among both middle-aged and elderly (over age 50 years) transgender adults receiving hormone therapy [33•, 34, 45, 46•, 48]. Comparison across studies may have limited utility due to different scales used to measure anxiety symptoms. GAHT also seems to have a positive effect on perceived stress as measured by the self-reported Perceived Stress Scale (PSS). After 12 months of GAHT, transgender patients ($n = 70$) had significantly decreased cortisol awakening response and perceived stress [36•].

The effects of GAHT on interpersonal and psychosocial functioning have also received much attention with mixed results. Bouman et al. [46•] noted fewer problems with socialization and interpersonal functioning in older MTFs ($n = 71$) receiving GAHT using a cross-sectional study design. Similarly, there have been reports of lowered global functional impairment, interpersonal sensitivity, and hostility following GAHT in both FTMs and MTFs [33•, 34, 44]. In contrast, a cross-sectional study—the first to investigate the effects of GAHT use in Southeast Asia—found that FTMs ($n = 60$) using GAHT scored worse on bodily pain, mental health, and vitality compared to non-users [50•].

Effect of GAHT on General Psychopathology, Personality, and Mental Well-Being

Studies have mostly described marked reductions in measures of global psychopathology after the initiation of GAHT. More specifically, transgender individuals undergoing GAHT reported better psychological adjustment and lower subject levels of gender dysphoria [35•], lower psychiatric stress and psychological symptoms [33•], and decreased psychoneurotic distress [34]. Using the Minnesota Multiphasic Personality Inventory (MMPI), three studies suggest a positive effect of GAHT on personality-related psychopathology as well, including significant reductions in psychasthenia, depression, hysteria, and paranoia [37, 38, 51]. Longitudinal studies completed in Turkey [39] and the Netherlands [52] find that GAHT generally has a positive impact on general psychopathological symptoms and functioning and general well-being (Table 1). However, the de Vries et al. study [52] used combined therapy of GAHT and gender reassignment surgery, so specific effects of GAHT are difficult to interpret.

Based on the limited literature, GAHT seems to have a mixed effect on emotional functioning. While some indicate that testosterone treatment in FTMs is associated with improved mental health on measures of anger [45], there is a report of increased anger expression after 7 months of continuous testosterone [40]. Interestingly, despite the increase in anger expression scores, this same study noted an improvement in inner ability to control angry feelings, possibly due to greater self-confidence and social functioning from

affirmation in the male gender role. Nevertheless, another study found that testosterone therapy was neither associated with an increase in aggression in FTMs nor a decrease in aggressive behavior in MTFs on anti-androgen and estrogen therapy [41•]. Even with fairly large sample sizes, these conflicting results may be due to the self-reported nature of the surveys administered in all three studies. Furthermore, the study by Davis and Colton Meier [45] operated on a cross-sectional design using between-subject comparisons, which makes it difficult to extricate significant changes from interpersonal variance and differences in GAHT plans. The increase in anger expression was noted after a relatively short-term testosterone administration of 7 months [40], but no change related to GAHT was observed over 3 years [41•]. Rather, Defreyne et al. [41•] noted that psychological and/or social factors, such as anxiety levels and lower support from friends, appeared to contribute to self-reported aggression instead. This potential contribution raises the probability of extra variables besides GAHT that may be affecting anger and aggression. Nonetheless, the existence of very few studies on this subject warrants further investigation.

Effect of GAHT on Quality of Life, Body Satisfaction, and Self-Esteem

Several studies confirm a statistically significant improvement in self-reported quality of life (QoL) in both MTFs and FTMs receiving GAHT [42, 44, 53]. Hormonal intervention is also associated with higher levels of body satisfaction and self-esteem [44, 46•, 47], perhaps with a gender-specific effect. One study showed that following GAHT, MTFs experienced less body uneasiness, but FTMs did not share the same benefit, possibly due to discomfort at a personal rather than social level [54]. The rest of the studies strongly established that GAHT reduces body discomfort and increases body-gender congruence and body image satisfaction, most likely due to a reduction of the discrepancy in characteristics between natal sex and gender identity [35•, 39, 42, 43, 48, 55, 56]. Finally, noticeable decreases in eating disorder psychopathology and symptoms were documented by Testa et al. [55] and Jones et al. [56], although Turan et al. [39] did not find a correlation between GAHT and eating attitudes or behaviors. Since all three of these studies—only one [39] of which was longitudinal (Table 1)—were conducted in different countries (USA, Canada, UK, Turkey) using different questionnaires, cross-cultural comparison among these data should be approached cautiously.

Effect of GAHT on Cognitive Tasks and Brain Structure

Among research that expressly examined the central nervous system and cognitive effects of GAHT, most studies focused on tasks of spatial rotation and verbal fluency, namely those which have established sex differences, to determine whether transgender individuals are more similar to cisgender individuals with the same natal sex or to cisgender individuals with the same gender identity. Using both cross-sectional and longitudinal design, the studies generally show that GAHT is correlated with changes in the direction of gender identity rather than natal sex with respect to global and regional brain volumes [57•, 58], white matter microstructure [59, 60], and cognitive performance on sex-biased tasks requiring verbal and visual memory [61]. To the best of our knowledge, no studies thus far have looked at how GAHT influences executive function and cognitive domains used for daily living.

Conclusions

Overall, this review demonstrates that GAHT generally has positive effects at multiple levels on mood and behavioral health of transgender and gender dysphoric individuals. Whether the impact of GAHT on the limited cognitive domains assessed actually leads to improvements in cognitive domains which are critical to day-to-day function is not known. GAHT generally enhances transgender individuals' similarity to their identified gender with respect to brain structure and sex-biased cognitive performance; however, we believe that this information is not practical or relevant to most transgender individuals and their healthcare providers regarding day-to-day quality of life. It is critical that upcoming research interests consider the brain domains important for goal-directed behavior and pay less attention to sex-specific cognitive processes. Research over the past few decades has also established that, following GAHT, transgender individuals report decreased anxiety, perceived stress, and social distress and report better mental health-related quality of life, self-esteem, and mood. However, some inconsistencies around GAHT effects on anger and aggression still need to be addressed.

Although the existing body of research supports GAHT improving mental wellness, many studies used cross-sectional and uncontrolled observational methods relying on self-report. Future research should focus on applying more robust study designs with large sample sizes, such as controlled prospective cohort studies using clinician-administered ratings and longitudinal designs with appropriately matched control groups. Additionally, studies that include more ethnically and socioeconomically diverse participants would better represent trans people. It is well-established that the improved mental health outcomes seen after GAHT can be largely attributed to greater congruence between identified gender and the person's secondary sexual characteristics, as well as external affirmation from healthcare providers, family, friends, and society.

We argue that lines of research focusing on differences between trans populations and general population controls without a specific intervention do not answer critical questions about how to improve the unique health needs of transgender people and can further stigmatize this community by deeming them as abnormal. In particular, more data are necessary to inform transgender patients about the long-term safety of GAHT with respect to brain health, mood, and cognitive function necessary for daily living, especially as it is becoming more common and accepted for transgender people to use GAHT to medically transition. Specifically, gonadal steroids can have great impact on brain structure, function, regional connectivity, and neurochemistry [14], which influences executive functions, affect, and reward processing. The prefrontal cortex—the site of estrogen modulation of executive function—is essential for cognitive processes such as sustained attention, working memory, organization, and planning [14, 31, 62]. FTM individuals taking high-dose testosterone and left in a hypoestrogenic and hypertestosterone state could be at risk for executive dysfunction, as exhibited in cisgender females experiencing premature loss of estradiol or polycystic ovary syndrome, respectively [63,64]. The field needs more high-quality longitudinal studies assessing multiple behavioral and cognitive domains, with and without neuroimaging, over a number of years as most individuals who initiate GAHT are considering lifetime use. Finally, future research in this population should consider

expanding to be more inclusive of genders beyond the binary and address related health disparities along the entire gender spectrum.

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Table 1
Longitudinal studies assessing GAHT effects on behavioral health in transgender individuals.

Author	Participants (# of months GAHT)	Behavioral health outcomes	Results
[36] Colizzi et al. 2013	70 transsexual patients (12 months)	Cortisol levels (Cortisol awakening response), perceived stress (Perceived Stress Scale), attachment style (Adult Attachment Interview)	When treated with GAHT, transsexuals reported significantly lower CAR (from elevated Cortisol levels prior to GAHT to normal range after 12 months) and perceived stress, regardless of attachment style.
[33•] Colizzi et al. 2014	118 transsexual patients (12 months)	SCID-I, Zung Self-Rating Anxiety Scale (SAS), Zung Self-Rating Depression Scale (SDS), Symptom Checklist 90-R (SCL-90-R)	After 12 months of GAHT, patients reported significantly lower SAS, SDS, and SCL-90-R scores. A lower percentage of patients also presented with psychiatric distress and functional impairment following GAHT.
[34] Heylens et al. 2014	46 MTFs (3–6 months) 11 FTMf (3–6 months)	Psychopathological parameters (Symptom Checklist-90), psychosocial variables (psychosocial questionnaires)	MTFs and FTMf scored significantly higher on psychopathology than a general population (norm group) at the time of presentation prior to GAHT, but this difference completely disappeared after GAHT. There was a significant decrease in the overall psychoneurotic distress sub-score of the SCL-90 after GAHT for both MTFs and FTMf. Furthermore, unlike scores at the time of presentation, SCL-90 scores following GAHT are more similar to the mean SCL-90 scores of the general population. From the psychosocial questionnaires, no variable showed a significant difference between baseline and follow-up, though some trends included an increase in social contacts and a decrease in substance abuse. Additionally, after treatment, most patients reported that they have better mood, are happier, and feel less anxious than before. They also appeared to be more self-confident and experienced a better body-related experience with less distorted self-image than before treatment.
[42] Manieri et al. 2014	56 MTFs (12 months) 27 FTMf (12 months)	WHO Quality of Life questionnaire	The majority of MTFs and FTMf felt a statistically significant improvement in body image. MTFs reported a statistically significant improvement in the quality of their sexual life and in the general quality of life 1 year after GAHT initiation.
[37] Keo-Meier et al. 2015	48 FTMf (3 months) 53 MC 62 FC	Psychological functioning (Minnesota Multiphasic Personality Inventory-2 [MMPI-2])	After 2 months of GAHT (testosterone) in FTMf compared with female controls, there were statistically significant reductions relative to baseline in MMPI-2 scale scores for hypochondria, depression, hysteria, and paranoia. There were also significant increases in masculinity-femininity scores, which may indicate endorsing stereotypical masculine interests and discomfort with the female gender role. Furthermore, the percentage of transgender men with co-occurring psychopathology significantly decreased from baseline compared with 3-month follow-up relative to control. In summary, testosterone GAHT resulted in higher psychological functioning on multiple domains in transgender men relative to non-transgender male and female controls.
[43] Corda et al. 2016	2 MTFs (2 months) 5 FTMf (2 months)	Acceptance of body image (Body Uneasiness Test [BUT])	GAHT seems to reduce body discomfort by reducing the discrepancy between biological sex and desired gender. Prior to GAHT, the BUT score was indicative of clinically significant distress, which decreased following 2 months of GAHT.
[35•] Fisher et al. 2016	28 MTFs (24 months) 26 FTMf (24 months)	Body uneasiness (Body Uneasiness Test [BUT]), GD (Gender identity/Gender Dysphoria questionnaire [GIDYQ-AA]), psychopathology levels (Symptom Checklist 90 revised [SCL-90-R]), depressive symptoms (Beck Depression Inventory [BDI])	MTFs and FTMf undergoing GAHT reported significantly lower subjective levels of GD, body uneasiness, and depressive symptoms. GAHT-induced body modifications were significantly associated with a better psychological adjustment. During GAHT, MTFs and FTMf reported a significant reduction of general psychopathology, depressive symptoms, and subjective GD.
[38] Oda and Kinoshita 2017	14 FTMf (519 ± 365 days)	Minnesota Multiphasic Personality Inventory (MMPI)	After GAHT, there were improvements in the clinical scale scores of the MMPI besides the masculinity/femininity scale score. More specifically, these significant improvements were in the depression, hysteria,

Author	Participants (# of months GAHT)	Behavioral health outcomes	Results
[41] Defreyne et al. 2018	56 FTMs (12 months) 84 MTFs (12 months)	Interpersonal problems and aggression (Inventory of Interpersonal Problems [IIP-32]), anxiety and depression (Hospital Anxiety and Depression Scale [HADS]), social support (Multidimensional Scale of Perceived Social Support)	psychiatric disease qualitative deviation, and psychasthenia scale scores. There was no clinical scale with a significantly higher value after the start of GAHT compared to the initial consultation. One year of testosterone GAHT was not correlated with an increase in levels of aggression in FTMs. One year of anti-androgen and estrogen GAHT was also not associated with a decrease in aggressive behavior in MTFs. In summary, changes in serum testosterone did not influence aggression in the transgender population studied. However, there was a link between increasing aggression and anxiety levels and low-perceived social support from friends.
[40] Motta et al. 2018	52 FTMs (at least 7 months)	Anger expression (Spielberger's State-Trait Anger Expression Inventory-2 [STAXI-2])	During 7 months of continuous GAHT, both anger expression and control of anger increased as measured by the STAXI in FTMs. However, besides the increase in these anger scores, there were no accounts of aggressive behavior, self-harm, or psychiatric hospitalization.
[39] Turan et al. 2018	37 FTMs (6 months) 40 FC	Body uneasiness (Body Uneasiness Test), eating attitudes and behaviors (Eating Attitudes Test), psychological symptoms (Symptom Checklist-90 Revised)	After 6 months of GAHT, FTMs reported a decrease in body uneasiness and general psychopathological symptoms. However, eating attitudes and behaviors had not changed compared to baseline.

FC, female control; MC, male control; FTM, female-to-male transgender individual; MTF, male-to-female transgender individual; GD, gender dysphoria