General

Gender Dysphoria and Its Non-Surgical and Surgical Treatments

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Gender dysphoria is defined by severe or persistent distress associated with an incongruence between one's gender identity and biological sex. It is estimated that 1.4 million Americans and 25 million people worldwide identify as transgender and that 0.6% of Americans experience gender dysphoria. The pathophysiology of gender dysphoria is multifactorial and incompletely understood. Genetics, androgen exposure, neuroanatomy, brain connectivity, history of trauma, parents with psychological disorders, and being raised by less than two parents are associated with gender dysphoria. Gender dysphoria most frequently presents in early teenage years but can present earlier or later. Anxiety and depression are the two most common comorbid diagnoses and may be the reason for presentation to medical care. Diagnosis is established through history and or validated questionnaires. Treatment includes psychosocial therapy, pharmacotherapy for underlying depression and/or anxiety, hormonal therapy, non-genital and/or genital feminization or masculinization operations. The frequency and severity of treatment related morbidity increases progressively as treatments go from conservative to more invasive. Gender dysphoria and its treatment is individualized and not completely understood.

INTRODUCTION

Gender dysphoria, also known as gender incongruence, is a condition that occurs when an individual's gender identity differs from their biological sex. This condition can cause severe physical and psychological stress.

One recent report finds that 1.4 million individuals or 0.6%, of the adult U.S. population identifies as transgender.[1] Another meta-analysis finds that prevalence is drastically different depending on how transgender is defined. There is a higher prevalence of people who self-report as transgender than there are of patients who are being treated for gender dysphoria.[2,3]

The pathophysiology of gender dysphoria is something under active investigation. There are twin studies with small sample sizes that demonstrate a genetic component of gender identity.[4] There is also evidence of neuroanatomical differences among transgender individuals.[5–7]

A diagnosis of gender dysphoria can be made if a patient is experiencing gender incongruence that causes significant distress. Individuals typically present with gender dysphoria during adolescence, but it is not uncommon for patients to present in early childhood or after the age of 18.[8,9]

Patients with gender dysphoria who receive treatment report happier lives. There is also a decreased rate of suicidality among patients who receive appropriate gender affirmation treatment.[10] Treatment starts with hormone therapy. Patients who have received hormone therapy for a year may qualify to undergo gender confirmation surgery. Adverse effects of certain treatments, especially surgical, can be significant.

This review paper aims to update the reader on the most recent research of all aspects of gender dysphoria.

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EPIDEMIOLOGY

It is estimated that there are 25 million transgender people worldwide.[11] Determining the prevalence of gender dysphoria and transgenderism is difficult as it varies based on the definition used. For example, there is a much higher prevalence of people who self-identify as transgender compared to people who have received hormone therapy or gender affirmation surgery.[2,3] Exact prevalence is difficult to quantify due to differences among geographical areas. One report shows that the prevalence among the total U.S. population is about 0.6%, but if broken down by state, it varies from 0.3%-0.76%.[1] This also holds true when comparing epidemiological studies of gender dysphoria across different countries.[3,12] Recent data shows that there has been an increase in the prevalence of individuals seeking treatment for gender dysphoria.[13] The aforementioned report shows that the prevalence of Americans identifying as transgender has doubled over the last 10 years.[1] The biggest increase is among children and adolescents.[14] It is unclear if this is due to an actual increase in the number of individuals with gender dysphoria or a societal shift towards openness and acceptance of variations in gender identity. Prior to the overall increase in prevalence, the sex ratio once favored birth assigned males to, now, favoring birth assigned females.[15] Recent data also suggests that individuals typically experience their first gender dysphoria symptoms by age 7 and often live for over 20 years before seeking treatment.[16]

PATHOPHYSIOLOGY/RISK FACTORS

There is growing evidence for a broad biological basis of gender identity. A variety of studies show evidence of genetic links, neuroanatomical differences, and prenatal androgen exposure that affect gender identity. Data in this field is more recent, as older studies mostly focused on psychosocial aspects of gender identity and gender dysphoria.

Genetic evidence is based on studies of sex hormone signaling genes and twin concordance studies. Foreman et al. finds statistically significant genetic differences in sex signaling genes in transgender women compared to cisgender males. These differences include differences in alleles, genotypes, and allele combinations mostly involving androgen receptor genes.[17] There are many, mostly small, twin heritability studies of gender dysphoria with a recent review showing that most estimates of heritability fall in the range of 30-60%.[18] Combined, this data supports a polygenic component of gender identity.

Neuroanatomical studies show the brains of gender dysphoric individuals resemble the gender they identify with as opposed to those of the gender they were assigned at birth. Studies in this field are mainly neuroimaging studies that find increased cortical thickness, and weaker connections in regions of the brain known for processing one's own body perception.[5–7] More recently, brain connectivity studies find that brain connectivity dynamics are similar among transgender individuals and the gender they identify with than with the gender they were assigned at birth.[19] While more studies need to be done to further elucidate the neuroanatomy and neurophysiology, the current research suggests that brain architecture and function play an important role in gender identity and gender dysphoria.

It is well established that androgens play a crucial role for the development of sex characteristics, sexual, and gender identity.[20,21] Studies show that women exposed to high levels of androgens due to congenital adrenal hyperplasia (CAH) are more likely to be dissatisfied with their gender assigned at birth.[20] On the other hand, patients with complete androgen insensitivity (CAIS) typically express female gender identification.[22] These individuals are XY, but develop female secondary sexual characteristics, and most often identify as females. This occurs due to androgen receptor defects which lead to androgen resistance. CAIS patients also have undescended male testis which cause them to have male levels of testosterone. Data from these patients shows a clear link between androgen exposure and gender identity.

There are also psychosocial factors that are associated with gender dysphoria. Early researchers hypothesized that gender dysphoria development was due to certain parental influences such as lack of paternal reinforcement and paternal absence among other factors. Some of these hypotheses have been tested but the data are not conclusive.[23,24] More recent data show that elevated levels of psychopathology in parents and childhood anxiety increase risk for development of gender dysphoria.[25,26] Overall, studies on the psychosocial factors of gender dysphoria are older and more scarce than recent data on the biological factors regarding gender identity.

CLINICAL PRESENTATION AND DIAGNOSIS

Gender dysphoria has become progressively more common and has been recognized and treated earlier over the last two decades.[27] The presentation and diagnosis of these individuals can often be a challenge due to the sensitive nature of the topic. These individuals often present in their adolescent and teenage years when their gender identity.[28] In studies of adolescents done in China, there was a high correlation between those who identified as transgender and non-binary and high scores on the generalized anxiety disorder scale as well as the suicidal ideation assessment. Early detection of adolescents with gender dysphoria helps establish psychiatric treatment of comorbid depression and anxiety.[29] The Diagnostic and Statistical Manual for Mental Disorders 5th edition (DSM-5) defined two criteria for the diagnosis of gender dysphoria in adolescents. The first is defined by "A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. a marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics);
2. a strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incon-

gruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
3. a strong desire for the primary and/or secondary sex characteristics of the other gender.
4. a strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. a strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
6. a strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)".

The second criteria states that "The condition is associated with clinically significant distress or impairment in social, occupational or other important areas of functioning".[30] Most often these adolescents present during the early stages of puberty with incongruence between sex assigned at birth and gender identity.[31] This can present as many different behaviors such as changing one's hair, clothing, behaviors, or name to match their preferred gender. Distress can be observed as outbursts against parents or peers who may attempt to make the child conform to their birth sex.[32] Distress may also present as the child being resistant towards going to school through means of pretending to be sick. Distress may also present as signs of physical abuse from bullying such as bruises or scrapes.[27] Studies done in Germany showed that 26% of patients that presented to the clinic with gender dysphoria endorsed negative responses to their outings at school.[33] Comorbid depression and anxiety might also prompt patients to present to clinic, and further questioning is often required to reveal underlying gender dysphoria.[28] Treatment of underlying anxiety and depression is important in individuals who suffer from gender dysphoria as they have been shown to have higher rates of attempted and completed suicide compared to cis-gender counterparts. Studies also show that individuals who received gender-affirming treatment at younger ages had less suicidal ideation than those who received treatment later.[34] While it is most common for gender dysphoria to present in early teenage years, it is not uncommon for individuals to present in early adulthood. Almost 25-30% of patients with gender dysphoria present after the age of 18. In many of these cases, pressures from peers and family often delays presentation and treatment.[35] Another common risk factor for individuals with gender dysphoria is a history of childhood trauma. A survey conducted of 95 transgender individuals who previously self-reported having symptoms of gender dysphoria showed that 56% of these individuals experienced four or more early traumatic events in their childhood. Most often, these experiences were physical or emotional abuse from parents. Trans women had more events involving physical and psychological abuse from their father while being separated from their mothers. Trans men had more events involving their mothers and were frequently separated from and neglected by their father.[36] Studies have also shown that children who experience trauma early in life are more likely to develop disorganized attachments. This makes children more likely to develop dissociative and avoidant strategies for dealing with complex emotions and thoughts such as gender identity incongruence. Children and adolescents with significant history of trauma present later and are less likely to present to clinicians for evaluation.[37]

Several tools have been developed to help clinicians diagnose gender dysphoria. These tools include self-surveys that can be given to patients to assess thoughts and symptoms of gender dysphoria. The most common and well-studied of these questionnaires is the gender identity/gender dysphoria questionnaire for adolescents and adults (GIDYQ-AA). This questionnaire has been verified to aid in the identification of individuals with gender dysphoria. The questionnaire has a sensitivity of 90.4% in the 73 transgender patients and a 99.7% specificity for the control group which included 389 university students that were both heterosexual and homosexual.[37] Additionally, the generalized anxiety disorder assessment (GAD-7) and the patient health questionnaire (PHQ-9) should be used in all adolescents, but this is particularly important in patients with gender dysphoria due to their higher incidence of anxiety and depression.[33] Many other tools have been recently developed to help diagnose and assess gender dysphoria. The gender identity reflection and rumination scale was developed to assess how often a person thinks about their gender identity. Higher scores correlated to more thoughts on gender identity which in turn correlated to higher frequencies of gender dysphoria.[38,39] Another aspect of the prognosis of adolescents with gender dysphoria is their sense of belonging they feel with their home community. Many studies have shown that trans-gender individuals who feel accepted in their communities or home have lower incidences of comorbid anxiety, depression, and suicide than those who are raised in communities where they feel mistreated.[40]

TREATMENT

The treatment for gender dysphoria is often multi-disciplinary, combining the efforts of several behavioral health and medical professionals. The World Professional Association for Transgender Health (WPATH) has developed recommended standards of care for treatment, and it's clearly stated that these standards are "flexible" clinical guidelines.[41] The importance of this flexibility is to ensure individuality in treatment, as each patient may present with different goals or needs. The treatments can be divided into two main categories: non-operative and operative. Non-operative treatment focuses on implementing psychosocial therapy and/or medical management with hormone replacement therapy. Operative treatments range from small cosmetic procedures to much larger genital transformation surgeries. It is important to consider that an individual's overall treatment may require a combination of both operative and non-operative practices.

NON-OPERATIVE TREATMENT: PSYCHOSOCIAL THERAPY

Of the many recommended treatments for gender dysphoria, the first non-operative option is psychosocial therapy and counseling. The overall goal of psychosocial therapy is to improve the patient's quality of life through open and consistent communication.[41] There are numerous aspects to this, but the objective is to support patients as they begin to implement their gender identity to their loved ones and society. Mental health professionals provide support by answering questions and discussing body image regarding the society-based gender normative. In addition, these professionals guide patients with coming out to friends, family, and colleagues.[42] The true benefit to therapy is that it is ongoing, rather than a single experience; patients can utilize this support lifelong, which is a key component to maintaining positive outcomes. For those who may not have access to a mental health professional, numerous support systems exist, including peer groups and internet-based support groups.[43] The WPATH recognizes that psychotherapy successfully helps individuals with their gender identity without needing hormone based medical therapy or gender affirmation surgery.[41,42]

NON-OPERATIVE TREATMENT: HORMONE REPLACEMENT THERAPY

The second non-operative treatment option is medical management with hormone replacement therapy (HRT). According to the WPATH, numerous hormone combinations have been used in the treatment of gender dysphoria, however the data lacks an established standard regiment.[41] HRT requires a very in-depth pre-treatment work-up, which includes risk screening, thorough history and exam, as well as numerous laboratory studies to evaluate the patient's ability to safely tolerate hormone replacement.[44] Some aspects of this pre-treatment work-up include medical and family history accessing for previous cardiovascular or thromboembolic disease, exam findings including weight, blood pressure, and secondary sexual characteristics, and finally laboratory testing focused on blood, liver, and current hormonal function.[45] It is imperative to confirm the diagnosis and ensure that a written indication for HRT is established by a psychotherapist or psychiatrist.[44] The goal of hormone replacement therapy is to promote the characteristics of the patient's desired gender while minimizing the characteristics of their biological gender.[42]

We will first discuss feminizing therapy for male-to-female (MTF) gender dysphoria. Feminizing HRT generates the following effects on the genetically male body: it softens the skin, decreases body hair production, reduces muscle mass, reduces testicular size, and encourages breast growth. The onset of these effects may begin within 6 months, while the maximum effects are expected to take place between 1-2 years.[41,45,46] These effects are achieved with a combination of pro-estrogen and anti-androgen therapy. Several sources suggest that treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone to the level of a normal female, hence the addition of anti-androgen therapy is needed.[46,47] Pro-estrogen therapy involves the oral or transdermal administration of 17β-estradiol, which activates estrogen receptors and produces the effects listed previously. The recommended anti-androgen therapy is spironolactone, which is an androgen receptor antagonist that is very effective at inhibiting the actions of testosterone; it also has some estrogenic activity.[48] Supplementing synthetic estrogen has its risks, and it is very important for clinicians to monitor serum estradiol levels routinely every 3 months. Although the risk of adverse effects is controversial, the data supports that elevated levels of blood estrogen may lead to increased risk of liver disease, cardiovascular disease, hypertension, hyperprolactinemia, hypertriglyceridemia, and thromboembolic events.[41,44,45,49]

The next discussion will be on masculinization therapy for female-to-male (FTM) gender dysphoria. This treatment is generally less complex than MTF therapy. Here, the primary hormone supplemented is testosterone. Several medications are available, which include testosterone enanthate and testosterone cypionate. These two specifically are administered via intramuscular injection, but other options are available that are administered via transdermal gels or patches. Administering testosterone activates androgen receptors which produces the following effects on the genetically female body: increased skin oiliness, increased facial and body hair production, increased muscle mass/strength, redistributed fat, halted menses, deepened voice, enlarged clitoris, and vaginal atrophy.[50,51] With FTM therapy, supplementing with testosterone provides individuals with the desired body changes. Anti-estrogen therapy is not needed to achieve the physiologic levels of testosterone in the normal male. This is what makes FTM therapy less complex than MTF therapy.[41,46] With testosterone supplementation, the adverse risks to screen and monitor for include erythrocytosis, liver disfunction, cerebrovascular disease, coronary artery disease, and breast or uterine cancer.[44,46,47,49]

OPERATIVE TREATMENT

Many patients with gender dysphoria require some form of surgery to fully achieve their desired body image and psychological gender identity. These procedures, both genital and non-genital, are collectively known as "Gender Confirmation Surgery" (GCS). Genital surgeries specifically are often the last recommended as part of the overall treatment of gender dysphoria. This is due to permanent alteration in fertility, as well as the risks that are associated with surgery in general. When applicable, GCS can be utilized by health care experts to enhance patients' gender identities in ways that psychotherapy and HRT may not be able to.[42,52] The WPATH recommends patients undergo some form of social transition utilizing psychotherapy and HRT prior to considering surgical treatment, but it is not a requirement for all procedures.[1] However, the WPATH has specific criteria for genital GCS, and this includes having at least 2 referrals from separate medical health professionals and complete patient compliance with at least 12 months of continued HRT. It is important to note that GCS is performed by many

surgical fields, including plastic surgery, urology, otolaryngology, gynecology, and general surgery.[41,52]

OPERATIVE TREATMENT: NON-GENITAL FEMINIZATION

There are several methods in which transgender women can surgically enhance their body image. The following are some of the procedures available: hair reconstruction and removal, voice modification, lipofilling, botulin toxin injections, mammoplasty, breast augmentation, gluteal augmentation, waist lipoplasty, and facial plastics. Facial plastics is the most sought after and contains an extensive array of options for patients. Some of the procedures that specifically fall under facial plastics include lip filler, face lifts, rhinoplasty, sinus surgery, forehead cranioplasty, supraorbital ridge reduction, mandibular reduction, and genioplasty.[50,53,54] There are several sources confirming that patients who undergo non-genital feminization surgery have high satisfaction rates and these procedures are often more desired compared to genital reconstruction surgery.[41,42,49,54]

OPERATIVE TREATMENT: GENITAL FEMINIZATION

The most important aspect to determining which type of genital feminization surgery a patient desires is whether the patient is wanting penetrative ability. If an individual desires just the feminine appearance without penetrable ability, the recommend procedure would be a bilateral orchiectomy with a penectomy and urethroplasty. The orchiectomy would remove the main source of endogenous testosterone production, while the penectomy and urethroplasty would remove the penis and leave a proper functioning urethra. If a natural appearing vulva without penetrative ability is desired, then the recommended surgery here would be a vulvoplasty with clitoro-labioplasty. Finally, if a patient desires the natural vulva appearance with penetrative ability, an even more complex procedure is recommended. Here, the surgeon would perform the previously mentioned procedures with the addition of a vaginoplasty.[52] The vagina would be created either by inverting the penile skin or utilizing an intestinal graft while the vulva will be shaped using various skin graft techniques.[55] There are numerous complications that may arise from these invasive procedures. The more prevalent complications include neovaginal bleeding, discharge, introital stenosis, misdirected urinary stream, urinary incontinence, would healing disorders, and infection.[56–58]

OPERATIVE TREATMENT: NON-GENITAL MASCULINIZATION

As compared to feminization surgery, there are fewer non-genital procedures performed for masculinization. The most popular and sought-after procedures involve masculinizing the chest which consists of subcutaneous mastectomy, chest contouring, pectoral implanting, and breast augmentation. For facial plastics, the most performed masculinization procedures are genioplasty, liposuction, and facial hair transplantation.[42,44,52,55] As with feminization, these non-genital masculinization procedures have high satisfactory rates from patients when combined with the additive effects HRT produces.[41,42,49,54] This is likely due to HRT for masculinization providing enough of an effect to reduce existing feminine characteristics.

OPERATIVE TREATMENT: GENITAL MASCULINIZATION

For genital altering masculinization, many transgender males prefer to start with removal of their biological reproductive organs. This consists of a complete hysterectomy, oophorectomy, and vaginectomy. Doing so permanently eliminates fertility and terminates menstruation; the termination of menstruation is one of the most desired outcomes. To achieve standing micturition, transgender males may undergo urethral lengthening. If the appearance of external male genitalia is desired, more complex procedures are required, such as metoidioplasty or phalloplasty with a scrotoplasty. The combination of these procedures allows transgender males to fully replicate external male genitalia.[58,59] As with feminization genital surgery, similar risks and complications exist with masculinization genital surgery which include including urinary incontinence, would healing disorders, and infection.[42,56,59]

CONCLUSION

In recent decades, changes in the acceptance of variations in gender identity have facilitated more individuals openly expressing themselves as transgender. This is evident by the increasing number of people who identify as transgender over the past decade.[1] There is also an increasing body of evidence of a biological basis of gender identity. The rate of increase of prevalence of transgender individuals has been highest among children and young adolescents.[14] These patients will often first present to their primary care providers (pediatricians in this case) with either complaints of depression or anxiety from suffering with their identity crisis, or questions or desire about gender transition treatment. Treatment decreases suicidality among individuals with gender dysphoria and leads to improved quality of life.[10] Treatment options include psychosocial therapy, medical treatment for underlying depression and/or anxiety, hormonal treatment, and more than a dozen possible surgical procedures. More invasive treatments are associated with more severe adverse effects. Gender identity research is increasing rapidly, but there are still gaps in knowledge. Also, there is a need for large studies of long-term health outcomes of transgender individuals receiving medical and/or surgical treatment for gender dysphoria. Overall, this review paper provides the most up to date information regarding gender dysphoria and its treatments.

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