CURRENT OPINION

Progress on the road to better medical care for transgender patients

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Purpose of review
In order to improve transgender individuals' access to healthcare, primary care physicians and specialists alike should be knowledgeable about transgender medicine. This review is intended to provide concise transgender hormone treatment guidelines.

Recent findings
Transgender individuals report that the lack of knowledgeable providers represents the greatest barrier to transgender medical care. Hormone treatments are generally well tolerated and greatly benefit transgender patients. After physicians recognize that gender identity is stable, hormone treatments for transgender patients are often straightforward.
A practical target for hormone therapy for transgender men (female to male) is to increase testosterone levels to the normal male physiological range (300–1000 ng/dl) by administering testosterone. A practical target for hormone therapy for transgender women (male to female) is to decrease testosterone levels to the normal female range (30–100 ng/dl) without supra-physiological levels of estradiol (<200 pg/ml) by administering an antiandrogen and estrogen. Patients should be monitored every 3 months for the first year and then every 6–12 months for hormonal effects.

Summary
Although more studies are required, recently published transgender medical treatment guidelines provide a good start toward making care of transgender patients more generalized and accessible to healthcare providers.

Keywords
female to male, hormone therapy, male to female, transgender, transsexual

INTRODUCTION

Transgender individuals have gender identities that differ from the biological sex assigned to them at birth. One study estimates that 0.3% of adults or 900 000 individuals are transgender in the USA [1]. Transgender individuals have limited access to healthcare due both to a lack of adequate insurance and to a lack of knowledgeable providers [2]. To begin to educate providers, both the World Professional Association for Transgender Health (WPATH) and The Endocrine Society have created transgender care guidelines for broad use by physicians in multiple specialties. To further improve transgender healthcare, transgender medicine needs to be included in general medical curricula.

BARRIERS TO CARE

Transgender individuals face many barriers to adequate healthcare. Some reports suggest that transgender individuals are less likely to have insurance [2]. For those who do, hormone therapy and sex reassignment surgery are often not covered [3■]. Difficulty finding knowledgeable providers is the most commonly reported barrier to healthcare for transgender individuals [2]. The lack of knowledgeable providers remains a barrier even as access to healthcare increases [2].

Hormone therapy has been shown to improve transgender patients' quality of life [4■]. Transgender patients who do not have access to physicians knowledgeable about transgender healthcare may

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KEY POINTS

- In order to improve transgender individuals' access to health care, the approach to transgender medicine needs to be generalized and accessible to physicians in multiple specialties.

- A practical target for hormone therapy for transgender men (FTM) is to increase testosterone levels to the normal male physiological range (300–1000 ng/dl) by administering testosterone.

- A practical target for hormone therapy for transgender women (MTF) is to decrease testosterone levels to the normal female range (30–100 ng/dl) without supra-physiological levels of estradiol (<200 pg/ml) by administering an antiandrogen and estrogen.

- Transgender adolescents usually have stable gender identities and can be given GnRH analogs to suppress puberty until they can proceed with hormone therapy as early as age 16.

seek hormones from other sources [2]. Although there has been increasing interest in teaching providers tolerance and cultural competency for lesbian, gay, bisexual, and transgender patients in general, sensitivity training alone is inadequate to increase the number of knowledgeable transgender healthcare providers.

LACK OF TRANSGENDER MEDICAL EDUCATION

Transgender medicine is not traditionally taught in medical school curricula. Whereas the majority of medical schools report teaching gender identity, only one-third of schools report teaching something about both hormonal and surgical transitioning, or either of them [5]. Even among that one-third of medical schools, it is unclear if the instruction is sufficiently detailed to result in physicians confident and knowledgeable in transgender medical care.

A common result of the failure to teach transgender medicine is that many physicians believe transgender patients are suffering from a psychological disorder that can only be treated through psychiatric intervention [6]. The assumption is that gender identity is malleable [6]. Once it is understood that gender identity is fixed, hormonal treatments for transgender individuals are straightforward.

EVIDENCE THAT GENDER IDENTITY IS NOT REVERSIBLE

Evidence for gender identity being fixed comes from the literature regarding 46 XY children with

congenital anomalies who were raised as girls. In a study of 14 genetically male children with cloacal exstrophy assigned female at birth, investigators found that eight of the children later identified as male [7]. Two additional children assigned as male continued to identify as male [7]. In a larger study of 46 XY children with penile agenesis, cloacal exstrophy, and penile ablation, investigators found that 15 of the 72 children assigned female at birth identified as male, and an additional 10 of the 72 children who continued to identify as female reported significant gender dysphoria [8]. All of the children assigned male at birth continued to identify as male, except one male child who reported gender dysphoria [8].

Studies of transgender individuals' brains suggest a physical manifestation of gender identity. A post mortem study of six male-to-female (MTF) transgender individuals found that the size of the bed nucleus of the stria terminalis (BST) in the hypothalamus was within the female range [9]. Examination of an MTF who did not undergo hormonal treatment also showed BST staining within the female range [10]. In addition, examination of one female-to-male (FTM) transgender individual revealed a BST within the male range [10]. These differences in BST staining were independent of sexual orientation and sex hormones [9,10]. A PET study found hormonally treated MTF individuals exhibited a pattern of hypothalamic activation that was intermediate between male and female when smelling certain steroids [11]. Diffuse tensor imaging studies showed that untreated FTM individuals exhibited white matter microstructure more similar to males than females, and untreated MTF individuals exhibited white matter microstructure intermediate between male and female individuals [12,13]. Although these studies are small and there has not been a sexually dimorphic function attributed to these areas of the brain in humans, the studies are consistent with an organic nature to gender identity.

Although research to support the organic nature of gender identity is modest, there is no convincing literature that demonstrates an ability to externally change a person's gender identity. The literature that does support this claim tends to confuse sex-stereotyped behaviors with internal gender identity [14]. Attempts to change gender identity rely on pressure to conform to sex norms [14], which only results in poor psychosocial outcomes [15].

HORMONAL TREATMENT FOR TRANSGENDER INDIVIDUALS

Both the WPATH's and The Endocrine Society's guidelines for the treatment of transgender patients

are examples of the trend toward more generalizable and evidence-based treatment guidelines. Both sets of guidelines give the same general approach to hormone therapy for transgender patients: androgens to virilize FTM patients and estrogens, in addition to antiandrogens, to feminize MTF patients [16,17]. In order to be conservative and avoid harm, most transgender hormone guidelines in the past suggested that transgender individuals undergo a 'real-life test' living in chosen gender prior to hormone therapy. Undergoing a 'real-life test' was thought to ensure that patients would be prepared for the social transition to desired gender [18]. Because of the difficulty of living in a chosen gender without matching physical characteristics, the 'real-life test' is impractical for many transgender individuals. It is no longer suggested that it be mandatory before the initiation of hormone therapy, but rather run in parallel [16,19].

Mental health support is integral to a good transgender health program. Patients should be screened for confounding psychiatric issues and the patient's psychological ability to undergo hormone therapy should be assessed. Although transgender individuals have a high incidence of psychological distress, it is often a result of social stigma, not gender identity [20■].

The following regimens are distilled from WPATH's and The Endocrine Society's guidelines [16,17], and are meant to be straightforward for most practitioners.

Transgender men (female-to-male)

The hormonal treatment for transgender men (individuals female assigned at birth who identify as men) is very similar to hormone replacement therapy for hypogonadal males. In order to achieve maximum virilization, testosterone levels should be increased to be within the normal male physiological range (300–1000 ng/dl). The exact effects and time course of testosterone will vary. However, patients can anticipate amenorrhea, increased facial/body hair, increased acne, increased libido, increased muscle mass, and redistribution of fat within the first 3 months of testosterone therapy. Deepening of the voice, clitoromegaly, and male pattern hair loss should be expected within the first year.

Testosterone can be administered orally, transdermally, or parenterally, although no oral products are available in the USA (Table 1). Testosterone can be started with half the anticipated dose and then titrated quickly to achieve the male physiological serum levels (300–1000 ng/dl). Oral testosterone undecanoate (160–240 mg/day) is available outside

Table 1. Hormone regimes for transgender men (female to men)

Oral	
Testosterone undecanoate[a]	160–240 mg/day
Parenterally (i.m. or subcutaneous)	
Testosterone enanthate or cypionate	50–200 mg/week or 100–200 mg/2 weeks
Testosterone undecanoate[a]	1000 mg/12 weeks
Transdermal	
Testosterone 1% gel	2.5–10 g/day
Testosterone patch	2.5–7.5 mg/day

i.m., intramuscular.
[a]Not available in the USA.

the United States. Testosterone enanthate or cypionate 50–200 mg weekly can be administered intramuscularly (i.m.) or subcutaneously [21]. Higher doses (100–200 mg) can be administered every 2 weeks, but may result in more significant periodicity in testosterone levels. Testosterone undecanoate i.m. (1000 mg every 12 weeks) is not available in the USA. Transdermal preparations such as testosterone 1% gel (2.5–10 g/day) or testosterone patch (2.5–7.5 mg/day) will achieve the same virilizing effects as intramuscular testosterone, but the patch may cause skin irritation. Although transdermal preparations may result in smoother testosterone levels, it may be harder to achieve desired levels with them.

Patients taking testosterone should be monitored for virilizing and adverse effects every 3 months for the first year and then every 6–12 months (given below).

Monitoring for transgender men (FTM) on hormone therapy:

(1) Monitor for virilizing and adverse effects every 3 months for first year and then every 6–12 months.
(2) Monitor serum testosterone at follow-up visits with a practical target in the male range (300–1000 ng/dl). Peak levels for patients taking parenteral testosterone can be measured 24–48 h after injection. Trough levels can be measured immediately before injection.
(3) Monitor hematocrit and lipid profile before starting hormones and at follow-up visits.
(4) Bone mineral density (BMD) screening before starting hormones for patients at risk for osteoporosis. Otherwise, screening can start at age 60 or earlier if sex hormone levels are consistently low.
(5) FTM patients with cervixes or breasts should be screened appropriately.

Serum testosterone levels should be monitored until stabilization within the male range. Patients taking testosterone enanthate or cypionate i.m. can have testosterone peak levels measured 24–48 h after injections and occasional trough levels measured immediately prior to injections. Patients taking testosterone transdermally can have levels sampled at any time after 1 week. Androgen-sensitive indices such as hematocrit (or hemoglobin) and lipid profile should be monitored at follow-up visits. Adequate levels of sex hormones are required to maintain bone mass. FTM individuals at risk for osteoporosis should have BMD measured before initiating testosterone. Otherwise, BMD screening can be initiated at age 60 or if testosterone levels are consistently low. Transgender men with cervixes or breast tissue should be screened accordingly.

Testosterone therapy should not be initiated in patients who are pregnant, have unstable coronary artery disease, or untreated polycythemia (hematocrit at or above 55%). Testosterone therapy may unmask polycythemia and hyperlipidemia, which should be treated appropriately. It is unknown if testosterone therapy puts transgender men at an increased risk for uterine or ovarian cancer, so a hysterectomy is still often considered as a preventive measure.

Transgender women (male-to-female)

The hormonal treatment for transgender women (individuals male assigned at birth who identify as women) is slightly more complicated than the regime for transgender men. In order to achieve maximum feminization, transgender women with testis require an antiandrogen in addition to estrogen. The goal in hormone therapy for transgender women is to decrease testosterone to the female range (30–100 ng/dl) without supra-physiological levels of estradiol (<200 pg/ml). The effects and time course of estrogen and antiandrogen therapy vary. Patients can expect decreased facial/body hair, decreased libido, decreased spontaneous erections, decreased skin oiliness, decreased muscle mass, redistribution of fat, and breast development within the first 3–6 months. Breast growth will usually peak after 2 years of hormone therapy.

Antiandrogens allow lower doses of estrogen (Table 2). Spironolactone inhibits the secretion and activity of testosterone (although the mechanism for the former is not known). It is the least costly antiandrogen used in the USA. Spironolactone is an aldosterone receptor antagonist that has been shown to decrease mortality in patients with New York Heart Association class 3+ congestive heart failure [22]. Spironolactone can be administered

Table 2. Hormone regimes for transgender women (MTF)

Anti-androgen	
Spironolactone	100–200 mg/day (up to 400 mg)
Cyproterone acetate[a]	50–100 mg/day
GnRH agonists	3.75 mg subcutaneous monthly
Oral estrogen	
Oral conjugated estrogens	2.5–7.5 mg/day
Oral 17-beta estradiol	2–6 mg/day
Parenteral estrogen	
Estradiol valerate or cypionate	5–20 mg i.m./2 weeks or 2–10 mg i.m./week
Transdermal estrogen	
Estradiol patch	0.1–0.4 mg/2X week

i.m., Intramuscular; MTF, male to female.
[a]Not available in the USA.

in doses of 100–200 mg daily, but sometimes levels up to 400 mg may be administered if tolerated. Doses can be divided, but patients should be aware that the weak diuretic properties of spironolactone may become more apparent at higher doses, making evening doses less attractive. Cyproterone acetate 50–100 mg daily is often used in Europe, but is not available in the USA. Gonadotropin Releasing Hormone (GnRH) agonists (3.75 mg subcutaneously monthly), such as leuprolide, inhibit the production of luteinizing hormone (LH)/follicle-stimulating hormone (FSH) and therefore testosterone, but are often very expensive. Although GnRH agonists have been used in adolescent transgender individuals and appear well tolerated, there are no studies demonstrating safety with very long-term use.

Estrogen can be administered orally, transdermally, or parenterally (Table 2). Oral conjugated estrogens 2.5–7.5 mg and oral 17-beta estradiol 2–6 mg daily are popular because they are easy to use and readily available. Whereas some metabolites of conjugated estrogens may be missed on serum estradiol tests, the testing is still used as a rudimentary indicator that estradiol levels are below a supra-physiological range (<200 pg/ml). Synthetic estrogens, such as ethinyl estradiol, have been associated with an increased risk of venous thromboembolism [23]. Estradiol can be started at 1/4 strength and increased until serum testosterone levels are within the female range (30–100 ng/dl). A transdermal estradiol patch 0.1–0.4 mg twice weekly can be used in transgender women who are at increased risk for thromboembolic disease. Estradiol can be administered parenterally with estradiol valerate or

cypionate 5–20 mg i.m. every 2 weeks or 2–10 mg i.m. every week, but levels are harder to monitor.

Transgender women on hormone therapy should be monitored for feminizing and adverse effects every 3 months for the first year and then every 6–12 months (given below).

Monitoring for transgender women (MTF) on hormone therapy:

(1) Monitor for feminizing and adverse effects every 3 months for first year and then every 6–12 months.
(2) Monitor serum testosterone and estradiol at follow-up visits with a practical target in the female range (testosterone 30–100 ng/dl; E2 <200 pg/ml).
(3) Monitor prolactin and triglycerides before starting hormones and at follow-up visits.
(4) Monitor potassium levels if the patient is taking spironolactone.
(5) BMD screening before starting hormones for patients at risk for osteoporosis. Otherwise, start screening at age 60 or earlier if sex hormone levels are consistently low.
(6) MTF patients should be screened for breast and prostate cancer appropriately.

Serum testosterone and estradiol levels should be monitored until they stabilize within the female range (testosterone 30–100 ng/dl; E2 <200 pg/ml). Spironolactone is a potassium-sparing diuretic and can cause hyperkalemia; so it is vital to monitor potassium for patients taking spironolactone. Estrogen-sensitive indices such as prolactin and triglycerides should be monitored also. Patients should also be screened for venous thromboembolism and other cardiovascular impairments. Adequate levels of sex hormones are required to maintain bone mass. MTF individuals at risk for osteoporosis should have BMD measured before initiating hormone therapy. Otherwise, BMD screening should be initiated at age 60 or if sex hormone levels are consistently low. Transgender women should be screened for breast and prostate cancer appropriately.

Whereas it is thought that feminizing hormone therapy may increase risk of venous thromboembolic disease, hypertriglyceridemia, cardiovascular disease, hypertension, hyperprolactinemia, and prolactinoma, the degree of risk remains an area for future study [24▪].

Children and adolescents

Treatment for transgender children and adolescents involves a 'wait and see' approach using puberty blockers. Children who identify with a gender other than the one assigned at birth do not become transgender adolescents the majority of the time [25,26]. Since it is difficult to know if a child's gender identity will persist into adulthood, it is important to limit permanent treatments. In addition, children should not be treated medically until after puberty begins because reactions to first changes of puberty often have diagnostic value [17]. Puberty suppression via GnRH analogs can be started at Tanner stage 2–3 [17]. Puberty suppression is reversible and provides time to determine if hormone therapy will be initiated (at the age of 18, or as early as 16) [17]. Unlike transgender children, transgender adolescents are likely to have persistent gender identities and become transgender adults [26]. Puberty suppression can decrease emotional and behavioral problems as well as increase functioning [27]. Permanent surgeries should be deferred until patients are able to consent (e.g. at age 18) [17].

CHANGE IS POSSIBLE

Hormone therapy is the most effective treatment for transgender patients. The number of transgender patients seeking medical care has risen dramatically [3▪]. Transgender patients are presenting to clinics for hormone therapy at younger ages and are less likely to acquire hormones from other sources [3▪]. These trends may be a result of increasing acceptance of transgender individuals [3▪]. To keep up with these trends, it is vital to mainstream transgender care among medical providers. Data suggest that such change would not be difficult. The simple addition of a 1-h lecture to the standard medical school curriculum at Boston University School of Medicine increased students' willingness to treat transgender patients [28▪]. In order to increase transgender patients' access to knowledgeable providers, transgender medicine needs to be taught to all physicians and to be included in medical education going forward.

CONCLUSION

Attention to transgender medical care is much improved. Recently published transgender medical treatment guidelines provide a good start toward making care of transgender patients more generalized and accessible to healthcare providers. A need remains for other maneuvers to improve access such as the implementation of routine insurance coverage and the introduction of transgender content into general medical curricula. More research is required to better define both benefits and risks of hormone therapy for transgender patients. There is reason for optimism, although much work remains.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■   of special interest
■■   of outstanding interest

1. Gates GJ. How many people are lesbian, gay, bisexual, and transgender? The Williams Institute; 2011.
2. Sanchez NF, Sanchez JP, Danoff A. Healthcare utilization, barriers to care, and hormone usage among male-to-female transgender persons in New York City. Am J Public Health 2009; 99:713–719.
3. Leinung MC, Urizar MF, Patel N, Sood SC. Endocrine treatment of transsexual
■   persons: extensive personal experience. Endocr Pract 2013; 19:644–650.
This study details demographics and trends among transgender patients seen by a single provider over two decades at a clinic in Albany, New York.
4. Gorin-Lazard A, Baumstarck K, Boyer L, et al. Is hormonal therapy associated
■   with better quality of life in transsexuals? A cross-sectional study. J Sex Med 2012; 9:531–541.
In contrast to studies that examine the effects of sex reassignment surgery on the quality of life of transgender patients, this study examines the effects of hormone therapy.
5. Obedin-Maliver J, Goldsmith ES, Stewart L, et al. Lesbian, gay, bisexual, and transgender-related content in undergraduate medical education. J Am Med Assoc 2011; 306:971–977.
6. Safer JD, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. Endocrine Pract 2008; 14:248–250.
7. Reiner WG, Gearhart JP. Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. N Engl J Med 2004; 350:333–341.
8. Meyer-Bahlburg HFL. Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. Arch Sex Behav 2005; 34:423–438.
9. Zhou J-N, Hofman MA, Gooren LJG, Swaab DF. A sex difference in the human brain and its relation to transsexuality. Nature 1995; 378:68–70.
10. Kruijver FP, Zhou JN, Pool CW, et al. Male-to-female transsexuals have female neuron numbers in a limbic nucleus. J Clin Endocrinol Metab 2000; 85:2034–2041.
11. Berglund H, Lindström P, Dhejne-Helmy C, Savic I. Male-to-female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. Cerebr Cortex 2008; 18:1900–1908.
12. Rametti G, Carrillo B, Gómez-Gil E, et al. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. J Psychiatr Res 2011; 45:199–204.
13. Rametti G, Carrillo B, Gómez-Gil E, et al. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. J Psychiatr Res 2011; 45:949–954.
14. Green R, Newman L, Stoller R. Treatment of boyhood 'transsexualism'. Arch Gen Psychiatry 1972; 26:213–217.
15. Liao L-M, Audi L, Magritte E, et al. Determinant factors of gender identity: a commentary. J Pediatr Urol 2012; 8:597–601.
16. World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. 7th ed.; 2011. http://www.wpath.org/documents/Standards%20of%20Care%20V7%20-%202011%20WPATH.pdf (Accessed on 24 December 2012)
17. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009; 94:3132–3154.
18. Gooren LJ. Care of transsexual persons. N Engl J Med 2011; 364:2559–2560.
19. Bhasin S, Safer J, Tangpricha V. The hormone foundation 's patient guide to the endocrine treatment of transsexual persons. J Clin Endocrinol Metab 2009; 94:.
20. Bockting WO, Miner MH, Swinburne Romine RE, et al. Stigma, mental health,
■   and resilience in an online sample of the US transgender population. Am J Public Health 2013; 103:943–951.
This study characterizes how stress among transgender individuals may be minimized through access to mental health services, peer support, and social change.
21. Olshan JS, Spack NP, Eimicke T, et al. Evaluation of the efficacy of subcutaneous administration of testosterone in female to male transsexuals and hypogonadal males. Endocr Rev 2013; 34:. (03_MeetingAbstracts): MON-594.
22. Nagarajan V, Chamsi-Pasha M, Tang WHW. The role of aldosterone receptor antagonists in the management of heart failure: an update. Cleve Clin J Med 2012; 79:631–639.
23. Asscheman H, Giltay EJ, Megens JAJ, et al. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2011; 164:635–642.
24. Wierckx K, Mueller S, Weyers S, et al. Long-term evaluation of cross-sex
■   hormone treatment in transsexual persons. J Sex Med 2012; 9:2641–2651.
This study characterizes consequences of 10 years on hormone therapy for a cohort of 100 transgender patients who have undergone sex reassignment surgery.
25. Wallien MSC, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. J Am Acad Child Adolesc Psychiatry 2008; 47:1413–1423.
26. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJG. The treatment of adolescent transsexuals: changing insights. J Sex Med 2008; 5:1892–1897.
27. De Vries ALC, Steensma TD, Doreleijers TAH, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. J Sex Med 2011; 8:2276–2283.
28. Safer JD, Pearce EN. A simple curriculum content change increased medical
■   student comfort with transgender medicine. Endocrine Pract 2013; 33:39–44.
This study demonstrates that a 1-h lecture on transgender medicine increased medical students' willingness to treat transgender patients.