

Clinical Update

Medical Care of Transsexual Patients

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Transsexual patients often have difficulty finding care because many physicians are not comfortable prescribing appropriate hormone regimens. Management of hormones for transsexual patients is not difficult, and these medications are safer than many therapies routinely prescribed by the primary care physician. The diagnosis of gender identity disorder (GID) must be established by an experienced mental health professional prior to consideration for hormonal management. Medical evaluation includes a thorough medical history, social history, family history, physical examination, and basic laboratory screening. If there are no medical contraindications, a variety of regimens for the male-to-female transsexual may be initiated, with initial close follow-up for medical and psychological well-being. There is less variation in female-to-male management with testosterone, but initial frequent follow-up is equally important. This review is intended to teach primary care providers how to initiate and maintain hormone regimens for transsexual patients and describe medical issues unique to transsexual patients.

KEY WORDS: transsexual; hormones; gender identity disorder; testosterone; estrogen; transgender.

Transsexuals are persons who are biologically one gender but who identify internally as members of the other gender. The term *transsexualism* was replaced in the *Diagnostic and Statistical Manual-IV* (DSM-IV) with *gender identity disorder (GID)*, a broader term inclusive of transsexualism, gender identity disorder of childhood, and gender identity disorder of adulthood (1). The term *transsexual* is still widely used in the medical and lay communities (2). The term *transgendered* is often used interchangeably with transsexual, but is a broader term, not found in the DSM-IV, referring to individuals who are transsexual, cross-dressers, biologically intersexed, or otherwise challenge strict gender norms.

Transsexual patients often have difficulty finding care because many physicians are not comfortable prescribing appropriate hormone regimens. Once one becomes familiar with hormone regimens, usual dosing schedules, and side effects, management of hormones is easier and safer than many therapies routinely prescribed by primary care physicians.

PROPER DIAGNOSIS AND ELIGIBILITY FOR HORMONAL THERAPY

The diagnosis of GID should first be established by a qualified, experienced mental health professional. The role of the primary care physician is to determine any medical contraindications to hormones once a mental health professional has determined that the patient is psychologically appropriate for hormonal therapy. DSM-IV diagnostic criteria for gender identity disorder are described in Table I.

The Harry Benjamin International Gender Dysphoria Association (HBI-GDA) is a professional group devoted to the understanding and treatment of gender identity disorders. This group originally published *The Standards of Care for Gender Identity Disorders* in 1979. They were most recently revised in 1998 and are available through the organization's web page: www.tc.umn.edu/nlhome/m201/cole001/hbgda/. The guidelines are intended to provide treatment consistency in the "psychiatric, psychological, medical, and surgical management of gender identity disorders" and are meant to "provide flexible direction in the treatment of gender identity disorders" (3).

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Table I. Summary of Diagnostic Criteria: Gender Identity Disorder in Adults and Adolescents

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- A. A strong and persistent cross-gender identification—Manifested by stated desire to be the other sex, desire to live or be treated as the other sex, or the conviction that he or she has typical feelings and reactions of the other sex.
- B. Persistent discomfort with his/her gender—Manifested by preoccupation with getting rid of primary and secondary sex characteristics (requests for hormones, surgery, or other procedures to simulate the other sex)
- C. Disturbance is not concurrent with a physical intersex condition
- D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
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These guidelines are generally well accepted in the medical community, although controversy regarding the guidelines exists in the transsexual community. Some believe they unnecessarily restrict access to hormones and surgery. Proponents argue that proper diagnostic assessment, psychotherapy, and “real-life experience” are necessary to ensure individuals are not subjected to inappropriate hormonal or surgical intervention. In the real-life experience, the individual lives as their internally identified gender, gaining a better appreciation for the profound personal and social changes involved. The real-life experience can be difficult for individuals who have trouble “passing” as the other gender without hormones, electrolysis, and cosmetic surgery. Transitioning gender at work can be a complex and difficult process, and some choose to “live the role” everywhere outside the workplace. The Standards of Care acknowledge these difficulties by allowing psychotherapy as an alternative to the real-life experience. HBGDA standards for hormone therapy are outlined in Table II.

INITIAL VISIT

The initial visit to the primary care provider to evaluate for hormone therapy should be long

enough to allow for a careful history, physical, and discussion of hormone risks, benefits, and expectations in the physician–patient relationship. Starting the interview by asking about the patient’s gender experience that has culminated in a visit for hormones allows a better appreciation for the patient’s journey and confirms the mental health professional’s diagnosis and recommendation for treatment. A complete medical history should probe for any history of hypertension, ischemic heart disease, thrombophlebitis or thromboembolic disease, cerebrovascular disease, hepatic dysfunction, renal insufficiency, refractory migraine headaches or seizures, poorly controlled diabetes, obesity, hyperlipidemia, and psychiatric illnesses.

Careful screening for tobacco use, alcohol use, and other substance use history is essential on the initial visit. Family history should include history of premature cardiac death, thromboembolic disease, breast cancer, and hyperlipidemia. Social history can elucidate the patient’s support system and whether family and friends know and are supportive of the planned gender transition. It is important to establish open and nonjudgmental communication regarding sexual history, obtaining gender of past partners, number of partners, sexual practices, and sexual identity.

Table II. Standards of Care for Gender Identity Disorders: Eligibility and Readiness Criteria for Hormonal Therapy in Adults

Eligibility Criteria

1. 18 years of age
2. Knowledge of what hormones medically can and cannot do, social benefits and risks
3. *Either* documented real-life experience^a for at least 3 months prior to hormones *or*
4. Psychotherapy of a duration specified by the mental health professional (usually 3 months)
5. Under no circumstances should a person be provided hormones who has fulfilled neither criteria 3 or 4

Readiness Criteria

1. Further consolidation of gender identity during the real-life experience or psychotherapy
 2. Progress in mastering problems leading to improving or continued stable mental health
 3. Hormones likely to be taken in responsible manner
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^aHormones can be given to those who do not desire surgery or real-life experience. However, they must be appropriately diagnosed and meet the criteria stated above for hormone administration.

This helps establish risk of HIV and other sexually transmitted diseases and establishes openness to such discussions in the future. It is not uncommon for sexual orientation to evolve as an individual changes gender. As one patient commented, "I had to get this gender thing figured out before I could figure out who I was attracted to."

A physical exam attempts to uncover any medical issues not recognized in the history. A complete exam must include a breast exam, pap test, and pelvic exam in the preoperative female-to-male (FTM) transsexual, and a genitourinary exam in all male-to-female (MTF) patients. In MTFs older than 40, this should include digital rectal exam and palpation of the prostate. Initial laboratory testing should include complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, liver function tests, thyroid stimulating hormone (optional), complete urinalysis, and lipid panel. MTF patients should also have an initial prolactin level drawn, and the provider may

choose to obtain a free testosterone level for use as a baseline.

The most important component of the initial visit is to discuss the risks and benefits of hormonal therapy. Patients must understand what physical changes to expect with the hormones that are often not reversible on discontinuation of therapy. It is equally important they understand what changes will not occur with the hormones. Physicians should outline patient expectations for continued hormone therapy, and may want to provide the HBGDA standards of care for patients. Medical insurance rarely covers hormonal therapy for gender identity disorder, so an anticipated schedule of follow-up visits and laboratory work is helpful so patients can financially prepare for future visits. Once questions have been answered, the patient should sign an informed consent form. Examples of patient educational handouts, expectations, and informed consents are provided in Tables III through VI. These may be photocopied or edited and copied,

Table III. Patient Handout: Guidelines for Hormone Therapy: Male-to-Female

The process of changing one's gender is a serious, important, and potentially dangerous project. The normal process of going through puberty is a gradual one, and to transform a male body to a female one also takes time. There are several things you can do to achieve optimum results both physically and psychologically in a safe manner.

In our program, we have some general principles that we address with you numerous times. They may be different from things you may hear from friends, on the Internet, or from other doctors. However, in reviewing the medical literature, communicating with other gender centers, and following patients for years, we have found them to be sound principles that result in safer transitions with excellent results.

PRINCIPLES

1. Gender change is a gradual change both physically and psychologically. Your body and mind need time to adjust in a healthy manner. It takes approximately 5 years to complete the process.
2. Living in your chosen role is the single most important thing that you can do in this process. For a variety of reasons, some transsexual individuals are not able or willing to live in their chosen role. Your physician may still prescribe hormones in these cases, assuming you continue psychotherapy. Your doctor will have ongoing discussions with you about your thoughts on this process.
3. Hormones are potent medications with potentially serious side effects. They must be used carefully and with regular monitoring.
4. We will work with you to optimize your health in all areas, not just specific to gender. We will have frank discussions about how cigarettes, alcohol, illicit drugs, and obesity may have an impact on your health and gender transition.

We ask that you agree to and follow these guidelines as you go through your treatment:

1. Because living in the role is an important step, we prefer that you have a defined plan to make this change. In most cases, it is preferable that you complete this transition within 2 years. If you do not complete this step, we may need to re-evaluate the appropriateness of hormone therapy. We will continue to check in about your plan, and may request permission to talk to your therapist.
2. Our goal is to give you the best clinical results in the safest manner possible. Larger hormone doses may be associated with more side effects than smaller ones, some of which are dangerous.
3. It is important that you take the hormones and medications as prescribed by your physician. Violation of this may mean termination from hormone therapy.
4. Cigarette smoking and estrogen are a dangerous mix. If you choose to smoke, your physician may choose not to prescribe hormones, or do so with lower doses.
5. Abuse of alcohol and other drugs must be dealt with before any other therapy is initiated.
6. We strongly recommend a continued relationship with a therapist who is experienced with transgendered issues. In many cases, hormonal therapy is contingent on a continued relationship with a therapist. If you need assistance finding a therapist, we can help.
7. You are responsible for your medical bills. Many insurances do not pay for gender change and will reject your claims. Your insurance company may ask for your medical records. We cannot falsify records to suggest another diagnosis. In general, the cost for initial consultation, physical exam, and laboratory testing is very expensive. Follow-up visits at 3 and 6 months and at 1 year tend to be less costly, with fewer laboratory studies.
8. Our transgendered program has as the highest priority the medical safety of persons receiving hormone therapy.

Table IV. Patient Handout: Guidelines for Hormone Therapy: Female-to-Male

The process of changing one's gender is a serious, important, and potentially dangerous project. The normal process of going through puberty is a gradual one, and to transform a female body to a male one also takes time. This process is potentially hard on one's body physically. Therefore, there are several things you can do to achieve optimum results both physically and psychologically in a safe manner.

In our program, we have some general principles that we will address with you numerous times. They may be different from things you may hear from friends, on the Internet, or from other doctors. However, in reviewing the medical literature, communicating with other gender centers, and following patients for years, we have found them to be sound principles that result in safer transitions with excellent results.

PRINCIPLES

1. Gender change is a gradual change both physically and psychologically. Your body and mind need time to adjust in a healthy manner. It takes approximately 5 years to complete the process.
2. Living in your chosen role is the single most important thing that you can do in this process. For a variety of reasons, some transsexual individuals are not able or willing to live in their chosen role. Your physician may still prescribe hormones in these cases, assuming you have continued psychotherapy. Your doctor will have ongoing discussions with you about your thoughts on this process.
3. Hormones are potent medications with potentially serious side effects. They must be used carefully and with regular monitoring.
4. We will work with you to optimize your health in all areas, not just specific to gender. We will have frank discussions about how cigarettes, alcohol, illicit drugs, and obesity may have an impact on your health and gender transition.

We ask that you agree to and follow these guidelines as you go through your treatment:

1. Because living in the role is an important step, we prefer that you have a defined plan to make this change. In most cases, it is preferable that you complete this transition within 2 years. If you do not complete this step, we may need to reevaluate the appropriateness of hormone therapy. We will continue to check in about your plan, and may request permission to talk to your therapist.
2. We will work to use the smallest dose of testosterone that gives you the best physical and psychological results. Hormone levels may need to be followed when decisions on dosing are made. Larger hormone doses may be associated with more side effects.
3. It is important that you take the hormones and medications as prescribed by your physician. Violation of this may mean termination from hormone therapy.
4. Testosterone increases risk of heart disease, as does cigarette smoking. If you choose to smoke, your physician may choose not to prescribe hormones or do so with lower doses. It is important to decrease other risk factors for heart disease, such as controlling cholesterol, maintaining normal body weight, and exercising.
5. Abuse of alcohol and other drugs must be dealt with before any other therapy is initiated.
6. We strongly recommend a continued relationship with a therapist who is experienced with transgendered issues. In many cases, hormonal therapy is contingent on a continued relationship with a therapist. If you need assistance finding a therapist, we can help.
7. You are responsible for your medical bills. Many insurances do not pay for gender change and will reject your claims. Your insurance company may ask for your medical records. We cannot falsify records to suggest another diagnosis. In general, the cost for initial consultation, physical exam, and laboratory testing is very expensive. Follow-up visits at 3 and 6 months and at 1 year tend to be less costly, with fewer laboratory studies.
8. Our transgendered program has as the highest priority the medical safety of persons receiving hormone therapy.

and used by physicians interested in providing care for transsexual individuals.

FEMALE-TO-MALE HORMONE REGIMENS

Initiating therapy for the FTM is relatively simple. Testosterone is usually administered by intramuscular injection starting at 150–250 mg every 2 weeks. Most androgen action is transmitted via androgen receptors, so effect is limited by number of receptors rather than dose (4). Testosterone oil is available as testosterone cypionate (cottonseed oil) and testosterone enanthate (sesame oil). Although some patients may express preference for one form or another, the bioavailability and masculinizing effects of the testosterone are equal across formulations. Patients or partners can be taught to give intramuscular injections in the lateral thigh by nursing staff in one to three teaching sessions, depending on the patient's comfort level.

Expected effects of testosterone therapy include cessation of menses, usually within the first month of therapy, deepening of voice, increased facial and body hair growth, increased clitoral size, increased libido, and enhanced ability to maintain and increase muscle mass. Testosterone will not decrease breast size. After masculinization has occurred, the testosterone dose can often be decreased for maintenance.

If a patient has undergone hysterectomy with oophorectomy, the testosterone dose can often be decreased to 100–150 mg IM every 2 weeks. Serum estradiol levels and leuteinizing hormone (LH) levels can document suppression of the hypothalamic–pituitary axis (6), but these are expensive and not routinely used by primary care physicians caring for FTM patients. In the Vancouver gender program, Prior (6) uses trough testosterone levels routinely to judge dosing adequacy. Others find that routine serum testosterone levels are not as useful because “normal” male levels of testosterone vary greatly, and masculinization does not always correlate well with free

Table V. Consent Form: Administration of Female Hormones to Biologic Males

The use of female hormones (estrogen) in males has profound and often irreversible effects. These effects include, but are not limited to: enlargement and increased sensitivity of the breasts, weight change, decreased muscle mass, shrinkage of the genitals, infertility, decreased libido (sex drive), and changes in mood and personality.

The use of female hormones can cause the following conditions: fluid retention, nausea, jaundice (yellowing of the skin), headache, dizziness, depression, changes in vision, and decreased glucose tolerance.

Estrogen use in biologic males has been associated with increased risk of liver abnormalities (including noncancerous and cancerous tumors); elevated blood pressure, gallbladder disease; milk production from the breasts; noncancerous growths of the pituitary gland (a part of the brain); blood clots in the veins, which may be crippling; blood clots in the lungs; stroke; heart attack; and breast tumors have all been documented in persons receiving female hormones.

Complications occurring from the use of female hormones can, very rarely, cause death.

Additional effects, risks, and adverse reactions not known at this time may also exist.

The effects associated with the use of female hormones may or may not be reversible by discontinuing their use.

I have read this document and have been given the opportunity to discuss the effects, risks and possible adverse reactions of the use of female hormones with Doctor(s) _____. Having discussed these matters, I voluntarily give my informed consent to use female hormones (estrogen and possibly progesterone) along with the anti-testosterone drug spironolactone for the purpose of transition to the female gender. I agree to undergo regular physical examinations and laboratory testing as required by my treating physician. I agree not to change hormone dosages without consultation with my physician. I realize that doing so may result in my discontinuation in the gender change program.

(Signature)

(Date)

(Print name as signed)

testosterone levels. These levels are costly, an expense the patient usually pays out-of-pocket. Patients may ask to increase the frequency of dosing (half the dose every week) if they notice decreased energy/interest or just a feeling of not being “quite right” at the end of the dosing time period. Some feel a marked improvement in emotional lability with anger, acne, and headaches at lower doses without sacrificing masculinizing effects.

Although less widely used, transdermal testosterone in doses of 5 mg per day serves as a nice alternative to injections. Testoderm TTS and Androderm are designed for transdermal use, whereas other formulations are designed for transscrotal use. Transdermal testosterone may be appropriate for maintenance after initial masculinization is complete, especially for those who have undergone oophorectomy. The main disadvantage of the testosterone patch is cost. Testosterone in aquaphor is used by some topically in an effect to maximize clitoromegaly, but its role in addition to systemic androgens remains unclear.

Health Risks and Side Effects of Testosterone

Health risks to testosterone therapy include hepatotoxicity, insulin resistance, weight gain (7), and a deleterious effects on lipid profiles (8) by decreasing high-density lipoproteins (HDL), increasing triglycerides, and increasing homocysteine levels (9). The erythropoietic effects of testosterone (10) may cause polycythemia in those already at risk with serious respiratory illness. There is a theoretical risk of breast cancer (11) and endometrial cancer (testosterone is aromatized to estrogen) (6), so patients who have not undergone mastectomy should be taught self breast exams, and abnormal uterine bleeding should be pursued to rule out hyperplasia or carcinoma. Some sources report that exogenous androgens may cause polycystic ovarian syndrome (12–14), whereas others (15) argue that polycystic ovarian syndrome is present prior to androgen therapy in a disproportionate number of FTM transsexual patients. One source (16) even recommends baseline pelvic ultrasounds for

Table VI. Consent Form: Administration of Male Hormones to Biologic Females

The use of male hormones (testosterone) in females has profound and often irreversible effects. These effects include, but are not limited to: increased growth and coarseness of body hair, including facial hair; male pattern, baldness; deepening of the voice; weight change; increased muscle mass; clitoral enlargement; infertility; increase in libido (sex drive); and changes in mood and personality.

The use of male hormones can cause the following conditions: acne; nausea; jaundice (yellowing of the skin); liver abnormalities; headache, which may be severe; depression; anxiety; and increased blood glucose and increased serum cholesterol levels.

Increases in the incidence of arteriosclerosis; coronary artery disease; congestive heart failure; abnormalities of the liver, including both benign and cancerous tumors; and ovarian cysts have been documented in persons receiving male hormones.

Complications occurring from the use of male hormones can cause death.

When taken during pregnancy, male hormones can adversely affect fetal development.

Additional effects, risks, and adverse reactions not at this time known to arise or on which research data is at present inconclusive may also exist.

The effects associated with the use of male hormones may or may not be reversible by discontinuing their use.

I have read this document and have been given the opportunity to discuss the effects, risks, and possible adverse reactions of the use of male hormones with Doctor(s) _____. Having discussed these matters, I voluntarily give my informed consent to use male hormones (testosterone) for the purpose of transition to male gender. I agree to undergo regular physical examinations and laboratory testing as required by my treating physician.

I agree not to change hormone dosages without consultation with my physician. I realize that doing so may result in my discontinuation in the gender change program.

(Signature)

(Date)

(Print name as signed)

FTM patients, but the clinical utility of such studies remains questionable. Most physicians would not withdraw androgens because of polycystic ovaries, and such changes are not a risk factor for ovarian cancer.

Common side effects of testosterone therapy include acne in about 12% of patients (7), increased oiliness of the skin, weight gain, fluid retention, and headaches. Acne can be managed by usual topical therapies and titrating the testosterone dose. When more severe, systemic antibiotics are useful, as in any other patient. Headaches often respond to a decrease in testosterone dose. Androgens tend to increase bone density or have negligible effect on bone density in FTM patients (17, 18).

FTM Follow-up and Monitoring

Follow-up care for FTM patients should occur at least at 3, 6, and 12 months after initiation of

hormones. Follow-up after the first year of therapy is usually once or twice per year, but should be individualized. One should assess for masculinization and the patient’s perspective on body changes and gender transition, medication administration, and partner/family/friends. Although many FTMs may “pass” after a year of testosterone therapy, complete masculinizing effects may take 3 to 10 years (6). Specifically asking about mood may uncover lability that usually improves with decreased testosterone doses. Laboratory follow-up should include a complete blood count, liver function testing, glucose or hemoglobin A1C, and lipid panel at 3 and 6 months and yearly thereafter.

Usual health-care maintenance is a central theme of subsequent visits: minimizing cardiovascular risk factors, screening for substance use, reinforcing safer sexual activity, and encouraging proper nutrition. Health-care screening should continue until the patient no longer has the screened organ: papanicolaou

smears until hysterectomy, breast exams, and mammograms if age appropriate until mastectomy.

MALE-TO-FEMALE HORMONE REGIMENS

Hormone therapy for the male-to-female (MTF) transsexual involves reducing androgen effects with spironolactone (cyproterone has been used in European countries) (19) and stimulating feminization of secondary sex characteristics with estrogen. The use of progesterone to augment breast development is controversial in physicians treating MTF transsexuals. When deciding on a hormone regimen, prescribers should remember that it is estrogen that causes the serious side effects, so the lowest effective dose should be used.

Estrogen

Estrogen dosing regimens for gender transition vary widely. Estrogen should be prescribed at the lowest possible effective doses to avoid the serious complications of high-dose estrogen therapy. Current recommendations for estrogen dosing range from starting doses of 0.625 to 2.5 mg of conjugated estrogen. Higher-dose estrogen regimens usually consist of 5 mg of conjugated estrogen or equivalent per day (5). Conjugated estrogens are discussed most extensively in transsexual literature, but estradiol (Estrace, 1–2 mg per day) or esterified estrogens (Estratab, 0.625–5.0 mg per day) are also logical choices. Ethinyl estradiol (Estinyl, 0.05–0.5 mg per day) is discussed in the transsexual literature, but is not widely used in the United States. There is no published evidence that injectable estrogen preparations provide long-term benefit over oral preparations other than reduction of first-pass hepatic metabolism. Estrogen patches also avoid hepatic first-pass metabolism and are believed by some to decrease thromboembolic risk (20).

Expected effects of estrogen therapy include breast development, redistribution of body fat to a female pattern, skin softening, testicular atrophy, loss of erections (21), and slowing of scalp hair loss. Estrogen does not cause voice changes or regression of a more prominent male “Adam’s apple.” Estrogen seems to increase bone mineral density in MTF transsexuals (22), although some investigators show no change in bone mineral density (18). Some patients report an emotional peace or sense of well-being after starting estrogen, and being “more emotionally sensitive.” Estrogen induces breast development, but results are

not strictly dose related (23). Before initiating therapy, it is important to have a frank discussion with patients concerning the fact that there is a wide range of normal breast size in women, and that breast development takes place over a long time period, up to 2 years.

Serious health risks of estrogen therapy include stroke (24), pulmonary embolism (25), myocardial infarction, and breast cancer (26, 27). These infrequent events can be minimized further by prescribing the lowest dose of estrogen possible. Hyperprolactinemia is a relatively common and dose-dependent side effect of estrogen therapy (28, 29). Galactorrhea may occur in 9–14% of patients on estrogen (30), whereas hyperprolactinemia is significantly more common. Elevated prolactin levels may be a risk factor for prolactinoma, so obtaining prolactin levels during estrogen therapy is prudent and may signal patients who are taking higher estrogen doses than prescribed.

Liver function abnormalities should be investigated by considering other causes such as infection or other medications. Depending on the severity, estrogen should be discontinued and abnormal liver function tests followed until they normalize, then consider switching to a transdermal delivery system. Significant liver abnormalities that do not improve after withdrawal of estrogen should be investigated further with hepatic ultrasound because hepatic cell adenomas, focal nodular hyperplasia, or hepatic cysts (15) have been reported in MTF patients.

Spironolactone and Other Antiandrogens

Spironolactone acts as an antiandrogen of testosterone to dihydrotestosterone (31). It acts on cytochrome P450 to reduce testosterone production and decreases testosterone and dihydrotestosterone (DHT) effects at the cellular level. Spironolactone in doses of 200–400 mg per day allows the practitioner to decrease exogenous estrogen doses to physiologic or “hormone replacement” levels while still obtaining desired effects of breast development, feminization of skin, and female fat distribution. It can also decrease erections and male hair pattern (32).

Spironolactone may be initiated at 200 mg per day in a single or divided doses. It is usually an effective antiandrogen at this dose, but may be increased to 400 mg per day (32). Spironolactone can usually be discontinued after sex reassignment surgery. For some MTF women, the beard androgen receptors are

very sensitive to testosterone, so that adrenal testosterone production causes increased facial hair growth. Spironolactone can certainly be continued without difficulty in these individuals.

Spironolactone has few serious side effects. Patients with low blood pressures can be started on lower doses or counseled to rise with caution to avoid hypotension. Polyuria usually diminishes after a few weeks of therapy. For those with good renal function who do not take potassium supplements or eat a diet extremely high in potassium, hyperkalemia does not pose a problem. Most, although not all, physicians prescribing spironolactone periodically check serum potassium levels.

Cyproterone acetate is a powerful antiandrogen and progestagen used in Europe for transgendered patients. Its use is limited by interference with corticosteroid production, high cost, and side effect profile (33). Several other antiandrogens are used for other indications but have no reported data in the transgendered patient. Finasteride is an antiandrogen that opposes the formation of DHT, but not of testosterone itself. Liver dysfunction is a possible side effect and is costly in comparison to spironolactone. Flutamine is a potent antiandrogen, but its short half-life and cost usually limit its use. Acetate of leuprolide (Leupron) can provide a chemical castration, but its very high cost and side effect profile limit its usefulness (34).

Progesterone

Progesterone is the third and optional component of the MTF regimen. Although some physicians working with transgendered patients do not prescribe progesterone, others argue feminization involves the actions of both estrogen and progesterone (31). Medroxyprogesterone is a weak antiandrogen, and testosterone suppression may be accomplished with lower doses of estrogen. Medroxyprogesterone is less androgenic than norethindrone and norgestrel. Progesterone is important for breast development (24). Unlike estrogen, progesterone does not carry the risk of thromboembolism, prolactinoma, and myocardial infarction. Although it has been noted that doses of 20–40 mg per day are required to suppress luteinizing hormone (20), medroxyprogesterone acetate may become androgenic at higher doses, so others (5) recommend 10 mg a day. Micronized progesterone (Prometrium) is advantageous because it has a more favorable side effect profile (anxiety and irritability) than medroxyprogesterone. It is also less an-

drogenic when higher progesterone doses are needed, but is more costly.

MTF Follow-up Care and Monitoring

Follow-up care for MTF patients should occur at least at 3, 6, and 12 months after initiation of hormones. Twice yearly follow-up is usually sufficient after the first year of therapy. Once the patient has undergone sex reassignment surgery and has fully transitioned to the female role on stable hormone doses, yearly follow-up is sufficient. During subsequent visits, providers should enquire about body changes, breast development, and mood. One should discuss the social impact of transitioning and understand the patient's perspective on body changes. It is quite common for patient to be frustrated about the length of time required to transition, be disappointed in breast size, and feel shame in their ability to "pass" as female. Although most breast development occurs in the first 1–2 years of hormonal therapy, 4–6 years may be required for full maturation (31). Specific techniques for measuring and quantifying breast development are described elsewhere for those interested (35).

Laboratory follow-up should include a liver function testing, and potassium levels at 3 and 6 months and yearly thereafter. Prolactin levels may be drawn after 6 months of therapy, then yearly for 3 years. Lipid profiles should be followed regularly, especially for those with elevated or borderline values. Serum testosterone levels within the normal female range help document adequate hypothalamic–pituitary suppression, but are expensive. They can be especially helpful when making decisions about whether to increase estrogen doses.

Usual health-care maintenance is a critical part of subsequent visits: minimizing coronary artery disease risk factors, reinforcing safer sexual practices, and performing sexually transmitted disease screening when appropriate. Mammography is generally recommended after 10 years of hormonal therapy for women older than 40, although there is no data to support or refute this practice. Given the controversial nature of prostate specific antigen (PSA) screening for men with normal testosterone levels (35), PSA screening is probably not indicated for MTF women whose testosterone levels are suppressed.

Many different hormonal regimens for gender patients exist. Table VII includes some sample regimens reflecting the author's approach. Although this

Table VII. Sample Hormonal Regimens for Transsexual Patients^a

	Medication	Starting Dose	Subsequent Dose	When to Change Doses
Female to Male	Testosterone enanthate or testosterone cypionate	200 mg IM q 2 weeks	100–150 mg IM q 2 weeks	After masculinization complete and/or oophorectomy/hysterectomy. Little data available on efficacy. Transdermal testosterone effective for maintenance and may be less efficacious during transition.
	Transdermal testosterone (Testoderm TTS, Androderm)	5 mg to skin QD	Usually stays the same	
Male to Female	Conjugate estrogens (Premarin ^R)	1.25 mg per day 0.625 mg per day (smoker)	2.5 mg per day Do not increase in smokers	To obtain best clinical results, or if testosterone is not suppressed After sexual reassignment surgery, dose may be decreased without losing secondary sexual characteristics
	or Estradiol (Estrace ^R) or Transdermal estradiol (Climara ^R)	1 mg per day 0.1 mg patch per week	2 mg per day Two 0.1 mg patches per week	
	Spirolactone	200 mg per day	May discontinue	
	Medroxyprogesterone ^b (Provera)	10 mg per day	May increase to 20–40 mg (usually not needed)	
	or micronized progesterone ^b (Prometrium)	100 mg BID	May discontinue after breast development complete	

^aProfessional consensus does not exist regarding the most efficacious and safest dosing regimens for gender transition. This table reflects reasonable starting and maintenance doses that are supported in the (admittedly less than optimal) medical literature, and reflect the author’s opinion and practice. The table is not meant to include all possible hormone regimens, only several of the most commonly used medications.

^bProfessional consensus does not exist regarding progesterone’s role in MTF transition. Refer to text for details.

paper provides a discussion of many possible risks and side effects of hormonal therapy, the overwhelming number of transgendered patients transition without any side effects. A retrospective study compared mortality in 816 MTF and 293 FTM patients with age- and gender-matched standardized mortality ratios from the Dutch population (36). Researchers found no increased mortality among the gender patients on hormones. A 20-fold increase in thromboembolic events was noted in patients on estrogen. Although encouraging, this study may be flawed because one would expect that patients with serious underlying illness would initially have been excluded from hormone therapy.

Providing medical care for transsexuals can initially be intimidating because no training is provided in medical school or residency, and resources on management are limited. However, once one becomes familiar with usual regimens, hormone management is easier and safer than many other therapies routinely prescribed. For the most part, patients are extremely grateful for usual care and respect. Physicians rarely have the opportunity to help patients improve their sense of self and well-being in such a profound

way. For all these reasons, providing medical care for transsexuals is rewarding work.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association, 1994.
2. Seil D. Transsexuals: The boundaries of sexual identity and gender. In: Cabaj RP, Stein TS, editors. *Textbook of Homosexuality and Mental Health*. Washington, DC: American Psychiatric Press, 1996:743.
3. *The Standards of Care for Gender Identity Disorders*. Harry Benjamin International Gender Dysphoria Association. 1998.
4. Schlatter K, Von Werder K, Stalla GK. Multistep treatment concept of transsexual patients. *Exp Clin Endocrinol Diabetes* 1996;104:413–19.
5. Futterweit W. Endocrine management of transsexual. *New York State J Med* 1980;80:1260–64.
6. Prior JC. Hormonal therapy of gender dysphoria: The female-to-male transsexual. In: Dallas Denny, editor. *Current Concepts in Transgender Identity*. New York: Garland Publishing Inc., 1998.
7. Asscheman H, Gooren LJJ, Eklund PLE. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism* 1989;38:869–73.
8. Goh HH, Loke DF, Ratnam SS. The impact of long-term testosterone replacement therapy on lipid and lipoprotein profiles in women. *Maturitas* 1995;21:65–70.

9. Giltay EJ, Hoogeveen EK, Elbers JMH, *et al.* Effects of sex steroids on plasma total homocysteine levels: A study in transsexual males and females. *J Clin Endocrinol Metab* 1998;83:550–53.
10. Rosenmund A, Kochli HP, Konig MP. Sex-related differences in hematological values. A study on the erythrocyte and granulocyte count, plasma iron, and iron-binding proteins in human transsexuals on contrasexual hormone therapy. *Blut* 1998;56:13–7.
11. Coulam CB, Annegers JF, Kranz JS. Chronic anovulation syndrome and associated neoplasia. *Obstet Gynecol* 1983;61:403–7.
12. Pache TD, Chadha S, Gooren LJ, *et al.* Ovarian morphology in long-term androgen-treated female to male transsexuals. *Histopathology* 1991;19:445–52.
13. Spinder T, Spijkstra JJ, van den Tweel JG, *et al.* The effects of long term testosterone administration on pulsatile luteinizing hormone secretion and on ovarian histology in eugonadal female to male transsexual subjects. *J Clin Endocrinol Metab* 1989;69:151–7.
14. Futterweit W, Weiss RA, Fagerstrom RM. Endocrine evaluation of forty female-to-male transsexuals: Increased frequency of polycystic ovarian disease in female transsexualism. *Arch Sex Behav* 1986;15:69–78.
15. Balen AH, *et al.* Polycystic ovaries are a common finding in untreated female to male transsexuals. *Clin Endocrin* 1993;38:325–9.
16. Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav* 1998;27:209–26.
17. Van Kesteren PJM, Lips P, Deville W, *et al.* The effect of one-year cross-sex hormonal treatment on bone metabolism and serum insulin-like growth factor-1 in transsexuals. *J Clin Endocrinol Metab* 1996;81:227–32.
18. Schlatterer K, Auer DP, Yassouridis A, *et al.* Transsexualism and osteoporosis. *Exp Clin Endocrinol Diabetes* 1998;106:365–8.
19. Jequier AM, Bullimore NJ, Bishop MJ. Cyproterone acetate and a small dose of oestrogen in the pre-operative management of male transsexuals. *Andrologia* 1989;21:456–61.
20. van Kesteren PJM, Asscheman H, Megens JAJ, Gooren LJG. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrin* 1997;47:337–42.
21. Kwan M, Van Massdam J, Davidson JM. Effects of estrogen treatment on sexual behavior in male-to-Female transsexuals: Experimental and clinical observations. *Arch Sex Behav* 1985;14:29–40.
22. Reutrakul S, Ongphiphadhanakul B, Paisue N, *et al.* The effects of oestrogen exposure on bone mass in male to female transsexuals. *Clin Endocrin* 1998;49:811–4.
23. Orentreich N, Durr NP. Mammogenesis in transsexuals. *J Invest Dermatol* 1974;63:142–6.
24. Biller J, Saver JL. Ischemic cerebrovascular disease and hormone therapy for infertility and transsexualism. *Neurology* 1995;45:1611–3.
25. Lehrman KL. Pulmonary embolism in a transsexual man taking diethylstilbestrol. *JAMA* 1976;235:523–33.
26. Ganly I, Taylor W. Breast cancer in a trans-sexual man receiving hormone replacement therapy. *Br J Surg* 1995;82:341.
27. Pritchard TJ, Pankowsky DA, Crowe FP, *et al.* Breast cancer in a male-to-female transsexual. A case report. *JAMA* 1988;259:2278–80.
28. Asscheman H, Gooren LJG, Assies J, *et al.* Prolactin levels and pituitary enlargement in hormone-treated male-to-female transsexuals. *Clin Endocrin* 1988;28:583–8.
29. Goh HH, Ratnam SS. Effect of estrogens of prolactin secretion in transsexual subjects. *Arch Sex Behav* 1990;19:507–16.
30. Gooren LJG, Harmsen-Louman W, Van Kessel. Follow-up of prolactin levels in long-term oestrogen-treated male-to-female transsexuals with regard to prolactinoma induction. *Clin Endocrin* 1985;22:201–7.
31. Prior JC. Hormonal therapy of gender dysphoria: The male-to-female transsexual. In: Dallas Denny, editor. *Concepts in Transgender Identity*. New York: Garland Publishing Inc., 1998.
32. Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. *Arch Sex Behav* 1989;18:49–57.
33. de Vries CP, Gooren LJ, van der Veen EA. The effect of cyproterone acetate alone and in combination with ethinylestradiol on the hypothalamic pituitary adrenal axis, prolactin and GH release in male-to-female transsexuals. *Horm Metab Res* 1986;18:203–6.
34. Kirk S. *Feminizing Hormonal Therapy for the Transgendered*. Pittsburgh: Together Lifeworks, 1999.
35. *Put Prevention into Practice: Clinician's Handbook of Preventive Services*, 2nd ed. U.S. Department of Health and Human Services, 1998.
36. Van Kesteren PJM, Asscheman H, Megens JAJ, *et al.* Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrin* 1997;47:337–42.