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Health Outcomes Subcommittee: Puberty Blocking & Hormone Therapy for Transgender Adolescents

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Overview:

Transgenderⁱ people who are visually gender nonconforming¹ are at heightened risk of negative psychological outcomes. Statistically, they are also disproportionately victimized by transphobic discrimination and violence². A primary contributing factor in this visual nonconformity, (assuming it is not an intentional form of self-expression) are natal pubertal changes that do not reflect the person's innate³ gender identity or social gender presentation.

For an ever-increasing number of transgender adolescents, these negative outcomes are avoidable, however many private insurers exclude coverage for such care and the out-of-pocket costs for this medically approved treatment are prohibitive for most families.

We believe this testimony will demonstrate the medical efficacy and urgent need for adding puberty blocking and cross-sex hormone treatment and medications for properly evaluated transgender adolescents to the list of covered therapies.

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ⁱ Transgender is an umbrella term applied to a variety of individuals whose gender identity or gender expression varies from culturally conventional gender roles. In this document, transgender is used exclusively to refer to those whose innate sense of their own gender identity is something other than what is indicated by their anatomy or assigned birth gender and who desire medical intervention to facilitate hormonal development consistent with their gender identity.

Defining The Need

- Current (minimum) prevalence estimate of transsexual [transgender] youth = 1:500⁴
- Oregon population (2010 Census) = 3,831,074
- Current (minimum) estimate of transsexual [transgender] youth in Oregon = 7,662

The medical and psychological needs of transgender adults have taken center stage while the needs and effective interventions on behalf of transgender adolescents have remained unknown or underground and as a result, underserved. This began to change somewhat in the 1990's with safe and effective gender-affirming care models⁵ being practiced in the Netherlands at the Amsterdam Gender Clinic and later at the Harvard-affiliated Children's Hospital Boston, Children's Hospital Los Angeles, Oregon Health Sciences University, Legacy Emanuel Children's Hospital and with family care physicians in private practice.

Medical care for transgender adults follows an almost exclusively *reactive* approach (*primarily focused on treating psychological trauma and correcting "wrong gender" pubertal changes*). This contrasts significantly with treatment options for pubertal (Tanner 2-4) transgender adolescents, which offer a proven⁶ *proactive* methodology that not only can minimize or prevent unwanted and irreversible "wrong gender" pubertal changes, it can eliminate the need for the costly and invasive procedures and treatments associated with the reactive transgender care model. This greatly enhances both psychological well-being and overall quality of life.

Denying or delaying access to puberty blocking (GnRH analogs) and cross-sex hormone (Estrogen, Testosterone) treatment exposes these adolescents to⁷:

- Social stigmatization related to "wrong gender" pubertal changes (deepening of the voice, facial hair growth, changes to anatomical structure, breast development)
- Heightened safety concerns due to cultural discrimination & transphobic violence
- Heightened levels of depression, anxiety and low self-esteem
- Suicidal ideation (83%)
- Suicide attempts (41%)
- Use of black market hormones
- Subcutaneous injection of industrial grade silicone to create feminine body contours
- Substance abuse and sexual exploitation
- Harassment, mistreatment or discrimination at work (90%)

- Negative impact on earning ability (4X as likely to have household income under \$10k)
- 2X as likely to be unemployed as general population (4X as likely for people of color)
- Generally poor future earning ability, employability and overall quality of life.

This treatment is fully reversible, and cessation of the GnRH analog will result in the adolescent resuming puberty in their birth-assigned gender (Cohen-Kettenis et al., 2008).

Pubertal delay can provide respite for the psychosocial pain of the transgender adolescent while simultaneously allowing time for the therapist and adolescent to further explore their gender identity and wish for sex reassignment, contributing to greater diagnostic precision (Cohen-Kettenis & van Goozen, 1998; Cohen-Kettenis et al., 2008). This can serve to satisfy any doubts the parents and doctor may have about proceeding with sex reassignment treatment, allow time for parents/family to get counseling and support as needed, notify and educate school personnel, and explore the full range of treatment options.⁸

Treatment Recommendations & Protocols

The Endocrine Society⁹

Over the past decade, clinicians have progressively acknowledged the suffering of young transsexual adolescents that is caused by their pubertal development. Indeed, an adolescent with GID often considers the pubertal physical changes to be unbearable. As early medical intervention may prevent this psychological harm, various clinics have decided to start treating young adolescents with GID with puberty-suppressing medication (a GnRH analogue). As compared with starting sex reassignment long after the first phases of puberty, a benefit of pubertal suppression is relief of gender dysphoria and a better psychological and physical outcome.

Recommendations

- 2.1. We recommend that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development.
- 2.2. We recommend that suppression of pubertal hormones start when girls and boys first exhibit physical changes of puberty (confirmed by pubertal levels of estradiol and testosterone, respectively), but no earlier than Tanner stages 2–3.
- 2.3. We recommend that GnRH analogues be used to achieve suppression of pubertal hormones.



Puberty Blockers & Puberty Inhibitors

by Karin Selva, MD
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Let's start by describing what happens during puberty. When the brain determines that it is time to start puberty, usually around age 11 in male bodied persons and 10 in female bodied persons, the pituitary gland releases 2 hormones called LH (leutinizing hormone) and FSH(follicle stimulating hormone). With a rise in these two hormones, they both then affect the sex gland at hand by producing sex hormones: testes produce testosterone, and ovaries produce estrogen. It is these sex hormones that cause the typical changes we see with puberty and they occur in a series of steps called Tanner Stages 1-5. Tanner Stage 1 is, generally speaking, the time from birth to the onset of puberty, at which point the child enters Tanner Stage 2.

In male-bodied persons:

- First, the LH and FSH cause increase in testicular size;
- Which then results in an increase in testosterone production;
- Testosterone causes increase in pubic hair and phallic size;
- There is more acne;
- They get axillary (armpit) hair and facial hair;
- Eventually they get a growth spurt and their voice changes;
- When they are around 18 years of age, puberty is complete and growth stops

In female-bodied persons:

- Estrogen causes breast development first;
- This progresses and the person then gets more curves, and fat deposits in the typical adult female places;
- About 2 years after the start of breast development, menstrual periods start;

 A female-bodied person does get pubic hair, axillary (armpit) hair and acne, but not from estrogen. These changes come from hormones that are produced from the adrenal glands, and happen independently of LH, FSH and estrogen.

What are puberty blockers and how do they work?

These are agents (or medicines) that block (or as we say suppress) the release of LH and FSH from the pituitary gland. This then stops testosterone from being released from the testes, and estrogen from being released from the ovaries. Thus, they SUPPRESS PUBERTY. Without exposure to the sex hormones, the body does not undergo the changes associated with them.

These agents (medicines) come in 2 forms:

<u>Leuprolide</u> or <u>Depot Lupron</u>: This form of the medicine is an injectible that is given on either a monthly or every 3 month basis. It is injected into the muscle. Often the patient or family members are taught how to administer this shot at home.

<u>Suprellin</u> or <u>Histrelin</u>: This form is an implant. A very small device is implanted under the skin of one's upper arm, and it slowly releases the agent (medicine) over a period of one year. The unit must be replaced on a yearly basis by a surgeon, but this can be done under local anesthesia.

Why are they used and when are they prescribed?

These agents (medicines) are used for many different reasons. In children they are used to treat precocious puberty, when puberty happens too early. They are given to a child until the child is older and mature enough to enter into puberty, and once these agents are stopped, puberty will start on its own.

In adults, they are used for treatment of certain sex hormone sensitive cancers, like prostate cancer, to prevent the patient from being exposed to hormones that can increase cancer growth.

These agents are also used to suppress <u>endogenous</u> sex hormone production in an adult individual who is undergoing cross-gender transition. By suppressing the individual's production of sex hormones, administering cross hormone therapy for transition is more effective.

In transgender youth, puberty blockers are used to suppress the endogenous pubertal changes that quite often worsen the individual's gender dysphoria. In addition, by not being exposed to

one's own sex hormones, cross hormone therapy is even more effective at achieving the desired physical appearance in gender transition.

Dr. Karin Selva was named a "Top Doctor" by Portland Monthly Magazine in 2011, 2010 and 2009. Her work has appeared in peer reviewed publications such as; Journal of Pediatrics, Hormone Research, Journal of Pediatric Endocrinology, Pediatrics and more.

In addition to being a valued member of the TransActive Advisory Board, Dr. Selva currently serves on the Portland Public Schools Wellness Advisory Committee, is a voting member of the board of STAND for Children and is a leading Portland and Northwest advocate for the medical rights of transgender adolescents to experience puberty in a way that is hormonally congruent with their gender identity.

A Client Services Perspective

By Sheryl Rindel, LPC, NCC Client Services Program Manager TransActive Education & Advocacy Portland. OR

I am a Licensed Professional Counselor in Oregon and a National Certified Counselor. I am also a member of the World Professional Association for Transgender Health¹⁰ which has established guidelines for therapists and doctors who work with transgender children, adolescents, and adults. I have been counseling children and families for more than 20 years.

As the Client Services Program Manager for TransActive Education & Advocacy, I supervise and provide counseling services to gender non-conforming and transgender children, youth and their families. I am writing on behalf of the children and youth that we serve and the economic difficulty their families face in paying out-of-pocket costs for puberty blocking and cross-sex hormone medications.

Families that come to us for counseling and advocacy are diverse in race, ethnicity, sexual orientation, gender, and socioeconomic status. One of the things these families have in common is they all have a child or youth that may not experience their gender in a way that corresponds to the sex they were assigned at birth. TransActive's client services program sees children as young as 4 years old up to young adults.

When a child's gender identity does not match their assigned birth sex, approaching pubertal development becomes a nightmare. It's as if their body is betraying them. This exacerbates the incongruence between anatomy and gender identity. As a result, many children and youth ideate suicide (83%) or attempt suicide (41%) if they are forced to experience these unwanted pubertal changes.

When supported and allowed to freely express their gender identity these children and youth are psychologically, emotionally and developmentally indistinguishable from the general youth population. Psychologically, it is common for children and youth who are not supported in their gender identity to have a history of low self esteem, depression, social anxiety, self harm, and suicidal ideation.

By providing coverage for medication that is established as a worldwide "Standard of Care" for transgender children and youth many lives will be saved and later financial and social costs to Oregonians will be reduced. These children will be able to experience a puberty that matches their gender identity and will not be destined to live in a body that does not represent who they are on the inside.

Sheryl Rindel is a graduate of North Texas State University and holds a Master's Degree in Counselor Education.

Prior to her position at TransActive, Sheryl served for eight years as the Director of the Family Violence Intervention Program at the Washington County Domestic Violence Resource Center and is a member of the Board of Directors for the Center for Gender Equity at Pacific University in Forest Grove, Oregon.

What Do They Cost, Are They Covered by Insurance?

These agents (medicines) are both medically necessary and expensive.

- > Typically, Depot-Lupron costs range from around \$700 (online) to \$800 (Portland area) to \$1,500 dollars a month elsewhere for the monthly preparation. The 3 month preparation is equivalent in price.
- ➤ The histrelin implant is approximately \$15,000 total for the device and the cost of surgically implanting it.
- Also, labs need to be monitored while on these agents. A pre-treatment LH, FSH and testosterone or estradiol level is checked, as well as a post treatment level to assess the level of suppression.

Some health insurance will cover them partially in cross-gender treatment, and some won't. As a result, the out of pocket cost of these agents can be quite substantial and out of reach for most youth and their families.

Appendix A

Addressing the Needs of Transgender Youth in Primary Care

Laurie Barclay, MD

February 14, 2011 — To minimize negative health outcomes and maximize positive futures for transgender adolescents, timely medical intervention to achieve gender/body congruence paired with affirmative mental health therapy is appropriate, according to a review in the February issue of the Archives of Pediatrics & Adolescent Medicine.

"Transgender is an umbrella term that is used to describe individuals whose gender self-identification or expression transgresses established gender norms," write Johanna Olson, MD; Catherine Forbes, PhD; and Marvin Belzer, MD, from Children's Hospital Los Angeles, in California.

"Specifically, it is the state of one's gender identity (self-identification as male, female, both, or neither) not matching one's assigned gender (identification by others as male or female based on natal sex). The identity and behavior of transgender individuals are socially and medically stigmatized, resulting in a notably underserved population at high risk for significant morbidity and mortality."

Support of Transgender Youth

Although the phenomenon of transgender is relatively uncommon, increasing media attention is resulting in more adolescents and young adults "coming out" at a younger age. Despite the highly specific medical and mental health needs of transgender adolescents, they continue to be an underserved and poorly studied group. Primary care clinicians are uniquely positioned to improve physical and mental health outcomes among transgender youth.

Most, but not all transgender adolescents wish to undergo phenotypic transition to match their gender and physical body. Because this process is complex, it mandates the involvement of a mental health therapist specializing in gender issues as well as a clinician, but it is often highly problematic for transgender youth to find needed comprehensive medical and mental health services.

Transgender youth are at increased risk for multiple psychosocial problems, including family and peer rejection, harassment and bullying, trauma, abuse, insufficient housing, legal problems, lack of financial support, and educational problems. "It is very important for primary care physicians to examine their own feelings, attitudes, and beliefs about gender-variant persons and consider how these affect their work with youth," the review authors write.

"Using supportive, affirming language with gender-variant youth, such as using the patient's preferred name and pronouns, can make all the difference between a trustworthy physician and one that makes a youth feel misunderstood, rejected, and unwelcome. In addition, medical professionals can be effective advocates for their transgender patients' needs and rights in settings outside of the home, such as clinics and schools."

Phenotypic Transitioning

Phenotypic transitioning occurs in reversible, partially reversible, and irreversible phases. The reversible portion includes adopting preferred gender hairstyles, clothing, and play, and sometimes adopting a new name, which may occur before age 10 years. Puberty may be suppressed with gonadotropin-releasing hormone analogues, which may have adverse effects on height and bone density.

The partially reversible phase of transitioning involves using cross-gender hormone therapy. The Endocrine Society guidelines recommend deferring estrogen and testosterone therapy until the patient is 16 years old, but the reviewers note that "it is often not pragmatic to delay the initiation of treatment with cross-gender hormones." The reviewers suggest using age 16 years as a guideline and considering starting cross-gender hormones earlier on a case-by-case basis.

Before starting cross-gender hormone therapy, patients should be assessed for readiness by a mental health professional as well as by a clinician who can exclude medical contraindications. Testosterone administration is indicated for female-to-male patients. For male-to-female patients, estrogen, usually in combination with spironolactone or other androgen inhibitor, may be offered. Progesterone may be considered but may lead to unwanted weight gain. In general, the benefits of cross-gender hormone therapy must be carefully balanced against potential adverse effects, especially since very little is known about the use of hormones in this population.

"The low prevalence of children and adolescents seeking care, combined with the historical refusal of most insurance providers to pay for care, has led to inadequate research in the United States, thus making care for this population uncommon," the review authors conclude. "Due to the tremendous paucity of research in transgender youth, specific medication regimens are neither standardized nor approved by the Food and Drug Administration for treatment of GID [gender identity disorder]. The Amsterdam Gender Clinic has demonstrated reasonable safety and thus far good outcomes in a small cohort of white youth."

Arch Pediatr Adolesc Med. 2011;165:171-176. Abstract

Appendix B

Care of the Child with the Desire to Change Gender - Part I

Bethany Gibson; Anita J. Catlin

Pediatr Nurs. 2010;36(1):53-59. © 2010 Jannetti Publications, Inc.

Abstract

This is Part I of a three-part series on children and young adults who desire to live as a gender different from which they were born. The series depicts the psychosocial, medical, and surgical components of transitioning from one gender to another. The medical and psychosocial issues of transgender change are complex, and ethical questions may be raised by those who would challenge these choices. Pediatric nurses will be best able to care for these patients with awareness of the multiple dimensions of these procedures and the ramifications of caring for these children and their families.

Introduction

In May 2007, Barbara Walters aired a television program on 20/20 called "My Secret Self." This program, still available in five parts on YouTube, depicts the lives of two young children who from birth informed their parents that they had the wrong genitalia for the gender that they were. Both Jazz and Riley, born with male external genitalia, were by two years old choosing to dress and live as girls. They clearly told their parents that "God had made a mistake" and that they were girl children. Another 16-year-old adolescent on the show, born as a girl, at 14 wrote his parents a letter and told them that he was absolutely in the wrong body and planned to begin to live as the young man that he was. Barbara Walters interviewed these children and their parents with dignity. The Walters special is a good accompaniment to this series of articles, which will inform the readers of *Pediatric Nursing* on the heath care needs of the transgender child. This three-part series will discuss the current status of the transgender child and hormonal treatments used to suppress and transition gender. Parts II and III will discuss transgender surgeries and the barriers transgender individuals face in obtaining health care.

The Condition

"Transgender" is an umbrella term that literally means to cross gender lines (Selekman, 2007). These children describe feeling trapped in the wrong body and born with the wrong genitalia. They may choose to have surgery to remove organs related to one gender and constructed to

resemble the other. The term gender identity disorder (GID) is the diagnostic category used to describe these children by the American Psychiatric Association, diagnostic code 302.2. To meet this diagnostic code, there are four components to GID or dysphoria.

- There must be persistent other gender identification: the desire to be or the insistence that one is of the other sex.
- There must be evidence of persistent discomfort about one's assigned sex or a sense of inappropriateness in the gender role of that sex.
- The individual must not have a concurrent physical intersex condition (such as androgen insensitivity syndrome or congenital adrenal hyperplasia).
- There must be evidence of clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Psychological Issues for Transgendered Children

Transgender individuals are often perceived to have mental illnesses, but "researchers have found no correlation between non-normative gender identification and mental illness" (Shield, 2007). Research has found that individuals who have consistently expressed cross-sex identification from early childhood (toddler age) onward develop psychological problems resulting from the pain of pubertal physical changes, including depression, anorexia, social phobias, and suicidality (Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008).

Research

The most prevalent research in the area of youth with GID has been done by researchers Cohen-Kettenis and colleagues in the Netherlands. In 1987, Dr. Peggy Cohen-Kettenis started the first outpatient clinic in Europe for children and adolescents with gender problems and intersex conditions. Cohen-Kettenis and colleagues (2008) state that 80% to 95% of prepubescent children with GID will resolve their GID prior to reaching adolescence. However, according to recent research, children who continue to experience GID into adolescence will pursue sex reassignment treatment and/or surgery (Shield, 2007). Therefore, a lengthy diagnostic process, including psychological screening and therapy, are important for children who express a persistent gender dysphoria in early childhood. Many believe that teens who have demonstrated persistent and unwavering identification with the opposite gender may be helped via early gender reassignment treatment.

Roughgarden (2004) wrote that gender dysphoria can occur in early childhood, with treating psychologist Mildred Brown reporting that 85% of her clients recognized their gender identity was different from their physical gender before grade school. Prepubertal gender dysphoria has also been documented by Dutch researcher Gooren (1999). The majority of transgender panelists at the Northern California Transgender Health and Wellness Conference expressed conscious recognition of their gender dysphoria prior to puberty as well (Gibson, 2008).

Hormones

Pediatric nurses are aware that all children face social, emotional, and physical changes as they enter puberty and adolescence. These changes are difficult for many, and the usual problems faced by adolescents are compounded for youth who have chosen to dress as and assume the identity of an alternative gender. Many transgender children experience great stress as their bodies begin to change in ways that conflict with their sense of gender identity (Cohen-Kettenis et al., 2008; Roughgarden, 2004). Testosterone and estrogen cause secondary sexual characteristics to develop. Transgender teens living as boys develop breasts and begin to menstruate, and transgender teens living as girls have their voices deepen, grow facial hair, have enlarged Adam's apples, and become taller than many women. In addition, a previously small penis begins to grow and become capable of erections. Many of these children wish to have something medical and/or permanent done to prevent these changes.

Pubertal Delay

The primary goals of hormone use for those children who believe they need sex reassignment are twofold. The first is to eliminate, to the degree possible, the hormonally induced sex characteristics of the birth-assigned gender, and secondly, to induce those of the desired gender (Gooren, 1999). Discussion of the first goal, suppression of the puberty-induced secondary sex characteristics of natal sex, will be discussed in this section. According to the Netherlands protocol, adolescents diagnosed with GID who "have suffered with extreme lifelong gender dysphoria, are psychologically stable and live in a supportive environment" are considered eligible for puberty suppression (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. 132). A letter of recommendation from a psychiatrist outlining the adolescent's identifying characteristics, gender and/or other psychiatric diagnoses, length of psychotherapeutic relationship, verification of eligibility criteria for hormone therapy and/or sex reassignment surgery, and whether the client has followed recommendations from the organization is required to initiate endocrine treatment (Meyer et al., 2006).

The suppression of puberty using gonadotropin-releasing hormone analogs (GnRHa) may be prescribed for adolescents aged 12 to 16 years old who have 1) fulfilled the criteria mentioned above, 2) reached Tanner stage 2 or 3, and 3) reached pubertal levels of sex hormones (Delemarrevan de Waal & Cohen-Kettenis, 2006). Early hormonal treatment can reduce the amount of invasive surgical procedures that may be required with later sex reassignment because irreversible physical development secondary to puberty can be avoided. Female-to-male transitions might avoid the need for mastectomy, and male-to-females might avoid the need for reduction thyroid chondroplasty and voice modification therapy. Initiating pubertal delay at an early age will "most certainly result in high percentages of individuals who will more easily pass into the opposite gender role than when treatment commenced well after the development of secondary sexual characteristics," which will likely result in better quality of life and perhaps decreased reports of post-operative regret due to poor functioning (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. 133).

As previously discussed, puberty in the birth-assigned gender can cause the transgender adolescent significant distress and discomfort, potentially leading to many negative emotional and psychological outcomes. While initial administration of GnRHa results in increased levels of circulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH), continuous administration results in decreased secretion of LH and FSH from the pituitary gland to levels of a castrated man or menopausal woman (Skidmore-Roth, 2007). Inhibition of LH and FSH inhibits the gonadal production of the sex hormones testosterone and estrogen. GnRHa administered prior to puberty will completely prevent puberty, and when administered after the start of puberty will halt the progression of puberty, effectively putting it on hold (Brill & Milazzo, 2008; Cohen-Kettenis & van Goozen, 1998; Cohen-Kettenis et al., 2008). Other drugs, such as progestins, antiandrogens (males only), and luteinizing hormone-releasing hormone (LHRH) agonists, may also be used to suppress the physical changes of puberty (Cohen-Kettenis & van Goozen, 1998; Cohen-Kettenis et al., 2008; Gooren, 1999; Meyer et al., 2006). Patients born as girls will experience a weakening of breast tissue, which may disappear completely, while those born as males will have a reduction in testicular volume. If this treatment is begun later in pubertal development, changes such as later stage breast growth in girls and deepening of the voice and facial hair growth in boys will recede, although not completely, while any further progression of puberty will be halted (Delemarre-van de Waal & Cohen-Kettenis, 2006).

This treatment is fully reversible, and cessation of the GnRH analog will result in the adolescent resuming puberty in their birth-assigned gender (Cohen-Kettenis et al., 2008). Pubertal delay

can provide respite for the psychosocial pain of the transgender adolescent while simultaneously allowing time for the therapist and adolescent to further explore their gender identity and wish for sex reassignment, contributing to greater diagnostic precision (Cohen-Kettenis & van Goozen, 1998; Cohen-Kettenis et al., 2008). This can serve to satisfy any doubts the parents and doctor may have about proceeding with sex reassignment treatment, allow time for parents/family to get counseling and support as needed, notify and educate school personnel, and explore the full range of treatment options.

Clinics in Boston, Gent, Oslo, and Toronto, all very experienced in treating gender dysphoric youth, have begun providing these interventions and/or referrals prior to 16 years of age as long as hormonal puberty has progressed to at least Tanner stage 2 (Cohen-Kettenis et al., 2008). Other criteria noted for initiation of GnRHa therapy include persistent GID since early childhood, exacerbated GID following early pubertal development, no co-morbid psychiatric issues that impede diagnosis or treatment, parental consent, and a social support network throughout the treatment. Additionally, the adolescent can use this time to learn about the effects of sex reassignment treatment, as well as the social consequences of that course, including GnRH analogs, cross-sex hormones, and surgery (Cohen-Kettenis et al., 2008).

GnRH analogs have long been used in medical treatment of precocious puberty in children, with the exact same purpose and effect, halting puberty (Skidmore-Roth, 2007). GnRH analogs used for pubertal delay include leuprolide (Lupron® [subcutaneous injection; 50 mcg/kg/day, may increase by 10 mcg/kg/day as needed] and Lupron® Depot [intramuscular injection; 15 mg every 4 weeks in children more than 37.5 kg or 22.5 mg IM every 3 months]) and histrelin (Supprelin® LA and Vantas® [yearly subcutaneous implant]) (Milazzo, 2008; Skidmore-Roth, 2007). LHRH agonist depot triptorelin is a 3.75 mg intramuscular injection given monthly (Skidmore-Roth, 2007) that has been safely used with good results in Dutch clinics (Cohen-Ketenis & van Goozen, 1998). Spironolactone (up to 100 mg twice daily, if tolerated) is a diuretic with antiandrogenic properties that has been used to suppress the effects of testosterone effectively (Gooren, Giltay, & Bunck, 2008; Milazzo, 2008). Cyproterone acetate (initial dose of 50 mg twice daily, reduced to 50 mg daily when testosterone levels are effectively suppressed) is a progesterone with antiandrogenic properties and is the most widely used drug for this purpose in Europe (Gooren, 1999; Gooren et al., 2008). Medroxyprogesterone acetate (5 to 10 mg daily) may be used if cyproterone acetate is unavailable, although it has been found to be less effective (Gooren, 1999; Gooren et al., 2008). Finasteride (1 mg) is a 5-reductase inhibitor that can be used as well (Gooren, 1999; Gooren et al., 2008).

A follow-up protocol has been developed to investigate the efficacy and safety of GnRHa treatment in adolescents suffering from gender dysphoria. Blood work should be done prior to the initiation of therapy to establish baseline levels of gonadotropins and sex hormones, and metabolic determinants, including fasting glucose, insulin, cholesterol, high and low-density lipoprotein levels, and renal and hepatic studies. Additionally, anthropomorphic measurements, such as height, weight, sitting height, hip and waist circumferences, and Tanner pubertal stage can be recorded initially and re-evaluated periodically to ensure normal growth and development. Follow-up protocol includes appointments with psychiatrist or psychologist every three months and laboratory measurements of factors described above (Delemarre-van de Waal & Cohen-Kettenis, 2006).

Cross-sex Hormone Therapy

The next action for gender transitioning is the second goal of hormonal therapy – induction of the secondary sex characteristics of the desired gender. The physician administering hormonal treatment and follow-up monitoring is not required to be an endocrinologist, but should be educated in the medical and psychological aspects of treating individuals with GID. The patient must have the "capacity to understand the risks and benefits of treatment, have his or her questions answered, and agree to medical monitoring of treatment" (Meyer et al., 2006, p. 17).

A study by Cohen-Kettenis and colleagues (2008) found that adolescents selected using HBIGDA eligibility requirements and beginning cross-sex hormone therapy between 16 to 18 years of age were no longer suffering from gender dysphoria and were both psychologically and socially "not very different" from their peers 1 to 5 years after sex reassignment surgery. Use of either sex steroid in high doses is contraindicated with serious liver disease, poorly controlled diabetes mellitus, serious cardiovascular disease, cerebrovascular disease, thromboembolic disease, and marked obesity (Gooren, 1999). The presence of a prolactin-producing pituitary tumor or a strong family history of breast cancer is a contraindication to beginning estrogen administration. Severe lipid disorders with cardiovascular complications are contraindicated to beginning testosterone administration (Gooren, 1999). Given that immobilization poses serious risks for deep vein thrombosis and that sex steroids increase that risk, hormone therapy should be discontinued 3 to 4 weeks prior to any elective surgical procedures. Treatment may resume once patients are fully mobile again (Gooren, 1999). It should be noted that suppression of the natal sex hormones combined with cross-hormone therapy will alter reproductive capacity in patients, so sperm storage for genetic males and cryopreservation of eggs for genetic females

might be presented as an option to maintain the possibility of having their own biologic offspring later in life (Jain & Bradbeer, 2007).

Side Effects of Cross-sex Hormone Treatment

A retrospective, descriptive study of 10,152 transsexual patients (816 MTF and 293 FTM) who received cross-sex hormone treatment from a knowledgeable physician demonstrated that this is an acceptably safe practice in the short and medium term. While there are side effects, as with any pharmaceutical therapy, mortality was not higher than a comparison group of age- and gender-adjusted Dutch citizens (Gooren, 1999; Gooren et al., 2008). In an effort to increase the body of medical knowledge regarding long-term side effects of cross-sex hormone treatment, Gooren and colleagues (2008) have established a Web site for reporting side effects that can be provided to both patients and clinicians (http://www.wpath.org/resources_transgender.cfm [click on transgender information: resource links]).

GnRHa administration will create a hypogonadotrophic state that in girls will suppress menses due to lack of estrogen and in boys will block the development of fertility due to lack of testosterone (Delemarre-van de Waal & Cohen-Kettenis, 2006). Specific to adolescent patients is the issue of growth. Pubertal growth spurt will be inhibited by hormone treatment, while the fusion of the growth plates in long bones will be delayed (Delemarre-van de Waal & Cohen-Kettenis, 2006). This is not a problem for MTF patients because women are approximately 12 cm shorter than males on average, so the progressive closing of the epiphyses during estrogen treatment results in a shorter than normal male, but an acceptable height for a woman. Alternatively, administration of growth stimulating drugs to FTM patients can assist in achieving an acceptable male height (Delemarre-van de Waal & Cohen-Kettenis, 2006). GnRHa treatment may interfere with accumulation of bone mass normally seen during puberty due to sex hormone exposure; however, studies have demonstrated that these levels increase to normal values during cross-sex hormone treatment and preserve bone mineral density (Delemarrevan de Waal & Cohen-Kettenis, 2006; Gooren et al., 2008). More studies are needed to determine if discontinuing cross-sex hormones later in life would significantly increase risks of osteoporosis and bone fractures.

Dutch researchers (Gooren et al., 2008) report extensive study of the effects of cross-sex hormone therapy on cardiovascular disease risk factors over the last 15 years. Studies of MTF transsexuals on estrogen and GnRHa treatment revealed a statistically significant increase in weight, total body fat, and visceral fat (Gooren et al, 2008). There was also a statistically

significant decrease in insulin sensitivity, which is believed to be caused by androgen deprivation. Blood pressure increased slightly, and there was also a slight increase on arterial stiffness; however, neither was a statistically significant change (Gooren et al., 2008). Studies on FTM transsexuals on testosterone and GnRHa treatment also resulted in a statistically significant increase in body weight and body mass index (BMI), as well as an increase in visceral fat that was not statistically significant. Other statistically significant changes that negatively affect cardiovascular health in FTM transsexuals are increased HDL cholesterol, triglycerides, and decreased insulin sensitivity (Gooren et al., 2008). The researchers contend that these negative changes may be attributable to increased body weight and fat. It should be noted, however, that overall cardiovascular mortality and morbidity in both MTF and FTM transsexuals was not elevated (Gooren et al., 2008). Gooren and colleagues (2008) recommend advising transsexual patients to maintain a healthy lifestyle and dietary behaviors to prevent cardiovascular disease and metabolic syndrome.

Research has found that "hormone-dependent tumors are practically not occurring in hormonally treated FTM and seem a rare occurrence in MTF" transsexuals (Gooren et al., 2008, p. 23). For those who begin cross hormones as adolescents, exposure is greatly increased over the course of a lifetime. Therefore, the lack of prevalence of hormone-related tumors in the transsexual population should not be considered irrelevant nor warrant reduced surveillance. Gooren et al. (2008) have documented several cases of prolactinoma (lactotroph adenoma) following high-dose estrogen treatment in MTF patients with normal serum prolactin levels prior to therapy, as well as the formation of a pituitary microprolactinoma in a patient on normal-dose estrogen for 14 years. Therefore, Gooren et al. (2008) recommend long-term monitoring of serum prolactin levels in MTF patients on estrogen. Two cases of breast carcinoma in MTF patients on estrogen treatment have been reported, as have breast fibroadenomas (Gooren et al., 2008). However, out of approximately 2,200 MTF patients with over 30 years of treatment in the Dutch clinic, no case of breast cancer had been observed until recently, when one case was reported (Gooren et al., 2008). Despite these statistics, Gooren and colleagues (2008) maintain that these subjects have had varying exposure to estrogen (from 1 to 25 years), which prevents one from drawing firm scientific conclusions about the risk of breast cancer with long-term estrogen exposure. In addition, breast cancer has also been reported in a FTM transsexual post-bilateral mastectomy while on testosterone treatment. Therefore, MTF transsexual patients should be advised to do breast self exams and have mammograms as recommended for

women, and FTM patients should have axillary lymph nodes examined as well (Gooren et al., 2008; Jain & Bradbeer, 2007; Sobralske, 2005).

Orchidectomy (surgical removal of the testes) prior to 40 years of age has been found to prevent the development of benign prostate hyperplasia and prostate cancer (Gooren et al., 2008). The ovaries of FTM transsexuals receiving testosterone treatment look similar to polycystic ovaries, which are more likely to develop malignancies (Gooren, 1999; Gooren et al., 2008). Oophorectomy (surgical removal of ovaries) is recommended in Dutch clinics once patients are eligible for surgical sex reassignment (Gooren et al., 2008). While not without risks, cross-sex hormone treatment has been shown to be acceptably safe by Dutch researchers at clinics that have been administering these treatments since the 1970s. Data should continue to be collected on adverse effects that present with long-term use to determine if long-term treatment with cross hormones is reasonably safe with lifetime usage, beginning in adolescence, or if the treatment should be discontinued at a certain age (Gooren et al., 2008).

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Endnotes

¹ Visual gender nonconformity refers those who through either circumstance of expression or anatomical phenotype do not "blend" easily into societal expression stereotypes. Known colloquially as "passing".

² "Hate Violence Against Lesbian, Gay, Bisexual, Transgender, Queer and HIV-Affected Communities in the United States 2010" — A Report from the National Coalition of Anti-Violence Programs; http://www.ncavp.org
³ Zhou, J.N. et al.; Hofman, MA; Gooren, LJ; Swaab, DF (1995). "A sex difference in the human brain and its relation to transsexuality". Nature 378 (6552): 68–70. Kruijver, F.P. et al.; Zhou, JN; Pool, CW; Hofman, MA; Gooren, LJ; Swaab, DF (2000). "Male-to-female transsexuals have female neuron numbers in a limbic nucleus". J Clin Endocrinol Metab 85 (5): 2034–41.

⁴ Olyslager, F. and Conway, L., "On the Calculation of the Prevalence of Transsexualism", presented at the WPATH 20th International Symposium, Chicago, Illinois, September 6, 2007

http://ai.eecs.umich.edu/people/conway/TS/Prevalence/Reports/Prevalence%20of%20Transsexualism.pdf ⁵ Cohen-Kettenis, P. T., Delemarre-van de Waal, H. A. and Gooren, L. J. G. (2008), *The Treatment of Adolescent Transsexuals: Changing Insights. The Journal of Sexual Medicine*, 5: 1892–1897. doi: 10.1111/j.1743-6109.2008.00870.x

⁶ See Appendix items A and B.

⁷ Grant, Jaime M., Lisa A. Mottet, Justin Tanis, Jack Harrison, Jody L. Herman, and Mara Keisling. *Injustice at Every Turn: A Report of the National Transgender Discrimination Survey*. Washington: National Center for Transgender Equality and National Gay and Lesbian Task Force, 2011.

⁸ Gibson, B, Catlin, A.J., *Care of the Child with the Desire to Change Gender – Part I*, Pediatr Nurs. 2010;36(1):53-59. © 2010 Jannetti Publications, Inc.

⁹ Wylie C. Hembree, Peggy Cohen-Kettenis, Henriette A. Delemarre-van de Waal, Louis J. Gooren, Walter J. Meyer III, Norman P. Spack, Vin Tangpricha, and Victor M. Montori, *Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline*, (2009), http://www.endo-society.org/guidelines/final/upload/Endocrine-Treatment-of-Transsexual-Persons.pdf http://www.wpath.org