

Biological and Psychological Influences of Cross-Sex Hormone in Transgender

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ABSTRAK

Transgender adalah satu keadaan biopsikososial yang kompleks dan merupakan sebahagian daripada dimensi seksualiti manusia. Ia merangkumi komponen kognitif-emosi dan tingkah-laku yang membuatkan seseorang insan itu unik di dalam ekspresi seksualitinya. Kaum transgender cenderung untuk menggunakan hormon-silang-seks untuk mengubah keadaan dirinya menyerupai gender bertentangan yang diingini dengan cara menutupi ciri sekunder seksnya. Seks hormon yang biasa digunakan ialah: “Female to Male Treatment Options (FMTO)” iaitu testosterone and hormon wanita pada “Male to Female Treatment Options (MFTO)”, di mana kombinasi estrogen dan anti-androgen digunakan. Hormon-silang-seks iaitu FMTO, atau MFTO mempengaruhi sifat biologi dan psikologi individu transgender. Namun begitu, hormon-silang-seks mempunyai profil kesan sampingan tertentu yang juga memberi impak biologi dan psikologi. Impak psikologi menjurus kepada masalah kesihatan mental dan bunuh-diri. Pelbagai tahap pengaruh biopsikososial kesan hormon-silang-seks diterangkan dan ulasan ini memberi ruang membincangkan kepelbagaian pilihan rawatan. Di dalam psikiatri, perubahan biologi memberi pengaruh yang besar ke atas individu transgender, terutamanya dari aspek psikososial dan budaya.

Kata-kunci: hormon-silang-seks, kemurungan, keresahan, masalah psikiatri, transgender

ABSTRACT

Transgender is a complex state of bio-psycho-social dimension of human sexuality. It encompasses cognitive-emotional-behavior component that makes the person unique in his or her sexual expression. Transgender tend to use cross-sex hormone in order to eradicate their secondary sexual characteristics and to facilitate the

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shift to their experienced gender. The common masculinising sex hormone use, i.e. Female to Male Treatment Options (FMTO) is testosterone and for feminising hormone i.e. Male to Female Treatment Options (MFTO) is a combination of estrogen with anti-androgen, respectively. Cross-sex hormone, i.e. FMTO, or MFTO has biological and psychological influences on the transgender individuals. Nevertheless, cross-sex hormone may also pose a range of side effect profiles, varies from the biological to psychosocial impact. The psychological impact can be paramount until it causes severe mental-health problems and even suicide. Numerous ranges of bio-psycho-social influence of cross-sex hormone were highlighted in this review as fundamental core knowledge in the art to know practice when dealing with the treatment options. In psychiatry, the change in the biological appearance may have great influence in the transgender individual, especially in the context of psychosocial and cultural perspective.

Keywords: anxiety, cross-sex hormone, depression, psychiatric co-morbidities, transgender

INTRODUCTION

The word “transgender” was first coined in the 1980s by Virginia Prince when referring to gender variant individuals (Prince 2005). Transgender is a term used when a person has discordant among their assigned gender at birth with their gender identity. Regarding the term ‘transsexual’, it is used for individuals who underwent or sought transition from male to female and vice versa mainly via cross-sex hormone management or sex reassignment surgery (Prince 2005; American Psychiatric Association 2013). The word ‘transvestite’ is a Latin word and it means cross-dresser was coined by Hirschfeld. It originally refers to the heterosexual cross-dresser, and it is a gender manifestation and not a sexual manifestation. In other words, a true transvestite is not a homosexual (Prince 2005). Many presumed ‘gender’ and

‘sexes’ as the same entities, but it is not, and commonly leads to misconception and misuse of terms. Gender is used within the context to the role within the society whereas sex is used in the context of reproductive capacity. So, gender identity is more like a social identity and gender dysphoria is a descriptive term of an individual’s cognitive or affective discontent due to the incongruence of one’s allocated gender with their experienced gender (APA 2013). Another new term which emerged from transgender activism is cisgender which can be used to describe individuals who is on the same side (cis-) as their birth assigned sex whereas transgender is on the other side (trans-) of their birth-assigned sex. This term was used to prevent marginalization of transgender and it is thought to be a positive identification by using terms likes cisgender, ‘cisman’ or ‘ciswoman’ alongside with the

usage of transgender, 'transman' or 'transwoman' (Aultman 2014).

Previously, the term gender identity disorder was used according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and now it has changed to gender dysphoria in the latest DSM-5 (APA 2013). The core features listed were the strong desire to be of opposite sex with preference to cross-dress and sturdy desire to have their sexual characteristics that matches one's experienced gender. It is controversial whether to include gender dysphoria into DSM as there are a lot of debates, whether transgender is a pathological condition or it is just a natural variation. In DSM-5, the word 'disorder' was removed. Gender-related dysphoria is a major criterion for limiting the diagnosis to those who have significant distress for their cognitive and affective component. This is to focus on the dysphoria as the clinical misfortune instead than on the identity itself. Not all individuals are distressed with their inconsistency of assigned gender. This nomenclature approach is an attempt to reduce psychiatric stigma and discrimination on transgender population. The main challenge encountered by a physician is diagnosing, and treating individuals with gender identity disorder, or gender dysphoria (Coleman et al. 2012).

There are few formal epidemiological studies on the transgender population which makes it difficult to know the accurate prevalence of transgender. Estimation on the prevalence of transgender varies widely, and it also depends upon the definition of transgender and also the population

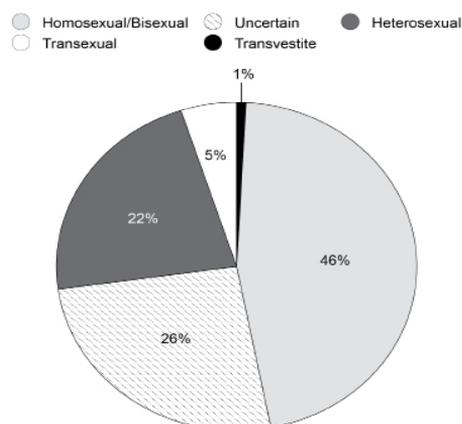


Figure 1: Long term follow-up studies of children with gender identity disorder and psychosexual outcome of these groups of children (Zucker 1985)

being studied. It was reported that a child with gender identity disorder had diverse clinical presentation of gender identity/orientation disorder (Coleman et al. 2012; Zucker 1985) where homosexual/bisexual formed a majority of presentations, i.e. 46% (Figure 1). It is interesting to note that about 1/4 of the children studied in this long-term follow-up fall under a category of the uncertain group of neither homosexual/bisexual, transsexual, heterosexual nor transvestite.

Earlier researchers described the prevalence of transgender to vary from 1:12,000 to 1:45,000 for transgender females and approximately 1:30,000 to 1:200,000 for transgender males (De Cuypere et al. 2007). Few other studies showed even higher prevalence of transgender depending on the type of methodology used. From a population-based household probability study of

28000 adults in 2010 in Massachusetts showed that 1 in 215 people were identified as transgender (De Cuypere et al. 2007).

Cross-sex hormone treatment use feminizing hormones on individuals who are assigned as male at birth and vice versa with the use of masculinizing hormones on individuals who are assigned as female at birth (Coleman et al. 2012). The main reason for transgender motivating to seek for cross-sex hormone is to eradicate most of their secondary sexual characteristics and also to attain the characteristics of the opposite gender (Colton et al. 2011). However, data on the therapeutic approach is scarce and there is lack of consensus on the treatment approach for different countries (Coleman et al. 2012). So, uncertainties in this specialized field of transgender medicine may make it difficult for this group of individuals to get the opportunity to receive appropriate treatment which may predispose them to suffer from discrimination and harmful social conditions. In order to help these group of individuals, it is necessary to probe further into more research to support current guidelines. As it is their rights in these population to get treatment without prejudice. With more interventions developed for these vulnerable population may help to reduce further victimization, violence or stigma in these population (Chakrapani et al. 2019; Gonzales & Henning-Smith 2017). James et al. reported that about 58% of transgender individuals had experienced discrimination which included loss of job, eviction, bullying, physical

harassment and even denial of access to medical services (James et al. 2017). Transgender individuals were found to be have higher unemployment rate and poverty issues compared to non-transgender counterparts. (Conron et al. 2012)

NEUROBIOLOGY IN TRANSGENDER

To date, there is paucity of data that provides credible information on etiology of transgenderism and no single factor has been proven with certainty that causes gender identity disorder (Cohen-Kettenis & Gooren 1999). Based on previous twin studies, it shows that there are strong genetic inheritance components of 62% for individuals with gender identity disorders in early development (Swaab 2004). Factors which influence the development of transgenderism are chromosomal disorders such as Klinefelter disorder, phenobarbital exposure during fetal developmental stage, and endocrine disorder (i.e. congenital adrenal hyperplasia, CAH) (Swaab 2004; Savic et al. 2010). However, only a small group of transgender have underlying endocrinology abnormalities (Swaab 2004; Savic et al. 2010). There were observations, which described possibility of abnormalities in the hypothalamus-pituitary-gonadal axis (Figure 2) in transgender as evidenced by a higher incidence of polycystic ovarian disease (PCOS) and menstrual cycle irregularities in female to male transgender (Swaab 2004). An earlier research found that males

had more androgen staining (AR) in the hypothalamus, especially in the medial and lateral mammillary bodies (Swaab 2004). Other nuclei within the hypothalamus such as the preoptic, periventricular and supraoptic nucleus were also shown to have the sex differences in AR staining, which is dependent on circulating androgen levels (Swaab 2004). It was observed in animal studies that lesions in pre-optic area in hypothalamus caused shift in sexual orientations.

It has been hypothesized that atypical sexual differentiation results in gender dysphoria with the physical sexual characteristics growing in one direction and with the brain and gender identity growing in the opposite sexual directions (Savic et al. 2010). The basis behind this theory is that during the prenatal period, there is a different sensitivity window for sex hormone for the brain and sexual organs (Savic et al. 2010; Berenbaum & Beltz 2011). Sexual development for the genitals and brain occurred at different stages with the genital differentiation in the first two months of fetal development. Subsequently in the second and third trimester of pregnancy, the differentiation occurred independently and may result in transgenderism (Savic et al. 2010).

Few studies showed that transgender's brain is different from their natal sex member's brain and more alike to the opposite sex (Savic et al. 2010; Swaab & Fliers 1985). Transgender's brain seemed to move more towards their experienced gender while receiving hormonal treatment (Gooren et al. 2015). This

evidence showed that the brain organisation may be under influence of prenatal sex hormone, which plays a role in the development of the neural circuit (Berenbaum & Beltz 2011; Slabbekoorn et al. 1999). These organisational effects are permanent and may not depend on subsequent hormone influences (Slabbekoorn et al. 1999).

Studies conducted over three decades described the human brain with the possibility of morphological sex differences (Swaab & Fliers 1985). Many observations failed to be replicated due to different methodology and sampling technique (Swaab & Fliers 1985). It has been observed that there are sexual differences in the shape of corpus callosum and suprachiasmatic nucleus (Swaab & Fliers 1985). The preoptic area, which is involved in gonadotrophin hormone release and sexual behaviour were found to be sexually dimorphic (Swaab & Fliers 1985). In this study, it was found that the sexually dimorphic nucleus was 2.5 +/- 0.6 times larger, and it contained 2.2 +/- 0.5 times as many cells in men (Swaab & Fliers 1985). Several studies also showed that sex hormone influenced verbal and spatial ability with androgen hormone favours visuospatial ability and oestrogen favours verbal fluency (Gooren et al. 2015; Slabbekoorn et al. 1999).

Few women who were subjected to diethylstilbestrol (DES) or children who have congenital adrenal hyperplasia (CAH) were observed to have masculinising effect. Such as a masculine pattern of lateralisation which shows right ear advantage in

the dichotic listening task in DES-exposed women and masculine cognitive pattern is seen in women with CAH in both spatial and verbal tasks (Slabbekoorn et al. 1999). Studies stated that three children born were transsexuals, and a few of the children had gender dysphoria symptoms in a group of children who had in-utero exposure to diphantoin and phenobarbital (Swaab 2004; Dessens et al. 1999).

Based on previous studies, there are significant relationships between sex-role identities with a serum testosterone level (Baucom et al. 1985). It has been shown that feminine-sex-typed

women had lowest concentration of testosterone compared to masculine-typed women had been higher level of testosterone level (Baucom et al. 1985). Baucom et al. also noted that females with higher testosterone levels perceived themselves as more resourceful, independent and goal directed. Women with a lower testosterone level described themselves as traditional females being more cared, anxious and dejected mood (Baucom et al. 1985).

PHYSIOLOGY OF SEX HORMONE

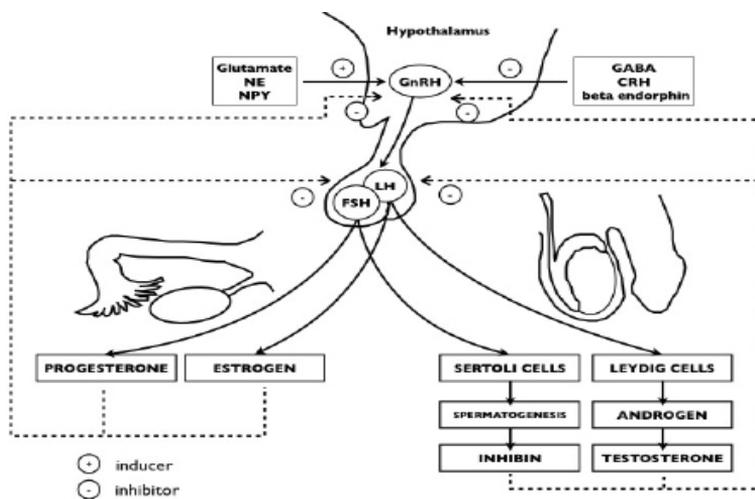


Figure 2: Hypothalamo-pituitary-gonadal axis highlighted the summary of regulation and feedback mechanism in reproduction for male and female from the higher mental centre [i.e. hypothalamus and anterior pituitary]. Gonadotrophin releasing hormone (GnRH) is produced in the hypothalamus which control secretion of luteinising hormone (LH) and follicle stimulating hormone (FSH) via the hypothalamic-pituitary hypophyseal portal system. LH and FSH stimulate target reproductive organs to produce sex hormone (i.e. progesterone, oestrogen and testosterone) for reproductive function such as spermatogenesis and development of secondary sexual characteristics. The sex steroid hormone together with FSH and LH will have negative feedback on the higher mental centers. Inhibin is being produced by Sertoli Cells and it acts on the anterior pituitary to suppress FSH release. Numerous neuromodulators are acted as inducer for GnRH release, i.e. norepinephrine (NE), neuropeptide Y (NPY) and glutamate, whereas γ -aminobutyric acid (GABA), beta-endorphin and corticotrophin releasing hormone (CRH) play a role acted as inhibitory factors (Hall 2015; Rhoades et al. 2003). The dotted line indicate negative feedback respond.

Testosterone is cholesterol based steroid hormone, which has a diverse effect throughout the body as androgen receptors are widely distributed (Baucom et al. 1985; Zitzmann & Nieschlag 2001). Hence, testosterone can have both physical and psychological effects in the body. Interstitial cells of Leydig produce testosterone in the testicles (Hall 2015; Rhoades & Tanner 2003). Its production and the serum levels are being regulated by complex mechanism, which can be affected by both the endogenous and environmental factors (Hall 2015).

Figure 2 showed hypothalamus liberates gonadotrophin releasing hormone (GnRH) to the vascular pituitary gland in order to stimulate the secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH) (Hall 2015; Rhoades & Tanner 2003). LH signal Leydig's cells to produce testosterone, which leads to development of male sexual characteristics (Hall 2015; Rhoades & Tanner 2003). However, the negative feedback mechanism and the complex interplay between the hypothalamic-pituitary-gonadal axis are still not fully understood due to its complexity (Baucom et al. 1985; Zitzmann & Nieschlag 2001; Rhoades & Tanner 2003). Testosterone has both androgenic and anabolic functions (Hall 2015). Regarding its androgenic function, it is mainly responsible for the development of masculine characteristics. During fetal development at the 7th week of embryonic life, XY chromosome causes the gonadal ridge to secrete testosterone and later the testes would

take over the function of secreting testosterone (Hall 2015). Male body characteristics such as penis, scrotum, prostate gland, seminal vesicles and male genital ducts are thus formed. At the same time, it also acts to suppress the formation of female genital organs in the fetus (Hall 2015).

Thereafter, testosterone is essentially not produced during childhood until about 10 to 13 years of age when the testosterone production starts again at puberty with the stimulus coming from the anterior pituitary gonadotrophic hormones (Hall 2015). Testosterone production continues throughout life until after 50 years of age, the level of testosterone drops to about 20 to 50% of the peak value reaches by 80 years of age (Hall 2015).

At puberty, testosterone plays a major role in adult primary sexual characteristic development (Hall 2015; Rhoades & Tanner 2003). Testosterone can influence the testes, penis and scrotum to enlarge up to be eight-fold before the age of 20 years (Hall 2015; Rhoades & Tanner 2003). Apart from that, testosterone is also involved in secondary sexual characteristic's development, which can distinguish a male from a female (Hall 2015; Rhoades & Tanner 2003). Body hair distribution in male is different compared to female such as growth of hair at the pubic region which goes up to the umbilicus along the linea alba of the abdomen, increased facial hair and hair on the chest or even the back (Hall 2015; Rhoades & Tanner 2003; Irwig 2017). Apart from that, testosterone also plays a role in hypertrophy of the laryngeal mucosa and enlargement of

the larynx causing gradual changes into masculine voice (Zitzmann & Nieschlag 2001; Hall 2015; Irwig 2017). Testosterone also causes significant changes in increasing thickness of the skin, increased ruggedness of the subcutaneous tissue and increases sebaceous gland activities, which may contribute to the acne problem (Irwig 2017). Over time, the skin slowly adapts to testosterone to overcome the acne problem (Hall 2015).

Regarding the musculoskeletal changes, testosterone is increased in muscle mass up to 50% more than that of the female counterparts (Hall 2015). It also affects the bone growth by increasing the bone matrix and intensifies calcium retention, which ultimately increases the size and strength of the bone (Rhoades & Tanner 2003; Irwig 2017). Other specific changes related to testosterone hormone are narrowing and lengthening of pelvic outlet, which causes funnel-like shaped pelvis (Hall 2015). These changes are as a result of increased protein level due to anabolic function of testosterone, and also due to the calcium deposition (Hall 2015).

Testosterone also plays a role in basal metabolic rate, which probably is due to protein anabolism whereby surge in protein would increase enzymatic function and activities of all cells (Hall 2015). Other changes observed are increased in the number of red blood cells, blood volume and extracellular fluid volumes in males (Hall 2015).

Basically, most sexual changes caused by testosterone are the effects of increased rate of protein synthesis in the target cells (Hall 2015).

Intracellularly, testosterone is mainly converted to dihydrotestosterone, and then it will induce DNA-RNA transcription to increase cellular protein production (Hall 2015). Once physical maturity is achieved, basically testosterone plays a role in homeostatic function by sustaining secondary sexual characteristics, continuous spermatogenesis, sexual function and maintains the muscle bulk.

ESTROGEN

Regarding the female counterpart, estrogens are primarily secreted in the ovaries from cholesterol and acetyl coenzyme A (Hall 2015). Primary function of estrogen is mostly on the reproductive system which is growth of the tissues and cellular proliferations on the reproductive organs (Hall 2015; Rhoades & Tanner 2003). Main carrier proteins for estrogen are plasma albumin and specific estrogen binding globulins, and they are bound loosely, which enable them to be rapidly released to the target tissues quickly (Hall 2015; Rhoades & Tanner 2003). Liver is involved in estrogen degradation via conjugation, and most of its by-products are excreted in the bile and some in the urine (Hall 2015; Rhoades & Tanner 2003).

In childhood, serum estrogen level is low and during puberty, the secretion of estrogen can be influenced by the anterior pituitary gonadotrophic hormones causing it to increase up to 20 folds or more (Hall 2015). This results in the enlargement of the reproductive organs and external genitalia and additionally there will be fat deposition

in the mons pubis and labia majora (Hall 2015; Rhoades & Tanner 2003). Regarding the uterine endometrium, there is important development, which is crucial to prepare female individuals for pregnancy later on, which are developments of endometrial glands and proliferation of the endometrial stroma (Hall 2015).

The changes are also seen in the fallopian tube with increment of glandular tissue's proliferation of the lining and also increase of ciliated epithelial cells, which are involved in propelling fertilized ovum to the uterus during pregnancy (Hall 2015). In addition to it, estrogen changes vaginal epithelium from the cuboidal cell epithelium in the pre-pubertal period to stratified type for it to be more resistant to trauma and infection (Hall 2015).

Regarding the secondary sexual characteristics, estrogen is involved in development of breast tissues together with growth of the ductile system in the breasts (Hall 2015; Rhoades & Tanner 2003). Estrogen also leads to increase in fat deposition in the breasts (Hall 2015). Estrogen inhibits osteoclastic activity in the bones which stimulates skeletal growth (Hall 2015). During menopause when there is virtually no estrogen secretion, osteoporosis is a common condition seen leading to weakening of bones and risk of fractures (Hall 2015; Rhoades & Tanner 2003).

When compared to testosterone, estrogen only causes a slight increase in protein position and basal metabolic rate (Hall 2015). Estrogen also causes an increase in fat deposition, which forms

a characteristic female figure with fat deposition at the breast, subcutaneous tissues, thighs and buttocks (Hall 2015; Rhoades & Tanner 2003). Other effects of estrogen include the soft and smooth skin texture compared to the males (Hall 2015).

PROGESTERONE

Progesterone is the most important progestin and it is produced normally by the corpus luteum at the second half of the menstrual cycle (Hall 2015). When progesterone is secreted, it is converted to other steroids quickly and liver plays a role in degradation of progesterone (Hall 2015; Rhoades & Tanner 2003).

The main function of progesterone in sexual development is secretory change in the uterine endometrium in order to prepare for fertilisation to take place (Hall 2015; Rhoades & Tanner 2003). Regarding the breast development, progesterone plays a role in alveolar cell proliferation to prepare the breast for its secretory function (Hall 2015; Rhoades & Tanner 2003). However, milk production only occurs with stimulation of prolactin hormone (Hall 2015; Rhoades & Tanner 2003).

CRITERIA TO START CROSS-SEX HORMONE

There are different criteria, which must be fulfilled before allowing an individual to start on cross-sex hormone therapy (Coleman et al. 2012; Irwig 2017). These criteria can be obtained from the World Professional Association for Transgender Health,

Standard of Care, version 7, WPATH SOC 7, i.e. for obtaining informed consent and the initial visits, assessment and intervention (Cavanaugh 2016). WPATH recommends that cross-sex hormone therapy can be initiated once psychosocial assessment has completed by a qualified mental health professional unless the prescribing provider is also qualified to perform this type assessment. After that the individual is deemed to be an appropriate candidate to go for hormone therapy and after obtaining the informed consent for treatment (Unger 2017).

It must be well documented that an individual has persistent gender dysphoria which was diagnosed by a mental health professional who is well versed in this field and the individual must have the capability to make an informed decision and give consent for the therapy. If the individual has significant medical or psychiatric comorbidity, it must be reasonably properly controlled (Coleman et al. 2012; Irwig 2017). There is also a minimum age for medical consent, and if the individual is a child or of adolescent age, there is a need for the individual's parents or caretaker to give consent and to be involved in supporting the individual during the treatment process (Coleman et al. 2012).

In the past four decades, real-life test (RLT) or real-life test experience (RLE) has been practiced which was likely derived from Dr. Harry Benjamin and subsequently it was reinforced by series of expert opinion through the revisions of Standards of Care (Levine

2009). However, there was lack of scholarly evidence or research ever done on it to support these practices and it was mainly based on level of expert opinion. So, there was lack of evidence to address its issues such as duration of real-life test, the purpose of test or assessment to use which sparks criticism and controversy of this practice. RLT is an extended period where individuals live as a member of desired sex full time prior to some irreversible social, medical or surgical step taken (Levine 2009). This practice gives the individual an opportunity to experience and to test their personal belief that life would be subjectively be better when they occupy their new gender role full time (Levine 2009). RLT would generally test the individual's conviction, courage and adaptive challenge in their daily life.

PHARMACOLOGICAL INFLUENCE AND INTERVENTION: CROSS-SEX HORMONE

Cross-sex hormone administrations of exogenous hormonal preparations, which lead to feminizing or masculinizing effects on the body. This treatment should be individualized based on individual's needs with consideration on patient's patient's background medical co-morbid, psychosocial issues and risk-benefit weighting of the treatment to the patient (Coleman et al. 2012). There is a wide variation of hormonal treatment with a different diversity of doses available in the market (Coleman et al. 2012). Currently, with the newer

transdermal preparations and the approach of using low doses may help to reduce adverse reactions, but it is still a concern for healthcare providers and patients (Coleman et al. 2012). To date, there is lack of study on the cross-sex hormone in transgender which is a major setback on gender affirmation treatment in transgender (Coleman et al. 2012). Another limitation noted is that it is different in countries and would vary in terms of availability of cross-sex hormone therapy. Fewer transgender even opted to take hormonal therapy without medical supervision as some parts of the world still have barriers in accepting transgender (Irwig 2017). Due to social stigma, lack of cultural acceptance and poor awareness on transgender, suboptimal transgender care is common (Coleman et al. 2012).

MASCULINISING HORMONE THERAPY (FEMALE TO MALE TREATMENT OPTIONS, FMTO)

TESTOSTERONE

Testosterone hormone comes in many different formulations such as oral, topical, transdermal and intramuscular form. The oral testosterone undecanoate can be given between 160 mg-240 mg OD, testosterone enanthate 50 mg to 200 mg weekly given intramuscularly or subcutaneously. For transdermal patch, the dosing can be between 25 mg to 75 mg daily and testosterone 1% gel at 25 mg to 100 mg daily. The main aim is to use the lowest possible dose to achieve masculinising effects in patients and have to balance it with

its potential adverse reactions (Irwig 2017). This treatment generally is quite similar to treatment of hypogonadal males and the testosterone level should be increased to achieve normal male's physiological range which is between 300 to 1000 ng/dL (Webb & Safer 2019).

There is no standard practice which can guide on the starting and maintaining dose. Usually, it is initiated at a low dose first and then gradually step up the dose with periodic monitoring of serum testosterone level to guide titration (Coleman et al. 2012). Testosterone therapy will change the body composition of fat and muscle bulk towards natal men (Colton et al. 2011). Usually, the agent of choice for testosterone would be intramuscular testosterone such as cypionate (Colton et al. 2011).

In the first year of treatment, patient is recommended to be monitored every 3 months to assess on the virilising effect and thereafter can be 6 monthly to yearly follow up. During each visit, it is recommended to monitor patient's serum testosterone level, hematocrit and lipid profile with a baseline result prior to starting hormonal therapy. Other screenings that should be done are bone mineral density, pap smear and mammography for patients with cervixes and breasts (Coleman et al. 2012; Webb & Safer 2019).

OTHER AGENTS

Progestins may be used to help in cessation of menstruation (Hall 2015)

FEMINISING HORMONE THERAPY (MALE TO FEMALE TREATMENT OPTIONS, MFTO)

Feminising hormone therapy is slightly more complicated than the regimen for masculinizing hormone therapy as female transgender requires antiandrogen in addition to estrogen. The main goal of treatment would be to aim for female range of testosterone level which is less than 100 ng/dL and be cautious to avoid supra-physiological levels of estradiol which is to keep it below 200 pg/mL breasts (Coleman et al. 2012; Webb & Safer 2019; Gardner & Safer 2013).

It was recommended that female transgender to have regular follow up every 3 monthly for the first year of initiation of therapy to monitor the feminizing effect as well as to watch out for any adverse effects (Webb & Safer 2019). Baseline lipid profile, serum prolactin should be obtained prior to therapy and then repeated during every visit together with serum testosterone and estradiol with the aim to maintain it between the range of testosterone at 30 to 100 ng/dL and estradiol less than 200 pg/ml (Webb & Safer 2019; Gardner & Safer 2013). Other important surveillance would bone density test, screen for cancers, metabolic syndrome including monitoring of weight and also look for gallstones if clinically indicated (Webb & Safer 2019; Gardner & Safer 2013).

ESTROGEN

There are a few routes of administration, i.e. oral, transdermal

form and parenteral estradiol valerate. However, oral estrogen, notably ethinyl estradiol is not advisable as there is an increased risk of venous thromboembolism (VTE) (Coleman et al. 2012). Due to safety concerns, transdermal is recommended and VTE is dose-related, so if possible, it is better to start at lower doses, particularly in individuals at risk to get VTE (Moore et al. 2003). Usually, the dose used for feminizing effect is about 2-3 times higher than the hormone-replacement therapy in post-menopausal women (Moore et al. 2003). After the age of 40 years, transdermal route was recommended as it bypass the first-pass metabolism which seemed to have better metabolic profiles (Unger 2017).

For oral estradiol it has been recommended to keep the dose between 2 to 4 mg OD, transdermal estradiol was between 0.1 to 0.4 mg biweekly and parenteral estradiol valerate was 5 to 30 mg once every fortnightly (Unger 2017).

ANTI-ANDROGEN

Primary objective of anti-androgen is to reduce the effect of endogenous testosterone activity to reduce masculine characteristics. Most studies suggested for combination of anti-androgen with estrogen for feminizing effects, and this combination may be the lower dosage of estrogen needed to reduce testosterone activity, which can reduce estrogen related adverse effects (Moore et al. 2003). So far, there are no consensus guideline on usage of anti-androgen (Unger 2017).

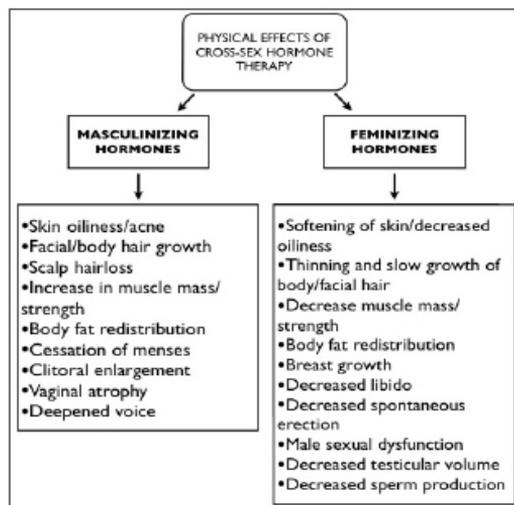


Figure 3: List of possible physical effects of cross sex hormones in transgender.

Anti-androgen came from a wide variety of different drug classes and below are the common anti-androgen drugs being used currently: (i) Spironolactone is one of the commonest drug being used which is a type of antihypertensive drugs that is known to directly inhibit testosterone secretion and binding of androgen to the androgen receptor (Aultman 2014). The dose being used commonly was between 100 to 200 mg OD and patients need to be monitored closely for hyperkalemia (Unger 2017), (ii) Cyproterone acetate is a synthetic compound of 17-hydroxyprogesterone and it was shown to have anti-androgen properties. It mainly acts as an androgen receptor antagonist (Wierckx et al. 2012), (iii) GnRH agonists are neurohormones, which comes in injectable forms or implants are a more expensive form of treatment. The GnRH agonist inhibits the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH). It functions

as a highly effective form of gonadal blocking (Coleman et al. 2012). GnRH agonist (leuprolide) can be given between 3.75 to 7.5mg intramuscularly every month (Unger 2017), (iv) 5-alpha reductase inhibitors, i.e. finasteride and dutasteride are known to inhibit testosterone from converting to its active form, which is the 5-alpha dihydrotestosterone (Coleman et al. 2012). Finasteride dosing commonly is 1 mg OD (Unger 2017).

PROGESTIN

Progestin usage is rather controversial as its usage was found that it did not enhance growth of breast tissue or lower down testosterone level (Coleman et al. 2012). In addition to it, progestins have an increase in risk for pulmonary embolism, coronary artery disease, cerebrovascular accidents and breast cancer risk, especially when used in combination with estrogen (Coleman et al. 2012). The dose for oral

Progesterone was between 20 mg to 60 mg OD (Unger 2017). Figure 3 shows the list of possible physical effects of cross sex hormones in transgender.

BIOLOGICAL INFLUENCES IN TRANSGENDER

Few researchers suggested that masculinizing treatment using testosterone or other androgenic sex steroids may further aggravate affective symptoms such as hypomania, mania or even psychotic symptoms in those individuals with co-morbid of psychiatric illness (Coleman et al. 2012; Seiger et al. 2016). With regard to the testosterone that may boost dopamine sensitivity in the brain as an adverse effect inducing psychotic disorders, studies in these areas of interest were contradictory and inconclusive (Elias & Kumar 2007; Trotman et al. 2013). On the contrary, estrogen may produce neuroprotective effect against psychotic disorders (James et al. 2016; Kirkbride et al. 2012; Weickert et al. 2016).

These adverse reactions seem to occur when there were higher doses or supra physiological serum testosterone level. However, evidence of such is limited and its risk is inconclusive.

PSYCHOLOGICAL INFLUENCES IN TRANSGENDER WITH CROSS-SEX HORMONE

Cross-sex hormone was found consistently to bring positive effects to be transgender psychologically, which was replicated in many studies (Colton et al. 2011). Regarding female-to-male

who are on testosterone therapy were observed to have improvement in quality of life, which was also seen for male-to-female counterparts (Gorin-Lazard 2012).

MAJOR DEPRESSIVE DISORDER

A low level of estrogen was found to be associated with depression, which is seen in normal physiology of females during their menstrual cycle, postpartum period and menopausal period. It was found that transgender women had higher prevalence of depression with an estimated prevalence rate to range between 48% to 62% and when compared to general population in the United States, it was about 16.6% (Hoffman 2014; Budge et al. 2013). Estrogen was found to have a calming effect, and it was used to augment the effect of antidepressant in patients with depression (Khobzi Rotondi 2011).

There is some evidence, which shows that androgen deprivation treatment in prostate cancer patients are linked to increased rate of depression, which may apply to male-to-female transgender taking anti-androgen treatment (Khobzi Rotondi 2011). Studies correlated the relationship between gonadal function and depressive episodes as it has been observed that hypogonadal men on testosterone treatment seemed to show improvement in the mood (Zitzmann & Nieschlag 2001). Cyproterone acetate usage has been observed to cause transient depressive symptoms during the first 6 months of hormonal treatment (Asscheman et al. 2011).

There are many risk factors apart from the hormonal effect which can predispose transgenders to depression, which are gender dysphoria, lack of social support, physical and verbal abuse, discrimination, being a sexual worker and socio demographic factors such as low education level and unemployment (Colton et al. 2011; Hoffman 2014).

ANXIETY DISORDER

Regarding anxiety disorder in transgender, the rate can range from 26% to 38% (Budge et al. 2013). Gómez-Gil et al. reported findings of transgender on cross-sex hormone showed to have lower levels of social distress, anxiety and even depression when comparing with transgender who were not on cross-sex hormone therapy (Gómez-Gil et al. 2009).

MORTALITY RATE AND SUICIDE

Earlier researchers reported that mortality rate for male to female group was about 51% higher than the general population (Assheman et al. 2011). However, in the same study, regarding relation of female to the male group, there was no significant difference in the mortality rate in comparison to the general population. There was increased mortality rate up to 8-fold times in the males compared to the females and was mainly due to non-hormonal related such as illicit substance usage, suicide and acquired immune deficiency syndrome (AIDS) (Assheman et al. 2011).

Regarding suicide, there was six-

fold increase in the male to female subjects, but it was pertinent to note that there were other confounding factors, which affected the results (Assheman et al. 2011). Individuals who were transgender, presented themselves to the Psychiatry Unit with history of suicidal attempts or substance abuse or affective disorder even prior to cross-sex hormone treatment. This was probably related to the psychological stress from gender dysphoria. Clements-Nolle et al. reported prevalence for suicide in transgender to be 32% (Colton et al. 2011; Clements-Nolle et al. 2006).

PSYCHOLOGICAL AND COGNITIVE EFFECTS OF CROSS-SEX HORMONE THERAPY IN TRANSGENDER

Generally, cross-sex hormone therapy can alleviate overall well-being and, mainly it reduces gender dysphoria irrespective for transgender men or transgender women (Colton et al. 2011). In one longitudinal study, it was shown that hormonal therapy demonstrated positive effects in transgender. The study was conducted on the transgender before and after 12 months of hormonal therapy and it was found that their emotions were stable using Zung Self-rating Depression Scale (SDS) and Zung Self-rating Anxiety Scale (SAS) (Colizzi et al. 2014). In this prospective study, it showed that there are lower psychological distress and lesser functional impairment with hormonal therapy compared to one prior the hormonal treatment. The results showed that for anxiety

before treatment, it was 50%, and it was only 17% following 12 months of hormonal treatment. The depressive psychopathology was 42% for pre-treatment group and 23% for those following 12 months of hormonal treatment. This study also used Symptom Checklist 90-R (SCL-90-R) to evaluate global psychological symptoms. The psychological distress is 24% at enrolment phase and 11% after being on hormonal therapy. Regarding functional impairment, it was 23% before hormonal treatment and 10% after hormonal treatment, respectively, using Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) (Colizzi et al. 2014). Current evidence on cross sex therapy with regards to improving psychological well-being is quite encouraging especially for male-to-female transgender (Nguyen et al. 2018).

In another study by Keo-Meier, Minnesota Multiphase Personality Inventory (MMPI-2) was used as it was believed that MMPI-2 results would remain stable even with intensive psychotherapy (Keo-Meier et al. 2015). This study showed that with 3 months of testosterone therapy, there was substantial improvement of transgender men in depression, hypochondria, hysteria and paranoia when compared to the female controls. The results showed that testosterone therapy in transgender men helped to improve multiple domains of psychological functioning.

The published data on effects of cross-sex hormone therapy to the person's cognition is limited. Slabbekkoorn reported that there was

a significant correlation with androgen treatment on spatial ability in female-to-male (FTM) transgender and these effects were not reversed after a five-week period of termination of androgen treatment (Slabbekkoorn et al. 1999). With regard to testosterone treatment option, it has an activating effect which is not rapidly reversible on spatial ability performance. However, in this study, anti-androgen treatment did not seem to show a decline in spatial ability nor improved in verbal fluency in male-to-female (MTF) transgender. Most studies to date suggested that masculinizing therapy enhances in visual memory and 3-dimensional spatial memory tasks but worsens verbal memory (Nyugen et al. 2018).

Studies showed that masculinizing therapy increases cortical thickness in the parieto-occipito-temporal regions may suggest possibility of some testosterone-induced structural connectivity. As for feminizing therapy, some research found that there was decreased in cortical thickness, decreased in subcortical volumetric measures and enlargement of ventricular system (Nyugen et al. 2018; Seiger et al. 2016; Spizzirri et al. 2018). Mueller et al. also found there was mean neuroanatomical volume for the amygdala, putamen and corpus callosum differed between transgender men and cismen in several brain structures including medial temporal lobe structures and cerebellum. He suggested that there is localized influence of sex hormones neuroanatomy (Mueller et al. 2017).

There was also a relationship between estrogens and borderline

personality where the latter may be adversely influenced by alterations in the estrogen levels, especially among women (Evardone et al. 2008). Estrogen regulation on the neurotransmitter systems in the CNS may explain the affective instability associated with borderline personality among the sample of women and men. Interestingly however, this relationship may also be greatly influenced by other variables, e.g. age, menopausal and genetic make-up and that this could potentially influence the interpretation of the results involved in this disorder (Mc Ewen 2001).

Generally, the studies to date on safety and effects of cross sex hormone towards the brain are very few to date with most studies limited to small sample size and most studies are cross-sectional in nature. So, future research should focus if these neuroanatomical changes gives impact to functional or cognitive changes as these domains are important in daily functioning

in individuals on hormonal therapy. Interestingly, Mohammadi & Khaleghi suggested that there is relationship and interaction between culture, behavior and brain structures. Transgender will experience changes in lifestyle and beliefs and these changes in new culture and concepts may alter brain's function and structure based on the culture-behaviour-brain loop model (Mohammadi & Khaleghi 2018).

AGGRESSION AND SEXUALITY

Animal studies showed that aggressive behaviour is found more predominantly in males, and some criminological studies showed that men use far more physical violence, and these studies linked testosterone to aggression. These include criminals who are involved in violent felonies were found to have higher testosterone levels compared to felons who were convicted for burglary or theft (van Goozen et al. 1995).

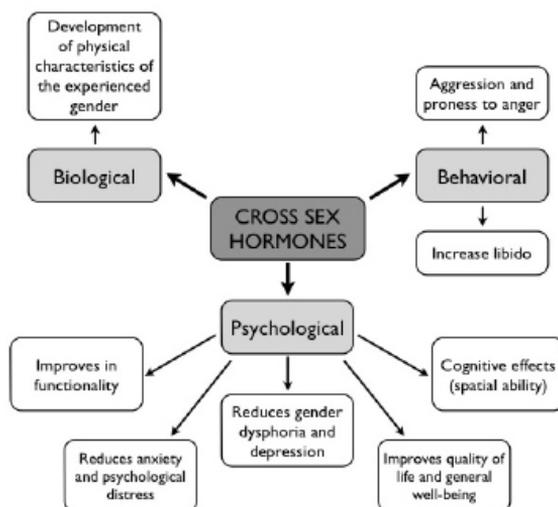


Figure 4: Summary of cross sex hormones having a role in the bio-psycho-behavioural domains (Coleman et al. 2012; Irwig 2017; Cavanaugh 2016; Unger 2017).

Regarding FTM treatment options, there are positive correlations of testosterone with aggression. In an earlier study by Slabbekoorn, it was shown that FTM who are on testosterone therapy have higher scores for anger proneness, which was replicated in a previous study by Van Goozen (van Goozen et al. 1995). In this same study, it was found that their increased sexual feelings measured by frequency of sexual activity after being on testosterone therapy for FTM and also general reduction in affect intensity. Interestingly, in an animal study where female rats were injected with testosterone, not only showed increased in aggressive behaviour but also showed an increase in the sexual behaviour (van Goozen et al. 1995). Based on these studies, it was suggested that females are more sensitive to minor variations in the circulating testosterone levels (van Goozen et al. 1995). However, there were conflicting results in which the administered exogenous supra-physiological levels of testosterone showed that there was no sufficient evidence to suggest link between testosterone with increased aggression (Anderson et al. 1992; O'Connor et al. 2002).

We represented the summary of cross sex hormones having a role in the bio-psycho-behavioural domains in Figure 4.

ADVERSE EFFECTS FROM CROSS-SEX HORMONES

It has been reported that male to female transgender on hormonal treatment, experience more

important adverse effects such as thromboembolism, cardiovascular event and osteoporosis. However, it has been found that female to the male transgender group on hormonal treatment seemed were relatively safer (Wierckx et al. 2012). It was reported that 12% of male to female transgender experiences thromboembolic or other cardiovascular event (Wierckx et al. 2012). Among the risk that comes with cross-sex hormone therapy are different for female to male group and male to female group. Another area to address is to look into possibility of sexual dysfunction in this population group as changes in level of hormones may interfere with sexual functioning. Validate questionnaire such as Female Sexual Function Index Questionnaire (FSFI) may be used during clinic visits (Tee et al. 2014; Hatta et al. 2007).

ADVERSE EFFECTS OF FEMALE TO MALE TREATMENT WITH REGARD TO HORMONAL THERAPY

Testosterone is the main hormone used and its adverse reactions are weight gain, blunting in the insulin receptor sensitivity, worsening of lipid profile, and hematocrit elevation. These combinations of antagonistic reactions have raised the concern for possibly increasing the risk of cardiac and thrombo-hemolytic events. Polycythemia was also reported as one of its rarer adverse reactions. Other masculinizing hormones adverse effects are acne, androgenic baldness, sleep apnea and liver enzyme derangement (Cavanaugh

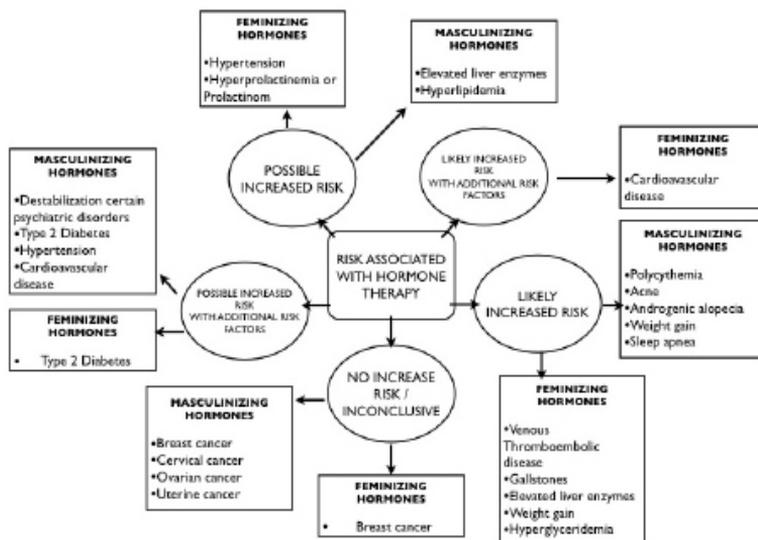


Figure 5: Side effects profile of cross sex hormone therapy (Coleman et al. 2012; Cavanaugh 2016).

2016). So, surveillance on metabolic syndrome during each follow up with basic anthropometric measurement may be useful such as weight, waist circumference, BMI, blood pressure and heart rate on every clinic visit apart from regular blood investigations. Imaging or further test may be necessary if clinically indicated during follow up.

ADVERSE EFFECTS OF MALE TO FEMALE TREATMENT WITH REGARD TO HORMONAL THERAPY

Research more than a decade (Cavanaugh 2016), reported 20-fold increase in the venous thrombosis and also an increase in serum prolactin in a retrospective morbidity and mortality due to feminizing treatment. This may possibly increase the growth of prolactinomas (Cavanaugh 2016). The adverse effects are dose dependent and

the risk further increased when other risk factors were present, e.g. Smoking, obesity, and advance age may increase the risk for cardiovascular event in transgender on feminizing treatment. So, regular follow-up is vital to watch out for these adverse effects by monitoring patient’s metabolic profile via anthropometric measurements and regular blood monitoring. Further investigations should be promptly initiated accordingly if patient has any early signs of any adverse effects (Figure 5).

CONCLUSION

In summary, cross-sex hormone generally gives benefits to be transgender, but it may also bring deleterious effects such e.g. FTM gets reduced in affect intensity, and MTF experienced more tension, gloomy mood and easy fatigability. The present review showed that there are

few heterogeneous results in some studies and one needs to take note on limitations in these literature. Inconsistent results may be due to limitations with methodology such as small sample size and issues with study design or sample distribution. Many definitive questions still remain unanswered due to lack of retrospective or prospective studies on cross-sex hormone. Generally, the evidence on cross-sex therapy is of low quality due to improper technique of randomization and control groups in the study performed. So, it is important to convey to patients regarding potential uncertainty and there is a need for individualised treatment approach based on risk and benefit ratio for each patient. Transgenderism is a complex disorder and treatment approach is not too easy, and it needs an integrated approach of physical, psychological, social and even cultural interventions. There are many issues to address on the care for transgender. Limited accesses for healthcare services for transgender and lack of trained mental health professionals are some of the important restrictions. Stigma and potential political discrimination to these special groups of individuals carry significant psychosocial issues to not only the transgender, but also pose a dilemma to the mental health professionals who are dealing with this special group of patients. So, it is important to educate the scientific community regarding treatment options that are available and also its latest evidence found. As it is important to mainstream transgender care among medical healthcare workers

and published transgender medical treatment guidelines may provide a foundation for more generalized patient care and more assessable to for transgender population.

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