

The primary health care of transgender adults

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Abstract. Gender dysphoria is associated with significant health disparity. Gender services perform specialised activities such as diagnosis, endocrine management and liaison with surgical services. Although providing these specialised transition services appears to be safe and improves well-being, significant health disparity remains. Engaging primary care providers is an important part of any strategy to improve the health care of transgender people. The relationships between gender dysphoria and a range of primary care issues such as mental health, cardiovascular disease and cancer are explored.

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Introduction

Transgender individuals experience gender dysphoria: discord between their self-identified gender and their assigned ('biological') sex. The diagnosis of gender dysphoria is outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5), and requires the elaboration of a history of enduring incongruence between the person's gender identity and their primary or secondary sex characteristics, identification with a gender that is different from their assigned sex, and the degree to which this incongruence causes distress and impairment.¹ Transwomen are natal males who are undergoing feminisation; transmen are natal females who are undergoing masculinisation. Cismen and ciswomen are terms to describe those whose gender aligns their assigned sex. Non-binary people identify with neither male nor female poles of the gender spectrum, but fall somewhere between.

Gender identity is an innate phenomenon. It is experienced and expressed in diverse ways, and this may be fixed from a very early age, or evolve with experience, circumstance, support and the availability of information. The cause of gender dysphoria (or gender congruence for that matter) is unknown, but most scientific evidence suggests, and most experts believe, it has a biological basis.²

Gender dysphoria poses challenges to the medical model; the diagnosis is framed within the domains of the mental health professionals. Management, however, usually involves medical interventions such as endocrine therapy or surgery, very often with mental health support. Other health professionals have roles in transgender health: speech pathologists deliver voice training, dermatologists may be required to deal with testosterone-mediated acne and dieticians may be required for limiting the metabolic effects of endocrine therapy. The World Professional Association for Transgender Health (WPATH) publish multidisciplinary guidelines known as the Standards of Care, currently version 7 (SOC 7),³ which acknowledge the importance of mental health skills to make the diagnosis.

In practice, transgender health networks evolve with the availability of local resources, and professionals adapt to meet the SOC as best they can. Given the multidisciplinary nature of transgender medicine, it is essential that mental health professionals, endocrine providers and primary care providers are familiar with each other's practices and perspectives.

The effectiveness of medically assisted gender transition is not completely understood, and is rapidly evolving. Overall, transition improves the symptoms of dysphoria and quality of life in ~80% of transwomen and transmen.² Endocrine therapy is associated with a significantly better quality of life, greater self-esteem, better mood,⁴ and reductions in psychological distress.⁵ Regret about gender transition is uncommon,^{6–8} experienced by 2.2% of those in a large Swedish cohort study,⁸ and the proportion of those who experienced regret was lowest among those who commenced transition in the current era. Presentations to gender services for medical management of gender dysphoria have increased markedly since 2000.^{8,9}

Guidelines have been constructed to provide a framework for delivering safe and effective medical care to transgender people.^{3,10} Guidelines have concentrated on the diagnosis, endocrine and surgical management of gender dysphoria, aspects that are mainly the focus of specialised gender clinics. Deaths from hormone treatments and gender surgery, however, are rare.^{11–14} Endocrine therapies for transgender people are generally safe and effective,^{2,3,8,12} and complications from endocrine therapies are not significant contributors to mortality in observational and cohort studies.^{11,14} This implies that delivering specialised endocrine and surgical interventions alone is insufficient to reduce health disparity, and primary health care is likely to be an important contributor for effecting meaningful improvements in the health of transgender populations.

Health disparities among transgender populations are described for a wide variety of mental health conditions,

suicide attempts, non-suicidal self-harm, sexually transmissible infections, HIV, blood borne viruses, anal dysplasia, cardiovascular disease, lung cancer and alcohol and other drug use are described in the literature.¹⁵ Mortality among transgender populations is significantly higher than the general population.^{11,14} Among those who have undergone sex reassignment surgery, mortality continues to exceed that of the general population.^{11,14} Suicide, HIV/AIDS, liver failure and cardiovascular disease contribute heavily to the excess mortality, suggesting that mental health and risk-taking behaviour are important issues to address.^{11,14}

The following introduces some selected topics in transgender health that have interest and relevance to primary care.

Mental health

Mental health problems commonly co-occur among people presenting with gender dysphoria.^{2,11,14,15} Among adults with gender dysphoria, most well-designed studies report a 30–40% prevalence of current psychopathology and a 50–80% prevalence of lifetime psychopathology,² much higher than the prevalence seen in controls and the general population.

Discarding the diagnosis of gender dysphoria in the setting of mental health problems is problematic; although caution must be taken with the diagnosis of gender dysphoria in this setting, most psychiatric comorbidity is secondary to the gender dysphoria, and delaying the diagnosis or treatment is likely to further harm the person.

Rates of suicide ideation, suicide attempts and completed suicide among transgender populations are consistently higher than cisgender controls¹⁴ and the general population.¹¹ Although treatment of gender dysphoria is associated with improvements,^{4,16} substantial mental ill-health persists after transition.¹⁴ In one large cohort, those who had undergone sex reassignment surgery (SRS) remained 4.9-fold more likely than controls to have attempted suicide, and 19.1-fold more likely to have died from suicide.¹⁴

Mood and anxiety disorders are the most frequently encountered psychiatric comorbidities among transgender populations.¹⁷ One recent, methodologically strong study in a clinic-based population⁵ demonstrated that 27% of transgender subjects had a current mood disorder, with a lifetime prevalence of 60%. Anxiety disorders were current in 17%, with a lifetime prevalence of 28%. Although oestrogen is associated with depression and subclinical mood decreases,^{7,18} this is frequently counterbalanced by the positive effects on mood that accompanies the reduction in dysphoria.¹⁹ Testosterone use in transgender men is accompanied by improvements in mood and libido.^{4,20}

Gender dysphoria occurs with higher frequency among those with autism spectrum disorders (ASD).^{21,22} Establishing the diagnosis of gender dysphoria in the presence of ASD requires involvement of mental health professionals with experience of both conditions. ASD is frequently associated with unusual and intense preoccupations, communication difficulties and cognitive deficits, which complicate the assessment of gender dysphoria. Poor social supports, unrealistic expectations and concrete thinking may complicate treatment with gender-affirming hormones, and ongoing mental health

professional involvement is frequently required. Recently published guidelines for the diagnosis and management of co-occurring ASD and gender dysphoria in adolescents are an important milestone in the development of evidence-based practice.²³

Personality disorders also occur with higher frequency in transgender populations than in the general population, with a 20–60% prevalence reported from well-designed studies.² As with other mental health conditions, the presence of a personality disorder may complicate the diagnosis, but is not necessarily a contraindication to transition. This population is likely to need greater support, and benefit from proactive engagement of mental health professionals and strategies to promote engagement.

Cardiovascular disease

The effects of cross-sex hormones on cardiovascular disease (CVD) risk is the main concern regarding safety of endocrine transition.²⁴ However, there are no large prospective trials of sufficient duration that examine cardiovascular risk secondary to cross-hormone therapy with clinical endpoints. A recent large retrospective cohort demonstrated an increase in risk of death from cardiovascular disease¹⁴ among transgender people in Sweden, but previous studies have not demonstrated this.^{25,26} The degree to which cardiovascular disease is attributable to traditional risk factors rather than hormone therapies themselves is uncertain. Large, prospective studies that include individuals over the age of 65 years are needed to better determine cardiovascular risk in this population.

Smoking induces the production of prothrombotic coagulation factors, some of which are also induced by oral oestrogen administration.²⁷ Smoking among transgender populations occurs at a greater frequency than the general population,^{10,11} and interventions to encourage smoking cessation are recommended at all ages, but particularly for those aged above 35 years.¹⁰

Testosterone administration in transmen has been associated with reductions in high-density lipoprotein, increases in total cholesterol and increases in triglycerides and inflammatory markers.^{20,28} Erythropoietic effects, weight gain and increased blood pressure are other known effects of testosterone that may increase CVD risk. Changes in body composition include protective metabolic features, including increases in muscle mass and reduction in total fat, as well as concerning features such as increases in visceral fat.^{29,30} The effect of exogenous testosterone on carbohydrate metabolism is unclear.^{13,31,32} No studies have demonstrated an increase in risk of cardiovascular events among transmen using testosterone.

The effects of oestrogen on cardiovascular disease are not well understood. Although increases in CVD have been observed among transwomen,¹¹ this is not conclusive.^{13,33,34} Oestrogen is associated with increases in blood pressure, but the degree to which this translates into clinical endpoints is unknown. Diabetes has been observed more frequently among transgender women,¹³ and high dose ethinyloestradiol was associated with impaired glucose tolerance.²⁷

It is expected that changing prescribing habits through evolution of guidelines has improved safety of oestrogen therapy among transgender women.^{12,13,35} Previously,

ethinyloestradiol and conjugated oestrogen use was common among transwomen, but has been strongly associated with an increased risk of CVD and venous thromboembolism, so is no longer recommended. Transdermal oestrogens have been associated with more benign metabolic profiles than oral administration, and this route should be considered for those with risks for CVD, venous thromboembolism and any transwomen over the age of 40 years.^{3,10,13,26,36,37}

In the absence of clear evidence of increased risk, absolute cardiovascular risk calculation should be performed in accordance with local guidelines for the general population. As it is unclear which reference ranges are more relevant for transgender individuals,³⁸ risk calculation using biological male calculator settings will provide a sensitive estimate of risk for both transmen and transwomen, but may lack specificity.

Osteoporosis

Both oestrogen and testosterone are important for bone mineral density (BMD), and hypogonadism in cismen or ciswomen is a cause of osteoporosis and fracture. The effects of exogenous sex hormones on BMD have been described in cross-sectional studies^{29,30} and a longitudinal study,³⁹ but there is a need for large prospective studies using fracture as a clinical endpoint.

Studies of oestrogen use and BMD among transwomen have mixed results. Some studies have found transwomen to have a higher prevalence of osteoporosis, while others have not.^{28–30,39,40} Reassuringly, low-dose oestrogen use in hormone replacement therapy (HRT) among menopausal cisgender women is protective against osteoporosis, and the doses used for cross-hormone therapy in transgender women are typically higher than those used in HRT. Several authors have hypothesised that antiandrogens may inhibit bone mineralisation,³³ and lead to osteoporosis despite adequate oestrogen levels. Many transgender women start endocrine therapy with lower bone mineral density than their age-matched peers,^{30,40} so may be predisposed to osteoporosis.

Bone mineral density testing is recommended for all transwomen over the age of 65 years, and for those aged 50–65 years who have been off oestrogen for more than 5 years.³³

Among transmen, maintaining physiological male levels of testosterone is protective against osteoporosis.⁴¹ In addition to exogenous testosterone, transmen usually have levels of circulating oestrogen that are likely to be protective against bone disease. The sources of oestrogen among transmen include the peripheral aromatisation of testosterone and ovarian oestrogen production, unless they have been oophorectomised. The increased muscle mass observed among transmen provides further protection against osteoporosis.^{29,30}

Post SRS, transmen and transwomen become hypogonadal if exogenous hormones are ceased, and treatment should continue for life.³³

The effects of gonadotrophin-releasing hormone (GnRH) agonists on BMD in transgender adolescents are unknown,^{42,43} but experience from using these drugs in the treatment of precocious puberty suggests that the small decreases observed in BMD during treatment are promptly reversed on cessation.^{44,45} How well this can be generalised to transgender populations

and cross-hormone therapy is unknown, as these young people generally do not start cross-hormone therapy until 16 years of age: beyond the normal range of pubarche, and well into the period in which peak bone mass is accrued.

Cervical cancer

Rates of cervical cancer in transmen are unknown. For transmen who do not undergo total hysterectomy, cervical screening is recommended.⁴⁶ For those who have undergone a hysterectomy, it is important to ensure that the cervix has been removed and that no history of malignancy preceded hysterectomy. Transmen who have undergone total hysterectomy for reasons other than malignancy do not require further screening.

Transmen are an under-screened population with regard to cervical screening. Uptake of cervical screening among transmen is lower than the cisgender female population,⁴⁷ confirming the anecdotal experience of clinicians. For those transmen with abnormal cytology, follow up is more likely to be delayed. Vaginal examination for cervical screening is unacceptable to many transmen, many of whom have intense dysphoria about their natal genitalia and may never have had vaginal penetration.⁴⁶

Atrophic vaginal changes are common among transmen treated with testosterone, and cervical samples from transmen have higher rates of unsatisfactory cytology.⁴⁸ Reductions in cellularity commence ~6 months after commencing testosterone, and progress with time. The discomfort associated with vaginal atrophy and dysphoric reaction to vaginal examination may make collecting an adequate sample technically difficult. Lubricant use in the setting of vaginal atrophy and discomfort may contribute to the rates of unsatisfactory cytology.

Replacement of cervical cytology with human papillomavirus (HPV) testing as the primary screening tool may offer benefits to transgender men. Self-collection of specimens for HPV is feasible,⁴⁹ and may be more acceptable to transmen than speculum examination.

Endometrial cancer

Unless oophorectomy has been performed, transgender men treated with testosterone continue to have circulating levels of oestrogen that might plausibly affect the endometrium.¹³ Oestrogen levels fall only moderately among transmen on testosterone therapy, and their levels exceed those seen in postmenopausal women.⁵⁰ Reductions in sex hormone-binding globulin may further increase the concentration of free oestrogen. Progestogens are not routinely used in this population,¹⁰ theoretically creating a scenario of unopposed oestrogen with an intact uterus. One case report of endometrial carcinoma exists,⁵¹ suggesting there is some risk, albeit unquantified. One prospective study showed no increase in risk, but the duration was relatively short.²⁸ Although long-term prospective evidence is lacking, two observational studies have demonstrated that endometrial hyperplasia is uncommon.^{52,53}

Uterine bleeding in transmen on testosterone therapy who have previously been amenorrhoeic should be investigated.³³

Breast cancer

Among transmen who have not had chest surgery, androgens may have a protective role in breast neoplasia.⁵³ Histology of specimens from mastectomies in a transmen show changes consistent with postmenopausal involution, and replacement of glandular structures.^{53–55} As described above, ongoing oestradiol production occurs in transgender men, making oestrogen-mediated carcinogenesis a theoretical possibility. Most studies of low-dose testosterone in postmenopausal ciswomen show no effect on breast cancer risk.³³

Chest surgery appears to reduce the risk of breast cancer among transgender men. Chest surgery among ciswomen reduces risk in proportion to amount of tissues removed.⁵⁶ Retrospective and case-control studies suggest the risk is comparable to cisgender men,^{28,54} but there are no long-term prospective studies. As some breast tissue remains after surgery, yearly chest wall examination is recommended. Although this is not evidence-based, it is likely to be a low cost and acceptable intervention, with few negative effects.³³

Among transwomen using feminising hormone therapy, the risk of breast cancer appears to be greater than for cisgender men, but lower than for cisgender women.^{25,57} There are no long-term prospective studies that address incidence. One prospective case-control study showed no difference in incidence of breast cancer, but the duration of follow up was short for a cancer study.²⁸ Retrospective studies have not shown an increase in risk of breast cancer,³³ but there are multiple published case reports.⁵⁷ Risks factors include the duration of therapy, family history of breast cancer and the use of progestogens.³³ Mammography is recommended for transwomen as for cisgender women, but the lower incidence of cancer alters the risks and benefits derived from screening. Individual discussions with transwomen should precede decisions to screen individual transwomen with mammography.

For transwomen who have not used feminising hormones, the risk is the same as cisgender men and screening is not recommended.

Prostate cancer

Prostatectomy is not carried out during sex reassignment surgery, potentially leaving the prostate susceptible to the development of carcinoma. As androgen deprivation has a protective effect on the development of prostatic adenocarcinoma, it is thought that transwomen are at lower risk of prostate cancer.⁵⁸ Some transwomen, however, may have prostate cancers *in situ* at the time of commencement of feminising hormones or SRS. Androgen deprivation escape does occur among cismen with prostate cancer, and the role of androgens in the pathogenesis of prostate cancer is questionable.⁵⁹ Androgen-independent tumours might be preferentially selected among transwomen receiving endocrine therapy.

Incidence of prostate cancer was low in a large contemporary cohort of transwomen,⁶⁰ who were both under and over 40 years-of-age. A case-control study,²⁸ and one retrospective study⁶¹ also demonstrated a low incidence of prostate cancer in transwomen.

Prostate-specific antigen screening is not recommended for transwomen; its use in general settings remains contentious, and its benefits must be less among transwomen unless they have a family history. Prostate-specific antigen may be low in prostate cancers that develop in the setting of androgen deficiency.⁵⁹

Prolactinoma

Use of cross-sex hormones continuously stimulates anterior pituitary lactotrophs. Theoretically, this may lead to an increase risk of prolactinoma.

There are several published case studies of prolactinoma,^{62,63} but no long-term prospective studies have been published.

Determining baseline prolactin is recommended before commencing cross-sex hormones, and this should be repeated on a yearly basis. It should be noted that many of the factors that lead to benign elevations in prolactin (oestrogen use, stress, psychotropic medications) are prevalent among transgender populations.

Discussion

There is emerging appreciation of gender dysphoria and its association of morbidity and mortality. Changes to the effectiveness, safety and availability of interventions for gender dysphoria,^{4,13,16,35} combined with an evolution of social attitudes, are possible reasons for the observed increase in presentations to gender services for transition.^{9,64} The burden of disease attributable to gender dysphoria is difficult to establish, but is likely to be significant.¹⁵ There are likely to be multiple points for interventions that could improve health outcomes.

Despite recent progress in attitudes, transgender populations are vulnerable and subject to discrimination.¹⁵ Discriminatory influences include upstream effects beyond the individual's control, including legislation and government/ institutional policies that limit the rights, protections and relief available. Midstream influences include discriminatory societal and institutional factors that may have a variable but direct personal effect, such as employment opportunities, schooling and educational systems, policing and interactions with businesses and organisations. Downstream influences include various interpersonal, family and social dynamics. Importantly, discrimination within health-care settings is commonly described by transgender people.^{65,66} It is therefore unsurprising that transgender populations experience significant health disparities, and that these span multiple health-care domains.¹⁵

Engaging primary care providers in improving the health of transgender populations is important in reducing the levels of morbidity and mortality, as specialised gender care alone does not entirely address this population's health needs.^{11,14,15} This will require several steps, such as improving the skills of primary care providers to engage with transgender people; increasing the accessibility of clinical environments for transgender people; and improving the evidence-base for the primary care of transgender people.

Education about gender dysphoria is rarely incorporated into undergraduate or postgraduate programs for health professionals; even training programs for those medical specialists who typically are involved in gender services

(psychiatrists, endocrinologists, sexual health physicians) do not include formal training in gender dysphoria and its management.^{67–70} Providing education to medical students about gender dysphoria is associated with improved knowledge, attitudinal change and professionalism.⁷¹ Like the cisgender population, transgender people experience health issues that are not related to gender at all; educating all health professionals about transgender people will improve the access of transgender people to the varied general health resources they may require.

Creating an environment that is not only accessible, but accommodating of gender-diverse clients is important.⁷² Advice about how to make practices more transgender friendly is available and can improve a service's engagement with transgender populations. Encouraging reflection on how one's clinical service caters for the needs of transgender people is valuable, but must include all aspects of the service to be effective. Improving the skills of clinicians is an obvious goal, but attention to non-clinical details such as administrative procedures, intake forms, recording of gender markers and use of preferred names and pronouns by administrative staff may be less obvious, but just as important.

Improving the evidence-base with high-quality basic science, clinical and epidemiological research is clearly needed. Much of the evidence used to guide primary care is extrapolated from the experience of hormone replacement therapy in postmenopausal women, combined oral contraceptives in women of reproductive age, and testosterone replacement therapy in hypogonadal men. There are limits to the value of these generalisations: the biological variables are different, and often the patterns, dose and duration of exogenous hormone therapy is different. At the level of guidelines, recommendations are largely based on expert opinion, case reports and observational studies rather than well-designed cohort studies or randomised controlled trials. Frequency of gender dysphoria is relatively low, making the construction of cohorts for prospective data collection difficult. Study populations are often derived from clinical settings, so may not represent the entire transgender population. Improvements in the medical care, social acceptability and mental health of transgender people in many countries may limit the applicability of studies from earlier eras, and significant differences in the legal, social and medical environments between countries limit generalisations from international studies.

In addition to the above lack of research into the effect of the treatment interventions, there is a need for better understanding of the effects of common health concerns, such as obesity on transgender populations. Involving primary care providers would be essential to coordinate interventions, mobilise resources such as dieticians and exercise physiologists, and act as disseminators of general health skills to the transgender population. Primary care providers are ideally placed for offering a wide range of other health interventions such as contraception, STI screening, drug and alcohol advice, and so on.

Many primary health providers already participate in the medical care of transgender people, and do so in a wide variety of ways. Some manage all aspects of gender dysphoria, while others refer to others for the more specialised areas of diagnosis and management of endocrine therapy. Primary

care providers are likely to be crucial in resolving health discrepancies among transgender populations, but should be reassured that they do not need to become experts in transgender health to be an effective part of a health team, and contribute significantly to improving the health of the transgender population.

Conflicts of interest

None declared.

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