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Priorities for Transgender Medical and Health Care Research

Jamie Feldman[a], **George R. Brown**[b], **Madeline B. Deutsch**[c], **Wylie Hembree**[d], **Walter Meyer**[e], **Heino F.L. Meyer-Bahlburg**[f], **Vin Tangpricha**[g], **Guy T'Sjoen**[h], and **Joshua D. Safer**[i]

[a]Department of Family Medicine and Community Health, University of Minnesota, Minneapolis, MN

[b]Department of Psychiatry and Behavioral Sciences, Quillen College of Medicine, East Tennessee State University, Mountain Home VAMC, Johnson City, TN

[c]Department of Family and Community Medicine, University of California, San Francisco, San Francisco, CA

[d]Program of Developmental Psychoendocrinology, Division of Gender, Sexuality, and Health, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY and NYS Psychiatric Institute, New York, NY

[e]Department of Psychiatry, University of Texas, Medical Branch, Galveston, TX

[f]Department of Psychiatry, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY

[g]Division of Endocrinology, Metabolism and Lipids, Department of Medicine, Emory University School of Medicine and the Atlanta VA Medical Center, Atlanta, GA

[h]Department of Endocrinology, Center for Sexology and Gender, Ghent University Hospital, Ghent, Belgium

[i]Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston, MA

Abstract

Purpose of Review—Transgender individuals experience unique health disparities but are the subject of little focused health research. This manuscript reviews current literature on transgender medical and mental health outcomes and proposes research priorities to address knowledge gaps.

Recent Findings—Published research in transgender health care consists primarily of case reports, retrospective and cross-sectional studies, involving largely European settings. Challenges to US-based transgender health research include a diverse population where no single center has sufficient patient base to conduct clinical research with statistical rigor. Treatment regimens are heterogeneous and warrant study for best practices. Current research suggests increased mortality and depression in transgender individuals not receiving optimal care, and possibly a modest

Correspondence to: Joshua D. Safer, MD, Section of Endocrinology, Boston University School of Medicine, 715 Albany Street, Room M-1016, Boston, MA 02467 USA, telephone +1 617-638-8530, jsafer@bu.edu.

Conflicts of interest

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increase in cardiovascular risk related to hormone therapy. Current evidence does not support concerns for hormone related malignancy risk.

Summary—The priorities for transgender medical outcomes research should be to determine health disparities and co-morbid health conditions over the life span, along with the effects of mental health, medical, and surgical interventions on morbidity and mortality. Specific outcomes of interest based on frequency in the literature, potential severity of outcome, and patient-centered interest, include affective disorders, cardiovascular disease, malignancies, fertility, and time-dose related responses of specific interventions.

Keywords

transgender; health research; medical outcomes; health disparities

INTRODUCTION

Transgender individuals experience unique health disparities but have been the subject of limited focused health research [1]. As a consequence of the HIV epidemic, research on transgender health in the US has focused primarily on HIV/AIDS or has been subsumed in larger studies of LGBT health. Recent work from the Veterans Health Administration (VA) in the US has focused on health disparities in a large population of transgender veterans [2,3,4,5,6,7]. However, similar work has not been completed in the general American population.

In order to determine optimal care paradigms, research should address multiple questions regarding mortality and morbidity in transgender individuals. Specifically, little is known regarding the health of transgender individuals with regard to both common medical and mental health outcomes along with co-morbid conditions over the life span. Although hypothesis generating surrogate studies exist, specific consequences of gender affirming interventions on mortality and morbidity are not known. Finally, patient centered outcome research including sexual function and fertility have not been well studied.

Challenges to transgender medical research in the United States include a diverse ethnic and socioeconomic population, where no single center has a sufficiently large patient base to study the population with statistical rigor. Other barriers include designating appropriate patient-oriented outcomes, handling gendered laboratory reference ranges, and the diversity of training and practice across providers. This paper offers an overview of the current state of the science and identifies key gaps and opportunities in transgender health research. A dedicated research infrastructure and funding are needed to support advancement of innovations in study design, recruitment, and long term community engagement in order to enhance the scientific rigor and reach of transgender health research.

RESEARCH TO DATE

Decades of both clinical experience and medical research demonstrate that medical interventions for gender dysphoria can be essential to achieving well-being for transgender and gender non-conforming individuals [8]. To date, literature on specific health outcomes

for transgender individuals consists of several modest cross-sectional studies, a series of large retrospective studies, [2,3,4,5,6,7] small series, and multiple case reports. While the gaps in our knowledge are large, the numerous observations from these studies are hypothesis generating [9].

Overall mortality/morbidity

A retrospective VA study involving 5,117 veterans with medical records linked to the National Death Index found that the top two causes of mortality among the general US population (cardiovascular and oncological) were not increased in a transgender subgroup [7]. This study did not control for gender affirming interventions such as hormones or surgery. This sole US study specifically examining mortality did suggest increased overall mortality related to suicide compared to the general population (see *Mental Health, below)*.

European studies have found increased overall mortality in transgender populations who have undergone both hormone and surgical treatment. These studies report increased mortality rates due to suicide, but also have found increases related to HIV, coronary artery disease (CAD), and substance abuse in comparison to general population, notably among transgender women [10,11].

There are no European comparison studies of transgender individuals without hormones or surgery. A large retrospective study in 15 different centers, both US and European, of over 2000 transgender adults treated with hormones with or without surgeries found significant co-morbidity at the start of hormone treatment: in particular > 20% depression among both transgender men and women, HIV in 2.6% of transgender women, and type 2 DM in 3.2% of transgender women [12].

Mental health mortality and morbidity

A US study of suicide related mortality suggested an increased rate compared to the general population [7]. In addition, in a VA study, transgender veterans had a more than 20 times higher rate of suicide-related events than the general VA population [6]. Several studies show increased rates of psychiatric events and conditions among transgender persons overall, including increased rates of suicide, suicide attempts, depression and anxiety [2,4,5,13,14]. An ongoing European multi-center study (ENIGI), found a 30% rate of suicide ideation or attempt [15]. Transgender care, including hormone therapy, appears to reduce or at least stabilize these effects [16,17]. A systematic review of low quality studies showed reduction or stabilization in rates of suicide, depression, and general mood with hormone therapy independent of surgery [18].

Hematologic disease

Historically, venous thromboembolic disease has been of concern in transgender women undergoing hormone therapy [9,19,20,21,22]. This risk has been primarily identified in older studies in which the thrombogenic synthetic estrogen, ethinyl estradiol, was used as opposed to estradiol or conjugated estrogens. Hypercoagulable risk factors have been associated with many of the cases of reported venous thromboembolism (VTE). Recent studies have reported the risk of VTE in transgender women may be substantially lower with the use of

transdermal estradiol [22,23,24]. In contrast, transgender men have not been observed to suffer similar thrombogenic complications [19,20,21]. There are published data suggesting a small erythropoetic consequence to androgen therapy, the health consequence of which remains to be established [25].

Cardiovascular disease

While larger, older retrospective studies are mixed in finding elevated risk of cardiovascular morbidity or mortality, more recent data show excessive mortality and morbidity, most notably among transgender women [26]. Wierckx et al. [20] (n = 214) reported an incidence of myocardial infarction (MI) among transgender women on hormone therapy that matched that of nontransgender male controls, but exceeded nontransgender female controls. In the same study, an increase in cerebrovascular disease and transient ischemic attack (TIA) among transgender women were also observed compared to nontransgender male controls. Wierckx et al. [21] examined 100 transgender men and women and found that 6% of transgender women had cardiovascular health problems after an average of 11.3 years on estrogen therapy. These studies involved a greater proportion of older subjects, smokers, and those with additional cardiac risk factors. Transgender men, notably, did not exhibit any difference in the rate of stroke, TIA or MI compared to nontransgender male controls in these studies.

Diabetes Mellitus

There are no data on the prevalence or incidence of diabetes among the US transgender population overall relative to non-transgender controls. With hormone therapy, transgender women are reported to have increased insulin resistance, increased or neutral fasting glucose, and increased subcutaneous fat. Transgender men are reported to have a slight increase in insulin resistance, a decrease in fasting glucose, and an increase visceral fat [27,28]. Wierckx et al. [20] reported an increase in type 2 diabetes among both transgender women and men, but notably with most of the diagnoses occurring prior to hormone therapy. A 2-year prospective study of metabolically healthy transgender men (n=43) and women (n=79) treated with hormone therapy showed 17.2% developing metabolic syndrome, higher than in the general population, with the highest risk among the 20 patients with parallel psychiatric morbidity. [29].

Hypertension

There are mixed reports on blood pressure impact from hormone therapy among transgender men and women. A systematic review and meta-analysis of multiple low quality studies did not identify significant blood pressure changes [26]. Short term (6–12 month) prospective studies show no significant change with estrogen plus spironolactone and no or small increase in systolic blood pressure with testosterone therapy in young, healthy sample populations [30,31]. However, in one cross sectional European study, 22% of patients who had been on feminizing hormones and 28% of who had been on testosterone for an average of ten years had elevated blood pressure or treated hypertension [21].

Lipids

Short term (6–12 month) prospective studies of estrogen therapy among transgender women show increases in HDL cholesterol and triglycerides [31], a finding also reported in cross sectional and retrospective cohort studies [21,32]. Similar studies of testosterone therapy in transgender men report decreases in HDL cholesterol, increases in triglycerides and either no change or increase in LDL cholesterol [30,31,33,34]. Cross-sectional studies, retrospective cohort studies, and a systematic literature review all have similar findings [21,26,32,35].

Oncological mortality and morbidity

Overall cancer incidence in transgender men and transgender women to date has not been found to differ relative to non-transgender controls [20]. One study using European retrospective data, found the incidence of breast cancer among transgender women on estrogen therapy to be similar to secular trends of male breast cancer, with 4.1 cases per 100,000 person-years among 2307 transgender women treated with hormones and genital surgery. Rates were lower relative to secular trends for female breast cancer. Among 795 transgender men treated with hormones and surgery (including mastectomy) there was a breast cancer rate of 5.9 cases per 100,000 person-years [36]. A US study of 5,135 transgender veterans, which did not examine hormone therapy or surgery, found no difference from the expected breast cancer rate in an age-standardized national sample [4,37]. Both of these studies calculated incidence based on the number of cases detected in a population without systematic screening, raising the possibility of underdetection.

While there have been multiple case reports of prostate cancer among transgender women [38,39], a Dutch retrospective chart review of 2306 orchidectomized transgender women reported an overall incidence of prostate cancer of 0.04%, limited by decreased screening and the young average age of 29.3 at the start of feminizing therapy with hormones and then surgery [40]. While transgender men have presented with ovarian, uterine and cervical cancers [41,42], there is no current evidence to suggest that the rates of these conditions among transgender men are higher than the background rate in nontransgender women [7,20]. However, most transgender men in the European studies have undergone hysterectomy within five years of starting hormone therapy, limiting their applicability to settings of prolonged testosterone exposure (see below).

Osteoporosis

Prospective and case-control studies of bone mineral density (BMD) in transgender men suggest that uninterrupted testosterone therapy maintains or increases bone density [43,44]. Prospective studies in transgender men with oophorectomy suggest that bone mineral density may decrease even with testosterone supplementation; this may be if testosterone use is interrupted or the dose is inadequate [45]. Low bone mass has been reported among transgender women prior to hormonal or surgical intervention, possibly due to reduced rates of physical activity or Vitamin D deficiency in this population [46]. Current studies on feminizing hormone therapy and BMD are mixed and some reports are limited methodologically by their use of a comparison group of nontransgender men rather than nontransgender women. The bone densities may depend on the specific hormone regimen

[21]. No long-term studies of fracture risk exist, especially in elderly transgender individuals.

Sexual function

Most transgender health studies on sexual function focus on post-surgical outcomes [47,48,49], with little information on sexual function or satisfaction in individuals without gender confirming surgeries. This may be a function of the larger number of studies from European centers, where hormone therapy is followed by genital surgeries within a few years. The vast majority of sexuality related studies in the US—indeed most NIH funded research in the transgender population–is focused on HIV and STI risk [50], usually in targeted at-risk or convenience samples.

Patient-Centered and Comparative Efficacy Studies

There is little research on patient centered physical outcomes of hormone therapy, such as studies comparing the effects and time course of different hormone regimens with identified objective outcomes, such as breast development. Small prospective studies exist which examine time to menstrual cessation with testosterone therapy [31,33]. Outcomes research on other transition related interventions, including speech therapy, are scattered throughout the literature [51,52,53]. Studies exist on patient satisfaction with surgical outcomes [54,55], but not on satisfaction with hormonal treatment outcomes separate from overall surveys of access to care or satisfaction with overall health care services in a given setting. Studies eliciting patient identified objective outcomes and priorities are themselves lacking.

Other reported morbidity

The literature contains multiple case reports of conditions that are observed in persons undergoing feminizing hormone therapy, including the incidence of meningiomas [56,57], benign pituitary tumors and prolactinomas [58]. There are reports of the occurrence of autoimmune conditions with a female predominance, such as systemic lupus erythematosus [59]. However, the data are too limited to make a conclusion. Neuroimaging changes have been reported in transgender men and women both prior to and after hormonal interventions [60,61].

Translational Research, Models of Care and Medical Outcomes—There is limited evaluation of the translation of research findings into clinical practice, focusing on data collection and electronic health records (EHR) [62]. Preliminary outcomes research has been done on models of providing appropriate, effective care to transgender populations, and focusing on issues of provider “gatekeeping” access to transition related interventions [63]. Research has begun to explore effective clinical venues for care (LGBT specialty clinics versus general practice) [64], and the role of specialists and primary care providers in care [65].

DISCUSSION

In summary, few prospective studies of transgender medical outcomes exist, and many of these are of short duration (6–24 months) with small sample sizes. The use of mortality as a

primary outcome in many studies limits the utility of these studies to describe the disease burden and health related quality of life. The study participants are usually young and most studies lack controls or comparison populations. The larger retrospective or cross-sectional studies currently available are, with the exception of the VA study, derived from European data. The vast majority of European research subjects have had mastectomy and/or genital surgeries. In a US survey of 6,450 transgender and gender non-conforming participants, only 41% of transgender men had had mastectomy and only 20% had hysterectomy, while only 21% of transgender women had orchiectomy and 20% had vaginoplasty [66]. In addition, the ethnic, socioeconomic and health care access demographics of US and European populations differ substantially. Finally, the studies have variable duration of hormone use and follow up interval along with a relative paucity of trans masculine data and participants over age 55.

Going forward, research in the US will be challenged by the heterogeneity of health care for transgender individuals. The US transgender population is ethnically and geographically diverse. Patients have variable health insurance, with primary and transgender-specific care in assorted clinical settings with a variety of providers. Patients begin gender interventions at differing ages, may go on and off hormone therapy for financial and other reasons, and have often self-medicated with hormones obtained through the Internet or social circles [67,68]. Defining and measuring appropriate medical outcomes involving persons with non-binary gender identities will present additional challenges.

CONCLUSION

Although the gaps in outcomes relating to transgender medical care are large, the current body of literature is increasing and hypothesis generating. The emerging priorities for transgender medical and health care research are outlined in Tables 1 and 2. The broad themes of these research priorities elucidate the health disparities and co-morbid health conditions of transgender persons over the lifespan, independent of gender interventions. Comparison groups of interest include non-transgender men and women overall, other sexual or ethnic minorities, and aging populations– with and without estrogen or testosterone replacement. Transgender communities share some similarities to other communities suffering from minority stress and lack of access to health care, but we anticipate critical differences as well. Additionally, we would expect from current research that transgender medical interventions—including mental health support, hormone therapy, and surgery—change the outcomes.

Studies will need to account for the role of access to knowledgeable care providers, and the role specific provider type, and clinical setting. Laboratory reference intervals for transgender individuals will need to be established in the course of developing accurate clinical research. Studies should develop outcome measures to evaluate non-mortality and surrogates, including a focus on patient centered effectiveness and optimal models of care. Finally, research efforts should prioritize comprehensive, multi-center studies to close as many of the knowledge gaps in as rigorous a fashion as possible.

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KEY POINTS

- Current published research in transgender health care consists primarily of case reports, retrospective and cross-sectional studies, involving largely European settings
- While gaps in outcomes relating to transgender medical care are large, the body of literature is increasing, suggestive of increased mortality and depression in transgender individuals not receiving optimal care, and possibly a modest increase in cardiovascular risk related to hormone therapy.
- The priorities for transgender medical outcomes research should be to determine health disparities and co-morbid health conditions over the life span, along with the effects of gender affirming interventions on morbidity, mortality, and patient centered outcomes.

TABLE 1

Transgender Medical and Health Care Research Questions.

1. What are the health disparities, comorbid health conditions over the life span—independent of gender interventions—relative to non transgender controls comparable in age, ethnicity, and other variables as indicated?

- Are they similar to other communities suffering from minority stress and lack of access to health care?

2. Do transgender-specific medical interventions—including mental health, hormonal, and surgical interventions change outcomes, in order of priority?

- Overall mortality
- Predicted mortality
- Clinical morbidity, based on the presence of clinical disease
- Surrogate markers predictive of clinical morbidity (e.g. low bone density, elevated cholesterol)

*Comparison groups of interest should include nontransgender men and women, other sexual minorities, and aging populations with or without estrogen or testosterone replacement.

3. Are there differences in outcomes among the most commonly accepted hormone regimens including the following categories of intervention-?

- Are there serum hormone levels which predict positive (effectiveness) and negative (safety) outcomes?
- Androgen therapy, including differences among routes of administration independent of levels achieved
- Estrogen therapies, including differences among types (eg. estradiol versus conjugated estrogens) and among routes of administration independent of levels achieved
- Anti-androgens, including inhibitors and agents where the mechanism of their action remains to be well-characterized. Agents include spironolactone, GnRH agonists, and cyproterone acetate along with other progestins.

4. To what extent do the following health systems interventions affect transgender health outcomes?

- Centralized versus decentralized delivery of transgender medical services
- Level or type of pre-medical intervention counseling
- Development of transgender friendly health care settings and systems
- Specialty or level of training of health care provider?

TABLE 2

Priority Medical Outcomes for Transgender Medical and Health Care Research

1. Specific outcomes of highest concern, based on existing data:
    - Impact of interventions on gender dysphoria itself
    - Affective mental health issues: suicide, depression and anxiety
    - Hematologic issues: venous thromboembolic events (related to estrogen), polycythemia concerns (related to androgens)
    - Cardiovascular/cerebrovascular disease including risk factors such as metabolic syndrome, hyperlipidemia(s), diabetes mellitus
    - Effects on pre-existing comorbid conditions

2. Medical areas of priority due to risk predicted from physiology and history, though not currently suggested by literature to date:
    - Breast neoplasms when exposed to estrogens
    - Breast neoplasms after masculinizing chest surgeries, androgens
    - Endometrial and ovarian neoplasms when exposed to androgens
    - Prolactinoma
    - Prostate neoplasms after estrogen exposure and/or orchiectomy
    - Osteoporosis
    - Neurocognitive function

3. Patient Centered outcomes priorities:
    - Research on identifying context sensitive patient centered outcomes
    - Sexual function/sexual satisfaction
    - Family planning/fertility
    - Breast development
    - Voice change
    - Time to menstrual cessation
    - Time and dose related responses to gender related interventions
    - Patient satisfaction with transition –related interventions