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REVIEW

The effect of cross-sex hormonal treatment on gender dysphoria individuals' mental health: a systematic review

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Rosalia Costa[1]
Marco Colizzi[2]

[1]Gender Identity Development Service, Tavistock and Portman NHS Foundation Trust, Tavistock Centre, [2]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

Abstract: Cross-sex hormonal treatment represents a main aspect of gender dysphoria health care pathway. However, it is still debated whether this intervention translates into a better mental well-being for the individual and which mechanisms may underlie this association. Although sex reassignment surgery has been the subject of extensive investigation, few studies have specifically focused on hormonal treatment in recent years. Here, we systematically review all studies examining the effect of cross-sex hormonal treatment on mental health and well-being in gender dysphoria. Research tends to support the evidence that hormone therapy reduces symptoms of anxiety and dissociation, lowering perceived and social distress and improving quality of life and self-esteem in both male-to-female and female-to-male individuals. Instead, compared to female-to-male individuals, hormone-treated male-to-female individuals seem to benefit more in terms of a reduction in their body uneasiness and personality-related psychopathology and an amelioration of their emotional functioning. Less consistent findings support an association between hormonal treatment and other mental health-related dimensions. In particular, depression, global psychopathology, and psychosocial functioning difficulties appear to reduce only in some studies, while others do not suggest any improvement in these domains. Results from longitudinal studies support more consistently the association between hormonal treatment and improved mental health. On the contrary, a number of cross-sectional studies do not support this evidence. This review provides possible biological explanation vs psychological explanation (direct effect vs indirect effect) for the hormonal treatment-induced better mental well-being. In conclusion, this review indicates that gender dysphoria-related mental distress may benefit from hormonal treatment intervention, suggesting a transient reaction to the nonsatisfaction connected to the incongruent body image rather than a stable psychiatric comorbidity. In this perspective, timely hormonal treatment intervention represents a crucial issue in gender dysphoria individuals' mental health-related outcome.

Keywords: estrogen, testosterone, transsexualism, psychiatry, psychosocial wellbeing

Introduction

A strong and persistent cross-gender identification as well as a persistent discomfort with one's natal sex or a sense of inappropriateness in the gender role of that sex has been considered as a core aspect of nonconforming gender identity since the first inclusion of the condition in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) of the American Psychiatric Association.[1] Until the last DSM revision,[2] the condition has been known as "transsexualism/gender identity disorder".[1,3,4] In 2013, the American Psychiatric Association has significantly revised the condition definition in an attempt to balance between the competing issues of depathologizing nonconforming

Correspondence: Marco Colizzi
Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF, UK
Tel +44 20 7848 0049
Fax +44 20 7848 0976
Email marco.v.colizzi@kcl.ac.uk

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gender identity vs access to care.[2,5] As a consequence, the condition has been renamed "gender dysphoria" in order to imply a diagnostic entity in its own right, not necessarily associated with severe comorbid psychiatric findings, and better characterize the gender incongruence-related experience and discomfort.[2] However, psychiatric comorbidity among individuals with gender dysphoria is still a matter of discussion. Some studies have reported a high prevalence of major psychiatric disorders in gender dysphoria.[6–8] Instead, other research suggests a low level of psychopathology.[9–11] A recent review has concluded that gender dysphoria individuals appear to have a higher risk of psychiatric comorbidity.[12] However, as reported by the authors, many studies were methodologically weak, and sex reassignment procedures appeared to be beneficial in reducing mental distress.[12] Therefore, the lack of consistency between studies about gender dysphoria individuals' psychiatric comorbidity could be partially explained by their design, which usually did not explore the role of the lack of treatment in gender dysphoria individuals' mental distress.

For most gender dysphoria individuals, the subjective experience of persistent cross-gender identification and discomfort with their natal sex may be a stressful situation and cause clinical distress or impairment in important areas of functioning.[9,13,14] Suffering from severe gender incongruence usually leads individuals to pursue hormone treatment and sex reassignment surgery. The purpose of these sex reassignment procedures is to alleviate the individual's distress by reducing the discrepancy between the individuals' biological sex and their experience.[15] Over the last few decades, research has prevalently focused on the effect of sex reassignment surgery on gender dysphoria individuals' mental health. In particular, previous research has suggested that sex reassignment surgery improves gender dysphoria individuals' well-being, increasing their personal and general satisfaction,[16–18] self-confidence with body image,[19–22] and quality of life.[23–26] In contrast, the role of the cross-sex hormonal treatment in the well-being of gender dysphoria individuals has been the subject of relatively little investigation. A 2010 meta-analysis has identified 28 observational studies of the effect of sex reassignment on gender dysphoria individuals' well-being.[27] However, only five studies specifically examined the impact of hormonal treatment and two of them focused on gender-related cognitive aspects, which could be influenced by cross-sex hormones and per se do not inform on hormone-treated individuals' mental health or well-being.[28,29] The remaining three studies addressed the effect of hormonal treatment on gender dysphoria individuals' psychological profile,[30] emotional repercussions,[31] and transformation satisfaction.[32] However, due to its design, the latter one[32] could not infer an association between hormonal treatment and better transformation satisfaction.

Studying the effect of cross-sex hormonal treatment on mental health in gender dysphoria may help to disentangle the burden of psychiatric comorbidity among individuals suffering from this condition. In recent years, a larger body of evidence has accumulated from studies on the specific effect of hormonal treatment on different mental health-related outcome measures. The purpose of this review is to bring together and discuss all available data generated by cross-sectional and longitudinal studies that have investigated the effect of hormone therapy on mental health by carrying out a systematic literature search for all such data.

Materials and methods

Inclusion/exclusion criteria

Inclusion criteria for studies were as follows: 1) studies in gender dysphoria, 2) studies investigating the mid/long-term effects of cross-sex hormonal treatment, and 3) studies measuring mental health-related parameters, including a) depression, b) anxiety, c) personality, d) quality of life, e) dissociative symptoms, f) psychopathology, g) psychosocial/emotional functioning, h) distress, and i) self-esteem. Exclusion criteria were as follows: 1) studies in which cross-sex hormonal treatment was not the intervention of interest (ie, studies including cross-sex hormonal treatment only as a confounder/covariate of no interest) and 2) studies in which the mental health-related outcomes were not directly reported upon.

Search strategy

A final search was undertaken on May 16, 2016. The search terms used were as follows: (gender dysphoria or gender identity disorder or transsexualism) and (hormon* or cross-sex hormonal treatment or hormone therapy) and (psych* or psychiatry or psychopathology or mental health or anxiety or depression). This search was undertaken in Medline, EMBASE, and PsycINFO using the OvidSP platform. All studies published in any language and indexed in the above databases were included. Reference lists from all identified relevant studies, reviews, and conference abstracts were screened for any additional relevant studies.

Data extraction

Demographic and methodological variables and outcome data for studies identified were extracted into a spreadsheet. Primary outcomes of interest were mental health-related parameters. These were compared within hormone-treated

cohorts and/or between hormone-treated and nonhormone-treated control groups.

Risk of bias

Risk of bias and quality assessment of the methodologically heterogeneous group of studies (Table 1) reviewed here required a suitably inclusive and flexible approach. For this purpose, an adapted set of criteria, suggested by the Agency for Healthcare Research and Quality guidance,[33] amended as appropriate for observational studies in humans were used (Table 2). Risk of systematic bias across studies was further identified by assessing all articles for possible confounding factors, such as study population definition, mental health comorbidity, attrition, comparability of subjects, cross-sex hormonal treatment duration, type, and dosage (Table 3).

Results

Study selection

In total, 680 records were identified. All abstracts of the records were screened against the inclusion and exclusion criteria. A final list of 17 studies was identified for systematic analysis in this review. Cumulatively, the included studies investigated different aspects of mental health (Table 1) in response to cross-sex hormonal treatment, using both independent-groups (cross-sectional studies) and repeated measures (longitudinal studies) designs. These include 1) depression, mood states, and self-esteem; 2) anxiety and tension; 3) global and personality-related psychopathology; 4) mental health-related quality of life; 5) dissociative symptoms; 6) psychosocial, interpersonal, and emotional functioning; and 7) social distress, perceived stress,

Table 1 Studies included in the review

Study	Type of study	Target population(s)	Mental health parameters
Bonierbale et al[42]	Cross-sectional study	GID adults with CSHT vs GID adults without CSHT	Personality-related psychopathology
Bouman et al[38]	Cross-sectional study	MtF adults with CSHT vs MtF adults without CSHT	Anxiety, depression, self-esteem, and interpersonal functioning
Colizzi et al[45]	Longitudinal study	GD adults before and after CSHT	Dissociative symptoms
Colizzi et al[37]	Longitudinal study	GID adults before and after CSHT	Anxiety, depression, psychopathological symptoms, and psychosocial functioning
Fisher et al[39]	Cross-sectional study	GD adults with CSHT vs GD adults without CSHT	Body uneasiness and psychopathological symptoms
Gómez-Gil et al[44]	Cross-sectional study	GID adults with CSHT vs GID adults without CSHT	Mental health-related quality of life
Heylens et al[40]	Longitudinal study	GID adults before and after CSHT	Psychopathological symptoms
Colizzi et al[14]	Longitudinal study	GID adults before and after CSHT	Perceived stress
Gorin-Lazard et al[36]	Cross-sectional study	GID adults with CSHT vs GID adults without CSHT	Self-esteem, depression, quality of life, and psychosocial functioning
Gómez-Gil et al[35]	Cross-sectional study	GID adults with CSHT vs GID adults without CSHT	Social distress, anxiety, and depression
Gorin-Lazard et al[43]	Cross-sectional study	GID adults with CSHT vs GID adults without CSHT	Mental health-related quality of life
Gómez-Gil et al[41]	Cross-sectional study	GID adults with CSHT vs GID adults without CSHT	Personality-related psychopathology
Miles et al[29]	1. Longitudinal study 2. Longitudinal study 3. Longitudinal study 4. Cross-sectional study	1. MtF GID adults before and after CSHT 2. MtF GID adults with CSHT and after withdrawal 3. MtF GID adults before and after CSHT 4. MtF GID adults with CSHT vs MtF GID adults without CSHT	Mood states
Newfield et al[24]	Cross-sectional study	FtM adults with CSHT vs FtM adults without CSHT	Mental health-related quality of life
Slabbekoorn et al[31]	Longitudinal study	MtF and FtM adults before and after CSHT	Emotional functioning, affect intensity, anger readiness, nonverbal emotional expressiveness, and mood states
Blanchard et al[34]	Cross-sectional study	MtF adults	Psychological (depression and tension) and social (cohabitation and involvement) adjustment
Leavitt et al[30]	Cross-sectional study	MtF adults with CSHT vs MtF adults without CSHT	Personality-related psychopathology

Abbreviations: CSHT, cross-sex hormonal treatment; FtM, female-to-male; GD, gender dysphoria; GID, gender identity disorder; MtF, male-to-female.

Table 2 Summary of studies of effect of hormonal treatment on mental health in gender dysphoria

Study	Aim of study	Population receiving CSHT	Age (years), mean ± SD	Sample (N)	Assessment instrument(s)	Type of assessment(s)	Results
Bonierbale et al[42]	Effect of CSHT on personality traits	37 MtF and 15 FtM	Median: 31, range: 18–58 (age at assessment; age information regarded both GID individuals with and without CSHT)	106	MMPI-2	Self-reported	Lower psychopathology in CSHT adults
Bouman et al[38]	Effect of CSHT on anxiety, depression, self-esteem, and interpersonal functioning	38 MtF	MtF: 58.03±5.87 (age at the assessment)	71	HADS, RSE, and IIP-32	Self-reported	Lower anxiety, higher level of self-esteem, less problems with socialization, and interpersonal functioning in CSHT MtF; no effect of CSHT on depression
Colizzi et al[45]	Effect of CSHT on dissociative symptoms	82 MtF and 36 FtM	MtF: 30.41±9.77; FtM: 29.81±6.39 (ages at onset of CSHT and at study recruitment were the same)	118	DES	Self-reported	Lower dissociative symptoms after CSHT with levels lower than that found in general population
Colizzi et al[37]	Effect of CSHT on anxiety, depression, psychopathological symptoms, and functional impairment	78 MtF and 29 FtM	MtF: 29.25±7.27; FtM: 29.08±8.48 (ages at onset of CSHT and at study recruitment were the same)	107	SAS, SDS, SCL-90-R, and SCID-I	Self-reported and clinical interview	Lower anxiety, depression, psychopathological symptoms, and functional impairment after CSHT
Fisher et al[39]	Effect of CSHT on body uneasiness and psychopathological symptoms	42 MtF and 26 FtM	MtF: 33.1±10.25; FtM: 28.7±6.5 (age information regarded both GID individuals with and without CSHT)	125	BUT and SCL-90-R	Self-reported	Lower body uneasiness only in CSHT MtF adults and positive effect of cumulative dose of estradiol on body uneasiness reduction; no effect of CSHT on psychopathological symptoms
Gómez-Gil et al[44]	Effect of CSHT on mental health quality of life	120 GID adults	31.2±9.9 (age at assessment; age information regarded both GID individuals with and without CSHT)	193	WHOQOL-BREF	Self-reported	Higher social and psychological quality of life in CSHT adults
Heylens et al[40]	Effect of CSHT on psychopathological symptoms	46 MtF and 11 FtM	Not mentioned	57	SCL-90-R and psychosocial questionnaire	Self-reported	Lower psychopathological symptoms after CSHT with levels similar to general population; no effect of CSHT on psychosocial parameters
Colizzi et al[14]	Effect of CSHT on perceived stress	45 MtF and 25 FtM	MtF: 29.25±9.87; FtM: 26.78±8.09 (ages at onset of CSHT and at study recruitment were the same)	70	PSS	Self-reported	Lower perceived stress after CSHT with levels similar to normative samples
Gorin-Lazard et al[36]	Effect of CSHT on self-esteem, depression, quality of life, and global functioning	29 MtF and 20 FtM	35.1±10.2	67	SSEI, BDI, SQUALA, and GAF	Self-reported	Higher self-esteem and quality of life and lower depressive symptoms in CSHT adults; no effect of CSHT on global functioning
Gómez-Gil et al[35]	Effect of CSHT and its duration on social distress, anxiety, and depression	84 MtF and 36 FtM	24.6±8.1 (at onset of CSHT); 33.6±9.1 (at study recruitment)	187	SADS and HADS	Self-reported	Lower social distress, anxiety, and depression in CSHT adults; no effect of CSHT duration on these parameters

Gorin-Lazard et al[43]	Effect of CSHT on mental health-related quality of life	25 MtF and 19 FtM	MtF: 39.4±9.8; FtM: 29.9±8.4 (age information regarded both GID individuals with and without CSHT)	61	SF-36	Self-reported	Higher emotional, social, and mental quality of life in CSHT adults, with higher mental health-related quality of life than in non-GID controls
Gómez-Gil et al[41]	Effect of CSHT on personality traits	69 MtF and 10 FtM	MtF: 29.9±9; FtM: 27.6±7.5 (age at assessment; age information regarded both GID individuals with and without CSHT)	163	MMPI-2	Self-reported	Lower psychopathology in CSHT MtF adults; no effect of CSHT in FtM
Miles et al[29]	1. Effect of CSHT on mood states 2. Effect of CSHT withdrawal on mood states 3. Effect of CSHT duration on mood states 4. Effect of CSHT on mood states	1. 27 MtF 2. 27 MtF 3. 20 MtF 4. 74 MtF	1. 37.07±8.68 2. 39.63±9.68 3. 40.30±7.50 4. X	103	POMS	Self-reported	1. Higher confidence and composure in CSHT MtF adults 2. No effect 3. No effect 4. Higher confidence and composure in CSHT MtF adults
Newfield et al[24]	Effect of CSHT and its duration on mental health-related quality of life	248 FtM	FtM: 32.6±10.8 (age at assessment; age information regarded both GID individuals with and without CSHT)	365	SF-36	Self-reported	Higher emotional, social, and mental quality of life in CSHT FtM adults, with CSHT duration associated with higher emotional quality of life
Slabbekoorn et al[31]	Effect of CSHT on emotional functioning, affect intensity, anger readiness, nonverbal emotional expressiveness, and mood states	54 MtF and 47 FtM	MtF: 32.9±10.8; FtM: 25.7±7.5 (ages at onset of CSHT and at study recruitment were the same)	101	ELOMS, AIM, ASQ, ACT, and PAF	Self-reported	Higher positive emotions, affect intensity, anger readiness, and emotional expressiveness in MtF after CSHT; higher aggressive emotions and anger readiness, and lower affect intensity in FtM after CSHT; and no effect of CSHT on mood in FtM adults
Blanchard et al[34]	Effect of CSHT on psychological (depression and tension) and social (cohabitation and involvement) adjustment	34 MtF	27.9±8.8 (age at assessment; age information regarded both GID individuals with and without CSHT)	55	Annual questionnaire and MMPI	Self-reported	No effect of CSHT on psychological and social adjustment
Leavitt et al[30]	Effect of CSHT and its duration on personality traits	22 MtF	26.6±3.6	41	MMPI	Self-reported	Lower psychopathology in CSHT MtF adults with scores tending to approximate the norms for male populations; positive effect of CSHT duration on psychopathology reduction

Note: N, entire sample involved in the study.

Abbreviations: AIM, affect intensity measure; ACT, affective communication test; ASQ, short anger situation questionnaire; BDI, Beck Depression Inventory; BUT, body uneasiness test; CSHT, cross-sex hormonal treatment; DES, Dissociative Experiences Scale; ELOMS, expectancy list of mood and sexual interest; FtM, female-to-male; GAF, Global Assessment of Functioning scale; GID, gender identity disorder; HADS, Hospital Anxiety and Depression Scale; IIP-32, Inventory of Interpersonal Problems-32; MMPI-2, Minnesota Multiphasic Personality Inventory-2; MtF, male-to-female; PAF, premenstrual assessment form; POMS, Profile of Mood States; PSS, Perceived Stress Scale; RSE, Rosenberg Self-Esteem Scale; SADS, Social Anxiety and Distress Scale; SAS, Zung Self-rating Anxiety Scale; SCL-90-R, Symptom Checklist-90-R; SCID-I, Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* I; SDS, Zung Self-rating Depression Scale; SSEI, Social Self-Esteem Inventory; SF-36, Short Form (36) Health Survey; SQUALA, Subjective Quality of Life Analysis; WHOQOL-BREF, World Health Organization Quality of Life-shorter version; "X", not mentioned.

Table 3 Methodological quality of studies of effect of hormonal treatment on mental health in gender dysphoria

Study	Defined study population	CSHT mean duration	CSHT type and dosage	Control
Bonierbale et al[42]	✓ GID formal diagnosis at a gender clinic according to DSM-IV criteria	✓/× 3 months at least for both MtF and FtM	× Not mentioned	✓/× No; comparison with 16 MtF and 38 FtM without CSHT
Bouman et al[38]	✓/× Formal diagnosis at a gender clinic, criteria not mentioned	× Not mentioned	✓/× MtF: estrogens, tablet form or patches (n=21); sometimes in association with cyproterone acetate, spironolactone, or finasteride (n=11); and no information provided for 17 individuals on CSHT dosage, molecule nature, or administration modalities	✓/× No; comparison with 33 MtF adults without CSHT
Colizzi et al[45]	✓ GD formal diagnosis at a gender clinic according to DSM-5 SCID-I criteria	✓ 12 months for both MtF and FtM	✓ MtF: transdermal estradiol gel (1.84±0.49 mg/d) in association with oral cyproterone acetate (100 mg/d) and FtM: IM testosterone (250 mg every 26.31±2.68 days)	✓/× No; normative data from a sample of 1,055 subjects
Colizzi et al[37]	✓ GID formal diagnosis at a gender clinic according to DSM-IV SCID-I criteria	✓ 12 months for both MtF and FtM	✓ MtF: transdermal estradiol gel (1.82±0.53 mg/d) in association with oral cyproterone acetate (100 mg/d) and FtM: IM testosterone (250 mg every 26.24±2.71 days)	× No
Fisher et al[39]	✓ GD formal diagnosis at different gender clinics according to DSM-IV criteria	✓ MtF: 467±323 days and FtM: 1,940±2,595 days	✓/× MtF: estradiol valerate (n=12), transdermal estradiol hemihydrate (n=12), estradiol gel (n=6), and oral cyproterone acetate (n=39) and FtM: IM testosterone enanthate (n=12), IV testosterone undecanoate (n=1), and transdermal testosterone (n=9); no information on four FtM and CSHT dosage	✓/× No; comparison with 57 GD adults without CSHT (24 MtF and 33 FtM)
Gómez-Gil et al[44]	✓ GID formal diagnosis at a gender clinic according to DSM-IV and ICD-10 criteria	× Not mentioned	× Not mentioned	✓/× No; comparison with 73 GID adults without CSHT
Heylens et al[40]	✓ GID formal diagnosis at a gender clinic according to DSM-IV criteria	✓/× 3–6 months for both MtF and FtM	× Not mentioned	× No
Colizzi et al[14]	✓ GID formal diagnosis at a gender clinic according to DSM-IV SCID-I criteria	✓ 12 months for both MtF and FtM	✓ MtF: transdermal estradiol gel (1.77±0.46 mg/d) in association with oral cyproterone acetate (100 mg/d) and FtM: IM testosterone (250 mg every 27.12±2.64 days)	✓/× No; normative data from a sample of 645 subjects
Gorin-Lazard et al[36]	✓ GID formal diagnosis at a gender clinic according to DSM-IV criteria	✓ 12 months at least for both MtF and FtM	✓/× MtF: cyproterone acetate followed by estrogens combined with antiandrogens (luteinizing hormone-releasing hormone analogs) and FtM: synthetic progestagens followed by testosterone (dosage, molecule nature, and administration modalities of CSHT not reported)	✓/× No; comparison with 18 GID adults without CSHT (seven MtF and eleven FtM)

Comparability of subjects	Statistical analysis	Mental health comorbidity	Attrition	Funding or sponsorship
✓ Sociodemographic characteristics for GID adults with and without CSHT not reported, however, analyses controlled for age, age on onset, and sexual orientation	✓ Mann–Whitney *t*-test, chi-square or Fisher's exact tests, and logistic regression	× Not mentioned	✓/× No available data in 26% of the original cohort (N=143) for different reasons (N=29 patients not eligible for sex reassignment surgery; N=6 with no valid MMPI; N=2 missing data)	✓ Declared
✓ Significant difference in age of referral, coming out, and transitioning; sociodemographic characteristics matched (ethnic group, employment, civil status, and children)	✓ Chi-square, Mann–Whitney *U*-test, and MANCOVA	✓ Psychiatric history was not exclusion criterion, however, clinical characteristics (psychiatric history and self-harm) matched	✓/× No available data in 7.8% of the original cohort (N=77; three did not attend appointment and three FtM excluded from analysis due to small number)	✓ Declared
✓ Pre/postgroups were the same	✓ *t*-test	✓ Unstable psychiatric comorbidity was exclusion criterion	✓ 0 lost at recruitment or follow-up	✓ Declared
✓ Pre/postgroups were the same	✓ McNemar test and *t*-test	✓ Unstable psychiatric comorbidity was exclusion criterion	✓ 0 lost at recruitment or follow-up	✓ Declared
✓ Sociodemographic characteristics for GID adults with and without CSHT not reported, however, analyses controlled for gender, age, gender role, and surgery	✓ ANCOVA and two-step hierarchical linear regression	× Not mentioned (mental retardation was exclusion criterion)	✓/× 55% of original cohort (N=275) were excluded for different reasons (CSHT treatment prior to the study, disorder of sexual development, internalized homophobia, transvestite fetishism, mental retardation, dropout during the assessment, and completed genital reassignment surgery	✓ Declared
✓ Sociodemographic characteristics for GID adults with and without CSHT not reported, however, analyses controlled for gender, age, education, working/student status, partnership status, and family support	✓ Multiple linear regression	× Not mentioned	✓/× No available data in 30% of the original cohort (N=277) for different reasons (N=17 patients refused to participate in the study; N=59 were incomplete answers; and N=8 previous genital surgery)	✓ Declared
✓/× Pre/postgroups were not the same, no mention of possible differences between GID adults completing/not completing follow-up evaluation	✓ Friedman test and Wilcoxon test	✓/× Personality disorder was exclusion criterion	✓/× No available data in 37% of the original cohort (N=90) for different reasons (refused to participate, attended the clinic once, GID NOS, and comorbidity) and 17.5% of the recruited subjects lost at follow-up	✓ Declared
✓ Pre/postgroups were the same	✓ *t*-test	✓ Psychiatric comorbidity was exclusion criterion	✓ 0 lost at recruitment or follow-up	✓ Declared
✓ Significant difference in age and sexual orientation, but corrected	✓ Mann–Whitney *U*-test and multiple linear regression	✓ Psychotic disorder and unstable psychiatric comorbidity (except nonmajor depressive disorder) were exclusion criteria	✓ 0 lost at recruitment	✓ Declared

(*Continued*)

Table 3 (*Continued*)

Study	Defined study population	CSHT mean duration	CSHT type and dosage	Control
Gómez-Gil et al[35]	✓ GID formal diagnosis at a gender clinic according to DSM-IV and ICD-10 criteria	✓ MtF: 11 years and FtM: 4.7 years	✓ MtF: oral estrogens (conjugated estrogens 1.8–2.4 mg/d or estradiol valerate 2–4 mg/d) or transdermal estradiol patches (3 mg twice per week, delivering 100 mg/d), generally in association with oral cyproterone acetate (25–50 mg/d) and FtM: IM testosterone (1,000 mg every 10–14 weeks), or daily transdermal testosterone gel (50 mg/d)	✓/× No; comparison with 67 GID adults without CSHT (29 MtF and 38 FtM)
Gorin-Lazard et al[43]	✓ GID formal diagnosis at a gender clinic according to DSM-IV MINI criteria	✓ 12 months at least for both MtF and FtM	✓/× MtF: antiandrogens along with estrogens and FtM: synthetic progestagens with testosterone (dosage, molecule nature, and administration modalities of CSHT not reported)	✓/× No; comparison with 17 GID adults without CSHT (six MtF and eleven FtM); controls from a normative sample of 3,656 subjects
Gómez-Gil et al[41]	✓ GID formal diagnosis at a gender clinic according to DSM-IV criteria	✓ 12 months at least for both MtF and FtM	× Not mentioned	✓/× No; comparison with 84 GID adults without CSHT (38 MtF and 46 FtM)
Miles et al[29]	✓ GID formal diagnosis at a gender clinic according to DSM-IV criteria	1. ✓/× 3–12 months for both MtF and FtM 2. ✓/× at least 8 weeks of withdrawal after at least 28 months of CSHT for both MtF and FtM 3. ✓/× 6–15 months for both MtF and FtM 4. ×	✓ Conjugated equine estrogens (1.25–7.5 mg/d) or ethinyl estradiol (10–15 μg/d), sometimes in association with cyproterone acetate (50–150 mg/d) or medroxyprogesterone acetate (15 mg/d)	✓/× No 4. Comparison with MtF without CSHT
Newfield et al[24]	× Not mentioned	✓/× <5 years for the majority of FtM (n=203)	× Not mentioned	✓/× No; comparison with 117 FtM adults without CSHT
Slabbekoorn et al[31]	✓/× Formal diagnosis at a gender clinic, criteria not mentioned	✓/× 14 weeks for both MtF and FtM	✓ MtF: oral cyproterone acetate (50 mg/twice a day) in combination with oral ethinyl estradiol (0.05 mg/twice a day, n=32) or 17β-estradiol plasters (0.1 mg/d, n=22); FtM: IM testosterone esters (250 mg/2 weeks, n=42),or oral undecanoate testosterone (200 mg/d, n=5)	× No
Blanchard et al[34]	✓/× Formal diagnosis at a gender clinic, criteria not mentioned	× Not mentioned	× Not mentioned	✓/× No; comparison with 21 MtF adults without CSHT
Leavitt et al[30]	× Not mentioned	✓ 12 months at least	✓/× Oral conjugated estrogens and medroxyprogesterone (cyclically each month in a dose sufficient to inhibit spontaneous erections)	✓/× No; comparison with 19 MtF adults without CSHT

Note: ✓, good quality; ✓/×, fair quality; ×, poor quality.

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CSHT, cross-sex hormonal treatment; DSM, Diagnostic and Statistical Manual of Mental Disorders; FtM, female to male; GD, gender dysphoria; GID, gender identity disorder; ICD-10, international classification of diseases – 10th revision; IM, intramuscular; IV, intravenous; MANCOVA, multivariate analysis of covariance; MINI, mini-international neuropsychiatric interview; MMPI-2, Minnesota Multiphasic Personality Inventory-2; MtF, male to female; NOS, not otherwise specified; SCID-I, Structured Clinical Interview for DSM I.

Comparability of subjects	Statistical analysis	Mental health comorbidity	Attrition	Funding or sponsorship
✓ Significant difference in age, MtF prevalence, and level of education (without CSHT < CSHT), but these were corrected. Other sociodemographic characteristics matched (living arrangements, sexual orientation, and employment status)	✓ ANOVA/ ANCOVA, chi-square, and Pearson's correlation	× Not mentioned	✓/× No available data in 6.5% of original cohort (N=200)	✓ Declared
✓ Sociodemographic characteristics matched (age for GID adults with and without CSHT and age and sex for GID adults and non-GID controls)	✓ Mann–Whitney test, multiple linear regression, and *t*-test	✓ Psychotic disorder and unstable psychiatric comorbidity (except non major depressive disorder) were exclusion criteria	✓/× No available data in 9% of original cohort (N=67)	✓ Declared
× Not mentioned	✓ *t*-test	× Not mentioned	✓/× No available data in 36% of the original cohort (N=254) for different reasons (N=24 patients failed to meet GID DSM-IV criteria; N=24 patients were administered the MMPI instead of MMPI-2; and N=43 were missing data)	× Not declared
1., 2., and 3. ✓ Pre/postgroups were the same 4. × Significant difference in age, not corrected	✓ MANOVAs and Pearson's correlation	× Not mentioned	✓ 0 lost at recruitment or follow-up	✓ Declared
✓/× Sociodemographic characteristics not reported; analyses were controlled for income and education	✓ ANOVA/ ANCOVA	× Not mentioned	✓/× No available data in 18% of the original cohort (N=446) for different reasons (not from the US, identified as female/no gender information, no information on quality of life or CSHT)	× Not declared
✓ Pre/postgroups were the same	✓ ANOVA and *t*-test	× Not mentioned	✓ 0 lost at recruitment or follow-up	× Not declared
✓ Sociodemographic characteristics for GID adults with and without CSHT not reported, however, analyses controlled for age and social feminization	✓ Multiple regression	✓/× Not mentioned (gender complaint-related psychotic delusion was exclusion criterion)	✓/× No available data in 44% of the original cohort (N=98) for different reasons (N=42 patients excluded because of not expressing – clear – homosexual orientation; N=1 excluded due to Klinefelter's syndrome)	× Not declared
✓ Sociodemographic characteristics matched (age and education)	✓ *t*-test and Pearson's correlation	× Not mentioned	✓ 0 lost at recruitment	× Not declared

and body uneasiness. Key findings are reported in Table 2, and a brief synopsis of them is reported later.

Effect of cross-sex hormonal treatment on depression, mood states, and self-esteem

Depression and its features have been the most extensively investigated mental health-related parameters in gender dysphoria individuals receiving hormonal treatment. The first study to investigate this issue was carried out in 1983.[34] This cross-sectional study assessed male-to-female (MtF) individuals' psychological adjustment depending on their hormonal treatment status. The research did not find any significant difference in terms of depressive symptoms between MtFs with and without hormonal treatment.[34] In a second study, Slabbekoorn et al[31] asked female-to-male (FtM) individuals to keep a mood diary during their testosterone administration. Results indicated no mood changes when assessing depressed mood and other mood-related parameters from baseline to after the fourth testosterone injection.[31] Miles et al[29] used a unique design to disentangle the hormonal treatment contribution to mood in gender dysphoria. Using both independent groups (longitudinal study) and repeated measure (cross-sectional study) designs, this study consistently indicated that hormone-treated MtFs are more composed and confident. Authors also tested for the effect of hormonal treatment withdrawal and duration on mood. Intriguingly, they reported no significant association.[29] In recent years, four more studies have investigated the association between hormonal treatment and depression, using commonly used questionnaires/scales.[35–38] Apart from a study,[38] which reported no significant differences in terms of depression (it only investigated MtFs), the remaining studies reported lower depressive symptoms in gender dysphoria individuals receiving hormonal treatment.[35–37] Two of these studies also assessed self-esteem, reporting higher levels of self-esteem due to the hormonal treatment intervention.[36,38]

Effect of cross-sex hormonal treatment on anxiety and tension

Different from depression, anxiety has been investigated only recently, with three studies addressing this aspect over the last 5 years.[35,37,38] All these three investigations (two cross-sectional studies and one longitudinal one) have consistently reported a reduction in symptoms of anxiety among individuals receiving hormone therapy. A previous research had studied tension as a measure of psychological adjustment, reporting no significant differences between MtFs with and without hormonal treatment.[34]

Effect of cross-sex hormonal treatment on global and personality-related psychopathology

This review has identified three recent studies about the effect of cross-sex hormonal treatment on a global measure of psychopathology.[37,39,40] Intriguingly, all these studies used the same questionnaire. However, while two studies described a significant decrease in global psychopathology occurring after the initiation of hormone therapy,[37,40] a third one did not find any difference between hormone-treated and nonhormone-treated individuals.[39] Interestingly, according to the authors, their negative finding may be attributable to the restricted range and low levels of psychopathology observed in their sample.

Three other studies investigated personality-related psychopathology as a function of cross-sex hormonal treatment, using a similar methodology.[30,41,42] Using a common measure of personality, this body of research has suggested a reduction in personality-related psychopathology among gender dysphoria individuals receiving hormone therapy. However, as one study focused only on MtF individuals[30] and a second study reported hormonal treatment to be beneficial only in MtF and not in FtM individuals,[41] there is still little evidence to suggest a positive effect of cross-sex hormonal treatment on FtM individuals' personality-related psychopathology.[42] Leavitt et al[30] also indicated that the hormone-treated MtF individuals' overall personality-related psychopathology tends to approximate the norms for male populations and negatively correlates with the hormone therapy duration.

Effect of cross-sex hormonal treatment on mental health-related quality of life

The first study to investigate the quality of life among gender dysphoria individuals receiving hormonal treatment was performed in 2006 on a large sample of FtM individuals.[24] With ~250 FtMs receiving cross-sex hormonal treatment, this study sample represents the largest one identified in this systematic review. The research reported higher emotional, social, and mental quality of life in hormone-treated FtM adults, with hormonal treatment duration associated with higher emotional quality of life.[24] Three more recent studies confirmed a better psychosocial and mental quality of life in both MtFs and FtMs receiving hormone therapy.[36,43,44] One study also compared hormone-treated individuals with

a control group, reporting a higher mental health-related quality of life in gender dysphoria individuals.[43]

Effect of cross-sex hormonal treatment on dissociative symptoms

To date, only one study has investigated the prevalence of dissociative symptoms among gender dysphoria individuals receiving cross-sex hormonal treatment.[45] Results of this longitudinal study suggest that suffering from dissociative symptoms may be a common clinical feature in the context of untreated gender dysphoria. Interestingly, this research indicated a significant reduction in gender dysphoria individuals' dissociative symptoms after the beginning of cross-sex hormonal treatment. It is worth reporting that the high prevalence of dissociative symptoms among untreated gender dysphoria individuals was greatly due to the gender-related sense of strangeness. This issue could explain why the dissociative experience was less intense when gender dysphoria individuals received hormone therapy. The unease with the biological sex and the aversion to the corresponding sex-specific body forms belong by definition to the gender dysphoria diagnosis.[2] Therefore, authors argued whether dissociation represents a genuine feature of gender dysphoria rather than a clinically relevant pathological manifestation, highlighting the need for additional/exclusion criteria for a differential diagnosis.[45]

Effect of cross-sex hormonal treatment on psychosocial, interpersonal, and emotional functioning

Psychosocial functioning has been the domain receiving most attention after depression in hormone-treated individuals. Different aspects have been investigated, such as emotional[31] and social components.[34,38] Also two studies have investigated a global measure of psychosocial functioning.[36,37] Impact of hormone therapy on emotional functioning appeared to be different in MtF and FtM individuals, with more generally positive effects in MtF and some undesirable effects in FtM individuals.[31] While Blanchard et al[34] did not find any effect of hormone therapy on social adjustment, a more recent study has identified less problems with socialization and interpersonal functioning in gender dysphoria individuals receiving hormone therapy.[38] Finally, mixed results have emerged from studies investigating global psychosocial functioning, with a study reporting less functional impairment after the beginning of hormone therapy[37] and another one finding no significant differences as a result of hormonal treatment.[36]

Effect of cross-sex hormonal treatment on social distress, perceived stress, and body uneasiness

This review identified three studies specifically analyzing distress intensity among gender dysphoria individuals and how it could be influenced by the hormonal treatment intervention.[14,35,39] These studies used the following three different measures of distress: 1) social distress, ie, avoidance and subjective distress about social interactions; 2) perceived stress, ie, perception of social life experiences as stressful and unpredictable/uncontrollable; and 3) body uneasiness, ie, gender-related distress and discomfort. Using a cross-sectional design, Gómez-Gil et al[35] reported that gender dysphoria individuals who have not received hormonal treatment show higher levels of social distress than those receiving cross-sex hormones. Consistent with these findings,[35] in a second study, hormone-treated gender dysphoria individuals showed lower perceived stress, which overlapped with that found in the normative sample.[14] The last study addressed the impact of hormonal treatment on body-related distress, suggesting a gender-specific effect. In fact, MtF individuals' body uneasiness was lower in the context of cross-sex hormonal treatment, and the reduction correlated negatively with the cumulative dose of estradiol.[39] Instead, FtM subjects did not appear to benefit from the hormone therapy in terms of body uneasiness. Authors themselves commented on it as an unexpected finding, which could be due to the individual's still unsatisfactory comfort with the body at a private/personal level rather than involving a social dimension.[39]

Risk of systematic bias across studies

While generally well designed, results mentioned earlier need to be considered in light of certain limitations. Apart from one study,[39] all the others came from only one clinic and some of them had a relatively small sample size. Most importantly, as no study used a blinded randomized controlled trial design, results could have also different explanations because of the study design(s). Moreover, type and dosage of cross-sex hormonal treatment were often not reported, and when reported, there was poor consistency across studies. The same weakness applied to hormone therapy duration. While differences between analyzed groups were generally taken into account, more than half the studies did not mention/control for psychiatric comorbidity, which could have represented a critical bias in this kind of investigation. Finally, while studies were generally strict on the defined study population (formal diagnosis according to DSM criteria used at the time

of the study), recruitment/follow-up attrition represented an issue for some of the studies identified in this review.

Discussion

This is the first systematic review of all studies examining the effect of cross-sex hormonal treatment on mental health and psychosocial well-being in gender dysphoria. A previous review has mainly focused on the psychosocial outcome of gender dysphoria individuals receiving sex reassignment surgery.[27] After the publication of that review, the literature has seen an increasing number of studies specifically interested in whether sex hormones induce any improvement in terms of mental health and psychosocial well-being. Overall, this review demonstrates that cross-sex hormonal treatment has definite effects on mental health, generally ameliorating gender dysphoria individuals' well-being at different levels. Taking into account the risks of bias reported earlier, cross-sex hormonal treatment does not seem to affect any of the parameters investigated, except emotional functioning, with a reported higher prevalence of aggressive emotions and lower affect intensity in FtMs receiving hormonal treatment.[31]

More specifically, when treated with hormone therapy, gender dysphoria individuals reported less anxiety,[35,37,38] dissociation,[45] perceived stress,[14] social distress,[35] and higher mental health-related quality of life[24,36,43,44] and self-esteem.[36,38] Also, compared to FtM individuals, MtF individuals seemed to benefit more in terms of body uneasiness,[39] emotional functioning,[31] and personality-related psychopathology.[30,41,42] More mixed results emerged from studies investigating other mental health-related dimensions. In particular, recent studies suggested reduced depressive symptoms in hormone-treated gender dysphoria individuals,[35–37] despite previous evidence of no association between cross-sex hormonal treatment and depression among MtF[34] and FtM individuals.[31] Similarly, global psychopathology appeared to be reduced in two studies,[8,37] while a third one did not detect any change.[39] Finally, while two studies indicated less functional impairment[37] and reduced problems with socialization and interpersonal functioning in gender dysphoria individuals receiving hormone therapy,[38] two other studies did not find any effect of hormone therapy on social adjustment[34] and psychosocial functioning.[36] Negative findings generally came from studies involving a cross-sectional design. On the contrary, the few longitudinal studies identified in this review were consistent in indicating an association between hormonal treatment and better mental health.[14,29,31,37,40,45] Conducting observations of the same subjects over a period of time, longitudinal studies can establish sequences of events and better detect changes in the characteristics of the target population, also due to their higher statistical power.

Some of the studies included in this review offered a comparison of hormone-treated gender dysphoria individuals to normal range values of normative data for a general population. Interestingly, all these studies indicated that after the beginning of the cross-sex hormonal treatment, gender dysphoria individuals express distress levels similar to the general population in several mental health-related dimensions, including perceived stress,[14] dissociative symptoms,[45] personality-related psychopathology,[30] mental health-related quality of life,[43] and global psychopathology.[40] These results are in-line with the majority of the previous studies, indicating that hormone therapy decreases the psychiatric comorbidities often associated with a lack of hormonal treatment.[27]

The finding of a reduced mental distress in the context of hormone-treated gender dysphoria may have several explanations. The question arising is whether cross-sex hormones exert a direct effect on distress levels, implying a biological explanation for their reduction, or rather indirectly elicit a better mental health, implying a psychological mechanism possibly related to the physical changes. Biologically, sex hormones may exert different effects on mental distress. Specifically, estrogens may increase mental distress, making individuals more prone to anxiety and depression.[46] Instead, androgens can reduce mental distress, promoting feelings of euphoria and energy[47] and also eliciting stress and hostility.[48] As a consequence, mental distress should increase in MtF individuals as a consequence of the biological effect of estrogens. Conversely, due to the biological effects of androgens, hormone therapy should induce both positive and negative effects on FtM individuals' mental distress, depending on the mental health parameters evaluated. The only finding in support of a biological mechanism for the observed changes in mental distress is the increase in the prevalence of aggressive emotions among hormone-treated FtM individuals.[31] Nevertheless, studies included in this review found that hormonal treatment has a positive effect on both MtF and FtM individuals' mental health. In addition, this amelioration is more pronounced in MtF individuals, who should be more negatively affected by the cross-sex hormonal treatment intervention according to the biological explanation. In light of all this evidence, this review does not support the hypothesis of a direct effect of hormone therapy on mental well-being in gender dysphoria. Instead, the distress reduction might be an indirect effect of hormone therapy, as already hypothesized by Kuiper

and Cohen-Kettenis.[32] Mental distress may be considered a reaction to the nonsatisfaction arising by the incongruence between the individual's experienced gender and biological sex. Cross-sex hormonal treatment is supposed to mitigate such incongruence, inducing desired physical changes that could eventually be responsible for the individual's better mental state and psychological well-being. In other words, thanks to the body changes obtained, gender dysphoria individuals may experience a reduction in their mental distress. In addition, other psychological explanations support the hypothesis of an indirect effect of hormonal treatment on mental well-being. Due to incongruence between their physical appearance and internal experience, nonhormone-treated gender dysphoria individuals may face major difficulties in managing their gender identity at a social level. Hormonal treatment may reinforce the gender affirmation with a better social recognition. This would explain why in some studies hormonal treatment seems to have a beneficial effect on the social dimension rather than on the private dimension of mental well-being.[39] Finally, as delaying hormonal treatment has been reported to often disappoint gender dysphoria individuals, also increasing their distress,[37,45] we cannot exclude that accessing care and receiving eligibility for hormone therapy may help in reducing distress, representing an acceptance of the individual's needs and requirements. In order to promote the highest standards of health for individuals seeking gender transitioning, the importance of facilitating access to care and reducing barriers across countries and cultures cannot be overemphasized. Several factors have been identified, which can affect gender dysphoria individuals' access to care and eventually lead to a nonsatisfactory outcome, such as stigma, violence, fear of being seen as different, lack of/inadequate access to specialized health care professionals and/or services, and poor access to health care pathway-related information.[49]

Conclusion

This review suggests that gender dysphoria-related mental distress may benefit from hormonal treatment intervention. Even recognizing the suffering of nonhormone-treated gender dysphoria individuals, which represents a possible risk factor for more severe or full-syndromal psychiatric disorders,[12] mental distress in gender dysphoria may be considered as a transient reaction to the nonsatisfaction connected to the incongruent body image and not necessarily a stable psychiatric comorbidity. In this perspective, timely hormonal treatment intervention represents a crucial issue in gender dysphoria individuals' mental health-related outcome.

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