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Mental Health Outcomes of Sex Hormone Therapy in Transgender Populations

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Zhang, MH; Chao, WZ; Feng, Y; Bai, W.

Corresponding author:
Menghan Zhang

yujiayi826@gmail.com

Author Affiliation:
Jilin University.

ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 July 2024 and was last updated on 29 July 2024.

INTRODUCTION

Review question / Objective In transgender populations (P), how do hormone therapy and puberty suppression interventions (I) compare to no treatment (C) and to baseline conditions in the same individuals (self-comparison) in terms of improving mental health outcomes (O), as studied in randomized controlled trials and cross-sectional studies (S)?

Rationale The mental health challenges faced by transgender individuals are well-documented, with higher rates of depression, anxiety, and other psychological stressors compared to the cisgender population. While hormone therapy and puberty suppression are recognized as beneficial interventions for transgender individuals, there is a significant gap in systematic research evaluating their long-term effects on mental health. This study is essential as it aims to provide empirical evidence on the effectiveness of these interventions in improving psychological well-being. By conducting a randomized controlled trial and a cross-sectional study, this research will address the critical need for robust data to guide clinical practices and policy decisions regarding the care of transgender individuals. Ultimately, this study aims to contribute to a better understanding of how medical interventions can enhance the mental health outcomes of transgender populations, thereby informing treatment protocols and improving their quality of life.

Condition being studied The condition being studied in this research is the mental health of transgender individuals, focusing specifically on the impact of hormone therapy and puberty suppression treatments. Transgender individuals often experience a range of mental health issues, including heightened levels of anxiety, depression, and suicide-related problems. These issues are exacerbated by gender dysphoria and societal stigma, which can significantly impair daily functioning and overall well-being. Hormone therapy and puberty suppression are medical interventions used to align an individual's physical body with their gender identity, which can

potentially alleviate psychological distress. This study aims to evaluate the effectiveness of these treatments in improving mental health outcomes within the transgender population.

METHODS

Search strategy The literature search was conducted using several electronic databases including Web of Science, PubMed, Embase, and PsycINFO. The search terms used were a combination of keywords related to the condition and the interventions: ("transgender" OR "gender diverse") AND ("hormone therapy" OR "puberty suppression") AND ("mental health" OR "psychological outcomes" OR "depression" OR "anxiety"). These terms were used to capture the broadest range of studies concerning the impact of hormone treatment and puberty suppression on the mental health of transgender individuals.

Participant or population This review encompasses studies involving participants across all age groups, genders, and health conditions who have undergone hormone therapy and puberty suppression. The review aims to capture a broad range of experiences and outcomes associated with these treatments, irrespective of the participants' specific characteristics such as age, gender identity, or the presence of a formal diagnosis of gender dysphoria. By including a diverse participant base, the review seeks to provide a comprehensive understanding of the impacts of hormone therapy and puberty suppression across different populations. Studies included in this review vary from those focusing on specific subgroups, like transgender adolescents, to those examining broader demographic categories.

Intervention The interventions evaluated in this review are puberty suppression therapy and hormone therapy, both administered pharmacologically. Puberty suppression therapy involves the use of gonadotropin-releasing hormone (GnRH) agonists to delay the physical changes associated with puberty, thereby providing transgender adolescents more time to explore their gender identity without the added stress of progressing secondary sexual characteristics. Hormone therapy typically involves the administration of estrogen or testosterone to align an individual's physical appearance more closely with their gender identity. This review includes studies that detail the dosage, duration, and administration methods of these therapies. Surgical interventions are not considered in this review as it focuses solely on pharmacological treatments.

Comparator In this review, the comparator groups include individuals who have not undergone any form of puberty suppression and hormone therapy, or drop-out during the research period, serving as a control to assess the baseline health and psychological outcomes in the absence of these interventions. Additionally, pre- and post-intervention comparisons within individuals who have undergone treatment are evaluated. This dual comparative approach allows for an analysis of the immediate and long-term effects of the interventions on physical and psychological parameters, comparing these outcomes against both untreated individuals and baseline conditions prior to the initiation of therapy.

Study designs to be included The review will include a variety of study designs to comprehensively address the objectives. Included study designs are: 1. Randomized Controlled Trials (RCTs) - To provide high-quality evidence of the efficacy and safety of puberty suppression and hormone therapy interventions. 2. Cohort Studies - Both prospective and retrospective, to observe long-term outcomes and potential side effects associated with the treatments. 3. Case-Control Studies - To identify and analyze factors and outcomes in individuals. 4. Cross-Sectional Studies.

Eligibility criteria In addition to the criteria defined in the PICOS sections, the following eligibility criteria will be applied:
1. Age Restrictions: No age restrictions will be applied to allow for a comprehensive analysis of treatment effects across all age groups.
2. Language: Only studies published in English will be included to ensure the feasibility of thorough assessment by the review team.
3. Publication Date: Studies published from January 2000 onwards will be considered to ensure that the evidence is relevant to current treatment protocols and societal contexts.
4. Study Quality: Only studies that score 3 or higher on the Jadad scale for assessing the quality of randomized trials will be included, to ensure a baseline level of study quality and reliability.
5. Geographical Restrictions: No geographical restrictions will be imposed to include a diverse and global perspective on the treatment outcomes.
Exclusion Criteria:
1. Non-peer-reviewed sources: Grey literature, abstracts, conference presentations, and non-peer-reviewed articles will be excluded to maintain a high standard of evidence.

2. Duplicate Studies: Studies reporting on the same data or participant group as another included study will be excluded to avoid data duplication.

Information sources The information sources for this systematic review will include:
1. Electronic Databases: Comprehensive searches will be conducted in multiple electronic databases, including PubMed, EMBASE, Web of Science, and PsycINFO to capture relevant published literature.
2. Trial Registers: Clinical trial registries such as ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform will be searched to find registered but unpublished trials.
3. Contact with Authors: Where necessary, corresponding authors of studies will be contacted for further information or clarification about their research, particularly in cases of data ambiguity or when additional data are needed for comprehensive analysis.
4. Grey Literature: Grey literature sources including conference proceedings, dissertations, government reports, and policy documents will be reviewed to identify additional data not available in peer-reviewed journals.
5. Reference Lists: Reference lists of all included studies will be hand-searched to identify additional studies that may not have been captured in the electronic database searches.
6. Search Engines: General search engines like Google Scholar will be used as supplemental sources to ensure that no relevant study is overlooked.

Main outcome(s) The primary outcomes of this review will assess the impact of puberty suppression therapy and sex hormone therapy on mental health issues including internalization disorders (anxiety, depression etc.) and suicidal tendencies. Specifically, we will measure:
1. Internalization Disorders: Changes in levels of depression and anxiety will be quantified using validated scales such as the Patient Health Questionnaire-9 (PHQ-9) for depression and the General Anxiety Disorder-7 (GAD-7) for anxiety. Measurements will be taken at baseline, 6 months, 12 months, 24 months and 36 months post-treatment initiation.
2. Suicidality: The incidence of suicidal thoughts and behaviors will be evaluated. This will also be assessed at the same intervals as internalization disorders to monitor changes over time.
Effect measures will include mean differences for continuous data and odds ratios for binary outcomes. In this review, the choice between a random-effects model and a fixed-effects model for meta-analysis will be determined based on the degree of heterogeneity among the included studies. Heterogeneity will be quantitatively assessed using the I^2 statistic. Studies with an I^2 value less than 50% will be considered to have low heterogeneity and will be analyzed using a fixed-effects model. Conversely, if the I^2 value is 50% or higher, indicating moderate to high heterogeneity, a random-effects model will be utilized.

Additional outcome(s) In addition to the primary mental health outcomes, this review will also analyze additional outcomes measured by the Child Behavior Checklist (CBCL) and the Youth Self-Report (YSR) scales. These tools provide comprehensive assessments of behavioral and emotional problems in children and adolescents. Specifically, the analysis will focus on:
1. Total Score: The overall score from the CBCL and YSR, which reflects the general psychological well-being of the participants.
2. Internalizing Behaviors: Scores related to internalizing behaviors (such as withdrawal, somatic complaints, and anxious/depressed behaviors) from both scales, providing insights into the subtler aspects of emotional distress.
3. Externalizing Behaviors: Scores associated with externalizing behaviors (such as aggressive and rule-breaking behaviors) from both scales, which help identify more outward-directed behavioral issues.

Data management Data management for this systematic review will be conducted using a structured approach to ensure accuracy, integrity, and confidentiality of the data collected from various studies. The key elements of our data management plan include:
1. Data Collection: Data will be extracted from selected studies using a standardized data extraction form. This form will capture essential information such as study characteristics, participant demographics, outcomes, and methodology.
2. Data Storage: All extracted data will be stored securely in an encrypted database with access limited to the research team. Regular backups will be performed to prevent data loss.
3. Data Checking and Cleaning: To ensure the reliability of the data, double data entry will be employed where two independent researchers will input the data into the database. Any discrepancies will be resolved through discussion or by consulting a third researcher. Data cleaning processes will be implemented to identify and correct any errors or inconsistencies.
4. Data Analysis: Data analysis for this systematic review and meta-analysis will be conducted using the `meta` package in R. The software will also be

used to generate tables, figures, and graphical representations of the data.
5. Data Sharing and Transparency: Upon completion of the review, the data will be made available in a public repository, subject to the data sharing policies of the funding bodies and in accordance with ethical guidelines. This allows for transparency and reproducibility of the research findings.

Quality assessment / Risk of bias analysis Quality assessment of primary studies included in this systematic review will be rigorously conducted using specific tools tailored to the study design:
1. Cross-Sectional Studies: For cross-sectional studies, quality will be assessed using an eight-item assessment instrument designed for epidemiological studies. Each study will be evaluated on the following criteria:
- Clear definition of the target population.
- Use of probability sampling methods or surveying of the entire population.
- Response rate of 80% or higher.
- Detailed description of non-responders.
- Representativeness of the sample to the target population.
- Standardization of data collection methods.
- Use of validated criteria for disease diagnosis.
- Detailed provision of prevalence estimates with confidence intervals and subgroup analyses.
Each criterion will be scored as '0 = No' or '1 = Yes'. Total scores will range from 0 to 8, with scores of 0–3 indicating low quality, 4–6 indicating moderate quality, and 7–8 indicating high quality.
2. Randomized Controlled Trials (RCTs): For RCTs, quality will be assessed based on the CONSORT (Consolidated Standards of Reporting Trials) guidelines. This comprehensive set of standards helps ensure transparency and completeness in reporting trial findings, focusing on elements such as:
- Adequate generation of the allocation sequence.
- Allocation concealment.
- Blinding of participants, personnel, and outcome assessors.
- Complete outcome data reporting.
- Analysis of intention-to-treat.
Each study will be critically examined against these criteria to evaluate the risk of bias and the overall quality of the evidence provided.

Strategy of data synthesis Data synthesis in this systematic review and meta-analysis will be performed using a two-stage approach:
1. Data Preparation: Initial data extraction will involve collating study characteristics, participant demographics, and outcome measures. Data will be standardized into a consistent format for further analysis.
2. Statistical Analysis:
- Pooled Estimates: For continuous outcomes, mean differences will be calculated, and for binary outcomes, risk ratios will be used. The choice of effect measure will depend on the nature and distribution of the data.
- Meta-Analysis: Data will be synthesized using common/random-effects models to account for potential heterogeneity among studies. The I^2 statistic will be calculated to quantify heterogeneity, and a threshold of 50% will be considered substantial.
- Subgroup Analyses and Meta-Regression: To explore potential sources of heterogeneity, subgroup analyses will be conducted based on predefined factors such as age, sex, and study quality. Meta-regression will be used to assess the impact of these variables on the overall effect size.
- Sensitivity Analysis: The robustness of the results will be tested by excluding studies with high risk of bias and observing the impact on the overall results.
- Assessment of Publication Bias: Publication bias will be assessed using funnel plots and Egger's regression test. If bias is detected, appropriate statistical techniques such as the trim-and-fill method will be applied to adjust the results.
3. Reporting Results: Results will be presented in forest plots to visually depict the effect sizes and their confidence intervals across studies. Summary tables will include detailed information on study characteristics, quality assessments, and synthesis findings.

Subgroup analysis Subgroup analysis in this systematic review will focus on gender, age, publication year, treatment duration, and follow-up duration etc. to assess how intervention effects vary across different demographic and study-specific factors. We will evaluate differential effects between males and females to determine if gender influences treatment effectiveness. Age-based analysis will help identify if intervention impacts differ significantly among children, adults, and the elderly, providing insight into age-related response variations. Analysis by publication year will explore changes in outcomes over time, potentially reflecting advances in methodologies or treatment protocols. Treatment duration will be examined to understand its influence on outcome efficacy, identifying optimal treatment lengths. Lastly, the duration of follow-up will be analyzed to assess the longevity of intervention effects and detect any delayed outcomes. Data for each subgroup will be analyzed using interaction tests to determine the statistical significance of differences observed,

with results presented as stratified effect estimates along with confidence intervals and p-values for interactions. This comprehensive approach will elucidate variations in treatment effectiveness across subgroups and aid in making tailored clinical decisions.

Sensitivity analysis Sensitivity analyses will be conducted to assess the robustness of our meta-analysis results and to identify the influence of various factors on the overall findings. The following strategies will be employed:
1. Exclusion of High Risk of Bias Studies: Studies identified as having a high risk of bias will be excluded in a separate analysis to observe whether the overall effect sizes and conclusions are significantly altered.
2. Varying Follow-up Durations: The analysis will be repeated by categorizing studies into short-term and long-term follow-up durations to explore how the length of follow-up influences the effect estimates.
3. Handling of Missing Data: Sensitivity to missing data will be evaluated by imputing missing values using multiple imputation techniques and comparing these results with the primary analysis which will use available case analysis.
4. Assessment of Publication Bias Impact: If publication bias is detected in the initial analysis, sensitivity analysis will be conducted using the trim-and-fill method to adjust for the potential effects of unpublished negative studies.

Language restriction English.

Country(ies) involved China.

Keywords Transgender Persons; Hormone Replacement Therapy; Mental Health; Gender Dysphoria.

Contributions of each author
Author 1 - Menghan Zhang - Author 1 played a pivotal role in this systematic review. She was responsible for shaping the research design and extracting data from the selected studies. Author 1 also conducted all statistical analyses and led the main writing efforts of the manuscript.
Email: yujiayi826@gmail.com
Author 2 - Wangzhe Chao - Author 2 contributed to the systematic review by assisting in the cleaning of articles and performing part of bibliometric analyses on the selected literature. He also played a supportive role in the writing process.
Author 3 - Yuan Feng - Author 3 provided expert guidance on the data extraction and processing tasks. Their expertise ensured that the data were handled appropriately and consistently, aligning with the review's objectives and methodological standards.
Author 4 - Wei Bai - As the corresponding author, Author 4 played a critical role in overseeing the entire project. She was ensuring that all stages of the research were aligned with the study's objectives. Author 4 also handled the submission and revision processes of the manuscript, and integrating feedback to refine the study.