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CoLab Network

Summary Report

Comparative Evidence Between Transdermal and Oral Estrogen as Part of Feminizing Hormone Therapy

Report Authors

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This work was conducted by the POst-market Drug Evaluation Team (PODET) team through the Post-Market Drug Evaluation (PMDE) CoLab Network.

Executive Summary

Gender-affirming hormone therapy (GAHT) may be prescribed to help individuals align their bodies or appearance with their gender identity. For individuals seeking feminization, estrogen is an established treatment, including oral (taken as a pill) or transdermal (absorbed through the skin) formulations. Decision-makers are interested in which formulation is the best first treatment option (first-line option) for gender-affirming care.

This rapid review aimed to compare the clinical efficacy and effectiveness, safety, and cost-effectiveness of transdermal estrogen therapy and oral estrogen therapy for gender-affirming care. We found a small number of studies — 1 systematic review and 3 observational studies, with no randomized controlled trials, health technology assessments, or cost-effectiveness studies — and 4 evidence-based guidelines.

Based on the limited evidence, both oral and transdermal estrogen appear safe, but it is uncertain if transdermal estrogen provides the same or better benefits for gender-affirming care. The guidelines, which are largely based on expert opinion, recommend transdermal therapy for specific patient groups, such as individuals aged 40 years or older or those at risk for cardiovascular issues or blood clots. The guidelines also advise starting treatment with the lowest possible dose and gradually increasing it as needed. Reimbursement policy-makers may consider individual risks for blood clots or other potential harms for those concerned about the risks of oral therapy.

Background

GAHT helps transgender, nonbinary, and gender-nonconforming individuals align their bodies with their gender identity. Feminizing hormone therapy (FHT) is a form of GAHT that is used to promote feminization using estrogen and suppress the effects of masculinizing hormones using antiandrogen therapy. There are various ways to take estrogen (administration routes), including oral or transdermal.

Policy Issue

The clinical efficacy and effectiveness, safety, and cost-effectiveness of transdermal estrogen therapy compared to oral estrogen therapy for FHT (and other uses, such as menopausal hormone therapy) are not clear. Decision-makers are interested in whether transdermal estrogen therapy should be covered by public funding as a first-line option for gender-affirming care, as an alternative to oral estrogen therapy.

Policy Question

1. Should transdermal estrogen be reimbursed in the first-line setting, as an alternative to oral estrogen, in the context of gender-affirming care?

Objective

The rapid review aimed to compare the clinical efficacy and effectiveness, safety, and cost-effectiveness of transdermal estrogen therapy versus oral estrogen therapy for gender-affirming care.

Findings

We identified 1 systematic review, 3 primary observational studies, and 4 evidence-based guidelines for this review, but no relevant health technology reports or cost-effectiveness studies. The primary studies include 2 prospective cohort studies (which track people over time) and 1 retrospective cohort study (which examines people in the past), with none of the studies being randomized controlled trials.

Systematic Review

The systematic review evaluated cardiovascular safety, such as changes in cholesterol levels and blood pressure, but did not report any relevant clinical efficacy or effectiveness outcomes. It explored several heart-related risk factors, but it described the comparison between oral and transdermal estrogen for gender-affirming care narratively, without a formal analysis. This limitation makes it challenging to draw conclusions about their relative safety. Although the review was generally well done, it lacked important information about the patient populations and treatments, which limits how we can use the findings.

Primary Studies

The primary studies focused on bone mineral density, which is an indicator of bone health, and body mass index, which measures the relationship between weight and height. Only 1 study looked at feminizing effects, like breast development and body fat percentage. Safety outcomes were also reported in just 1 study. The results for each of these outcomes were similar for transdermal and oral estrogen therapy. However, 1 study found that more patients taking transdermal estrogen developed higher cholesterol levels.

Importantly, none of the primary studies considered other significant patient outcomes, such as additional feminizing effects, sleep quality, health-related quality of life, or long-term side effects. All 3 studies also had several limitations. They did not adequately address factors in the study populations that could influence the results, known as confounders, and the sample sizes for patients receiving FHT were limited, ranging from 49 to 231 patients.

Evidence-Based Guidelines

The evidence-based guidelines offer recommendations for transdermal or oral estrogen as part of FHT. They also considered other areas such as physical, psychological, and reproductive health outcomes as well as side effects and hormone levels. All 4 guidelines recommend transdermal estrogen therapy for persons older than either 40 or 45 years or for those with increased cardiovascular or blood clot risks. They also advised starting at a lower dose and gradually increasing as needed.

The guidelines from the Endocrine Society primarily relied on expert opinion and did not clearly outline their methods for selecting evidence. The Australian Professional Association for Trans Health and Rainbow Health Ontario guidelines also lacked detailed explanations of their evidence selection processes and relied partly on expert opinions without discussing the strengths and weaknesses of the evidence. In contrast, the World Professional Association for Transgender Health guideline distinguished itself by using a strong systematic review process for selecting evidence and providing detailed consideration of the benefits and risks of its recommendations.

Patient Engagement

As part of our review, we engaged with 4 transgender women who have living or lived experience receiving transdermal or oral estrogen for gender-affirming care. Our goal was to understand their treatment priorities and perspectives on relevant outcomes and to gather their feedback on the report's content and language. It allowed us to proactively address the needs, concerns, and opinions of those potentially impacted by the outcomes of the review and ensure the research is relevant and useful for decision-makers.

Interviews with 3 transgender women revealed that feminization — particularly breast development, facial features, skin, and body fat distribution — is the primary desired outcome of FHT. During the interviews, safety emerged as the main concern. All 3 participants faced challenges in finding appropriate estrogen dosage levels and often had to switch formulations due to issues with dosing. They also indicated a preference for starting treatment with the safest, lowest risk dose possible.

Limitations

This customer-requested rapid review has several limitations in comparing transdermal and oral estrogen for gender-affirming care. The rapid review approach balances rigour and timeliness, which limits the search strategy, involves a simpler bias assessment, and uses stricter inclusion criteria. The small number of included studies makes it challenging to draw clear conclusions and increases the risk of bias.

The limited data on clinical outcomes also make it difficult to create clear guidelines, especially for younger and more diverse populations. In some cases, data from cisgender individuals informed guidelines, which may not be relevant for transgender patients, who have different treatment goals and biological responses.

While engagement was crucial in this area where research is limited for this equity-deserving population, it is important to note that the individuals we engaged cannot fully represent the experiences of the broader patient population. Additionally, we did not conduct any qualitative research or analysis of patient perspectives as part of this review.

Implications for Policy-Making

Both transdermal and oral estrogen appear safe, but it is unclear if transdermal estrogen offers the same or greater benefits in gender-affirming care. Expert guidelines recommend considering transdermal estrogen in certain groups of patients, including those who are older than either 40 years or 45 years, or those with cardiovascular or blood clot risk factors. The guidelines also recommend starting with the lowest dose and gradually increasing as necessary.

Given these findings, reimbursement policy-makers may consider individual risks for blood clots or other potential harms for those concerned about the risks associated with oral therapy.

Considerations

Post-Market Drug Evaluation (PMDE) projects aim to produce health policy issue evidence and are not linked to a recommendation.

We conducted a similar rapid review comparing transdermal estrogen and oral estrogen for menopausal hormone therapy. However, the applicability of that evidence to FHT is limited because therapy goals, biology, and age ranges of individuals receiving menopausal hormone therapy differ.

This work was intended to inform health policy. Clinical questions regarding FHT should be directed to a health care professional.

For more information on CoLab and its work, visit the **CoLab website**.

For the full scientific report, visit:

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CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with the Post-Market Drug Evaluation Program to produce credible and timely evidence on postmarket drug safety and effectiveness.

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