Prescribing isotretinoin in the United States for transgender individuals: Ethical considerations

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CASE SCENARIO

A 22-year-old transgender man presents to the dermatology clinic with severe inflammatory acne vulgaris not responsive to topical clindamycin, topical benzoyl peroxide, and long-term oral doxycycline. He identifies as a heterosexual man and reports monogamy with his girlfriend. He denies prior or current sexual intercourse with men. He receives weekly intramuscular testosterone cypionate injections for gender dysphoria. He has had bilateral chest reconstruction surgery but has no plan for hysterectomy or tubal ligation. He reports being currently amenorrheic. He is interested in isotretinoin therapy and has no medical or psychiatric contraindications. The dermatologist notes that iPLEDGE, the US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy for isotretinoin, requires physicians to register patients taking isotretinoin in 1 of 3 categories: male, female of nonchildbearing potential, or female of childbearing potential.

The dermatologist should:

A. Not offer isotretinoin treatment because the patient, a *man of childbearing potential*, does not clearly fit into iPLEDGE patient categories.

B. Offer isotretinoin treatment and, because the patient is currently amenorrheic from testosterone therapy, discuss iPLEDGE requirements for *females of nonchildbearing potential*.

C. Offer isotretinoin treatment and, because the patient identifies as male, discuss iPLEDGE requirements for *male* patients.

D. Offer isotretinoin treatment and, because the patient's sex assigned at birth was female, discuss iPLEDGE requirements for *females of childbearing potential*.

DISCUSSION

Individuals who identify as transgender are a diverse group of people whose gender identity differs, to varying degrees, from the sex they were assigned at birth.[1] Approximately 700,000 adults, or 0.3% of the US population, identify as transgender.[2] Some transgender individuals experience gender dysphoria, or a marked and persistent incongruence between one's assigned and experienced gender; some may also seek medical or surgical gender-affirming treatments. Transgender individuals experience unique health needs and specific health

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disparities, as outlined in a landmark Institute of Medicine report; however, research into the causes of and solutions to those disparities is lacking.[3]

Dermatologists' roles in contributing to the health of transgender persons are increasingly recognized.[4] Acne is a common adverse effect of testosterone treatment, occurring in 88% of transgender men within 6 months of testosterone initiation in 1 study.[5] Isotretinoin has been reported to be effective in treating severe testosterone-associated acne in transgender men.[6]

Isotretinoin is highly teratogenic and can cause craniofacial, cardiovascular, central nervous system, and other malformations in the exposed fetus.[7] In the United States, FDA implemented the iPLEDGE program in 2006 as an enhanced pregnancy prevention program—with the goal of minimizing fetal exposure to isotretinoin.[7] The first step in registering patients into iPLEDGE mandates that prescribers classify patients into 1 of 3 mutually exclusive categories: male, female of nonchildbearing potential, or female of childbearing potential. Females of childbearing potential, but not males or females of nonchildbearing potential, are subject to stringent requirements for monthly pregnancy testing and contraceptive counseling. Here we will focus on a specific scenario, considering prescribing isotretinoin for a transgender man of childbearing potential—ie, a person whose assigned sex at birth was female, who retains a natal functional uterus and ovaries, and whose gender identity is male—while maintaining compliance with iPLEDGE requirements.

In this case, physicians considering prescribing isotretinoin must attempt to reconcile 2 bioethical principles—nonmaleficence and respect for autonomy—that support conflicting courses of action. The principle of nonmaleficence obliges physicians not to harm. It compels physicians to take all reasonable measures to prevent fetal exposure to isotretinoin by ensuring that individuals of childbearing potential use effective contraceptive methods and comply with pregnancy monitoring requirements while taking isotretinoin.

Of note, iPLEDGE does not provide guidance regarding, or even specifically mention, transgender individuals in its information for prescribers.[7] iPLEDGE defines a female of childbearing potential as "a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure" characterized by "permanent cessation of previously occurring menses… with documentation of hormonal deficiency."[7] Effects of cross-sex hormone therapies, such as testosterone and gonadotropin-releasing hormone analogues, may be reversible and, therefore, will not necessarily result in permanent ovarian failure.[1] Notably, transgender men with retained functional natal uterus and ovaries have become pregnant, both during and after testosterone therapy.[8] In accordance with current standards of care for transgender health, effective contraceptive options for transgender individuals at risk for unplanned pregnancy should be addressed.[1] Highly effective primary forms of contraception, as defined in iPLEDGE, including complete abstinence with male partners, tubal ligation, partner's vasectomy, and nonhormonal intrauterine device, should be discussed; hormonal contraceptives are contraindicated for transgender men receiving cross-sex testosterone therapy.

The principle of respect for patient autonomy obliges physicians to ensure patients make their health decisions of their own free will, to the greatest extent possible. Respect for autonomy is rooted in the right of moral agents to self-determination and, by extension, self-identification. To provide culturally competent, patient-centered care, physicians must demonstrate respect toward patients' dignity by recognizing and affirming their gender identity, gender expression, and sexual orientation; therefore, physicians would need to register their patients in iPLEDGE according to the gender with which the patients identify. The only option within iPLEDGE to provide a patient of childbearing potential with stringent pregnancy monitoring requires classification as a "female of childbearing potential." Registering the patient as a female of childbearing potential, however, would require the patient to accept registration and monitoring as a female despite his male gender identity. He would have to sign a written consent entitled "for female patients who can get pregnant" and affirm that he has read and understood the iPLEDGE program guide for females of childbearing potential. Understandably, this approach may be unacceptable to some transgender men and some have forgone isotretinoin treatment based on this culturally insensitive designation.[9] Of a historical note, obsolete medical institutions and treatments aimed at aligning one's gender identity and expression to be more congruent with sex assigned at birth have been unsuccessful and are now deemed ethically unjustifiable.[1] Psychological and physical harms to a transgender male patient, faced with the dilemma of choosing between treating his severe acne and affirming his gender identity, must be considered.

We may also consider alternate scenarios in prescribing isotretinoin to transgender patients lacking childbearing potential—such as a transgender man who has undergone hysterectomy and/or bilateral oophorectomy, or a transgender woman with natal male anatomy. In these cases, the ethical choices are