Removal of Isotretinoin Gender-Based Guidelines: Inclusivity Takes Precedence

Sonali Nanda, MD

RESIDENT **PEARLS**

- Major changes in the iPLEDGE Risk Evaluation and Mitigation Strategy (REMS) system recently took place, including simplifying registration categories while making the process more inclusive for patients.
- It is important to practice culturally sensitive language when discussing subjects regarding gender identification and sexual practices. Sample questions have been provided to help familiarize practitioners with optimal ways to approach these patient encounters.
- There likely will be more changes with iPLEDGE REMS in the future as the American Academy of Dermatology Association continues to work on solutions regarding decreasing monthly qualifications for patients who cannot get pregnant and possible removal of patient attestation requirements.

The iPLEDGE Risk Evaluation and Mitigation Strategy (REMS) system recently underwent major structural changes. After many years of advocacy by physicians and patients, the program has changed to reflect more inclusivity in the enrollment process. Specifically, the risk categories of females of reproductive potential, females not of reproductive potential, and males were replaced by 2 categories: (1) people who can get pregnant, and (2) people who cannot get pregnant. The importance of this change is detailed here along with proposed questions we can ask patients to understand their pregnancy-related risks with isotretinoin. As allies to our patients, we strive to create an environment of equal care for all, and this change moves us in a more inclusive, patient-centered direction.

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Isotretinoin is one of the most highly regulated dermatologic medications on the market. The main reason for regulation through the US Food and Drug Administration (FDA)–managed iPLEDGE Risk Evaluation and Mitigation Strategy (REMS) is to minimize the drug's teratogenic potential, as isotretinoin can cause profound birth defects. The program originally categorized patients into 1 of 3 categories: (1) females of reproductive potential, (2) females not of reproductive potential, and (3) males. Unless the patient commits to abstinence, the program required female patients of childbearing potential to be on 2 forms of birth control and undergo regular pregnancy testing before obtaining refills. Over the last few years, the American Academy of Dermatology Association (AADA) has been advocating for changes to the iPLEDGE system. Proposed changes have included decreasing attestation frequency for patients who cannot get pregnant, increasing contraception counseling and options, and changing enrollment guidelines to encompass all gender and sexual minorities. As of December 13, 2021, the iPLEDGE system changed enrollment categories to reflect the AADA's wishes and rolled out gender-neutral categories for enrollment in iPLEDGE. This change will simplify and enhance patients' experience when starting isotretinoin.

Developing Inclusive iPLEDGE Categories

In recent years, dermatologists and patients have viewed these strict gender-based categories as limiting and problematic, especially for their transgender patients and female patients of childbearing potential who exclusively engage in intercourse with cisgender females. The United States has more than 10 million LGBTQIA+ citizens and an estimated 1.4 million adults who identify as

From the University of Oklahoma, Oklahoma City.
The author reports no conflict of interest.
Correspondence: Sonali Nanda, MD (Sonali-Nanda-1@ouhsc.edu).
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transgender individuals, rendering the previously established gender-binary iPLEDGE categories outdated.[1,2]

As a result, over the last few years, dermatologists, LGBTQIA+ allies, and patients have urged the FDA to create a gender-neutral registration process for iPLEDGE. With support from the AADA, the new modifications were approved for implementation and include 2 risk categories: (1) people who can get pregnant and (2) people who cannot get pregnant.[3]

As exciting as these changes are for the future of dermatologic practice, the actual transition to the new iPLEDGE system was described as a "failure, chaotic, and a disaster" due to additional changes made at the same time.[4] The iPLEDGE system was switched to a new website administered by a different vendor and required providers to confirm each patient online by December 13, 2021. In addition, the new system required pharmacists to obtain risk management authorization via the iPLEDGE REMS website or by calling the iPLEDGE REMS center before dispensing isotretinoin. This overhaul did not work as planned, as the new website was constantly down and it was nearly impossible to reach a contact over the telephone. The complications resulted in major disruptions and delayed prescriptions for thousands of patients nationwide as well as a great disruption in workflow for physicians and pharmacists. The AADA subsequently met with the Isotretinoin Products Manufacturers Group to create workable solutions for these issues.

On January 14, 2022, the FDA posted updates regarding access to the iPLEDGE system. They have worked with the Isotretinoin Products Manufacturers Group to create workable solutions for patients and physicians while transferring the patients' information to the new database. Their solution includes allowing physicians to send patients login links through their email to access their account instead of waiting for the call center. The majority of iPLEDGE users now have access to their accounts without issues, and the gender-neutral guidelines have been in place since the original change.

Impact of iPLEDGE Categories on Transgender Patients

These changes specifically will improve the experience of transgender men and cisgender women who are at no risk for pregnancy and could be subjected to monthly pregnancy testing when it is not medically necessary.

Consider the following patient scenario. A transgender man presents to your dermatology office seeking treatment of severe nodulocystic acne. He was placed on hormonal replacement therapy with exogenous testosterone—injections, oral pills, topical gel, topical patches, or subdermal pellets—to achieve secondary sex characteristics and promote gender congruence. The patient mentions he has been amenorrheic for several months now. He has tried many topical acne treatments as well as oral antibiotics without much benefit and is now interested in enrolling in iPLEDGE to obtain isotretinoin. With the prior iPLEDGE registration packets, how would this transgender man be classified? As a female with childbearing potential due to his retained ovaries and uterus? What if he did not endorse engaging in sexual intercourse that could result in pregnancy?

Transgender patients have unique and unmet needs that often are overlooked and prevent them from equitable, gender-affirming health care. For example, in a prospective study following 20 transgender men starting hormone replacement therapy, the percentage of patients with facial acne increased from 35% to 82% after 6 months of therapy.[5] In addition, the increased psychosocial burden of acne may be especially difficult in these patients, as they already report higher rates of depression and suicidal ideation compared with their heterosexual cisgender peers.[4] Further, the primary patient populations receiving isotretinoin typically are adolescents and young adults who are undergoing major physical, mental, and hormonal changes. Self-discovery and self-actualization develop over time, and our role as physicians is to advocate for all aspects of our patients' health and eliminate barriers to optimal care.

Inclusive Language in iPLEDGE Categories

It is important to streamline access to care for all patients, and gender-affirming, culturally sensitive language is essential to building trust and understanding between patients and providers. Howa Yeung, MD, MSc, a dermatologist at Emory University (Atlanta, Georgia) who advocated for gender-neutral iPLEDGE registration, welcomes the change and stated it "will make my job easier. I no longer have to struggle between respecting the patient's gender identity and providing medically necessary care for patients with severe acne."[3]

Sanchez et al[6] provided a list of structured questions providers can ask their patients to assess their risk regarding pregnancy: (1) Do you have a uterus and/or ovaries?, (2) Are you engaging in sexual intercourse with a person who has a penis?, and (3) If yes to these questions, what form(s) of birth control are you using? Providers should preface these questions with the following statement: "It is important that I ask these questions to assess your risk for becoming pregnant on this medication because isotretinoin can cause very serious birth defects." It is important to review these questions and practice asking them so residents can operate from the same place of openness and understanding when caring for their patients.

Final Thoughts

The landscape of isotretinoin prescribing currently is changing on a day-to-day basis. As residents, it is important we stay up to date with the changes regarding our regularly dispensed medications. The main modification made to the iPLEDGE REMS system was switching the risk categories from 3 (females who can get pregnant, females who cannot get pregnant, males) to 2 (people who can get pregnant,

people who cannot get pregnant). This change will make registration for iPLEDGE less complex and more inclusive for all patients. It is important for residents to stay at the forefront of these patient health issues and barriers to equal care, and this change represents a step in the right direction.

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