

Administrative Burden of iPLEDGE Deters Isotretinoin Prescriptions: Results From a Survey of Dermatologists

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PRACTICE POINTS

- Of clinicians who regularly prescribe isotretinoin, approximately 30% have at times chosen not to prescribe isotretinoin to patients with severe acne because of the burden of the iPLEDGE program.
- The US Food and Drug Administration should consider further streamlining the iPLEDGE program, as it is causing physician burden and therefore suboptimal treatment plans for patients.

The requirements of the iPLEDGE program place burdens on both patients with severe recalcitrant nodular acne and prescribers of isotretinoin. We sought to investigate the changes in dermatologists' acne treatment patterns due to the administrative burden of iPLEDGE by assessing whether dermatologists chose not to prescribe isotretinoin to appropriate patients because of the labor of iPLEDGE requirements. Additionally, we investigated the medications that were substituted for isotretinoin. An anonymous online survey was created and posted on a dermatology group on social media. The survey respondents (N=510) consisted of board-certified dermatologists across the United States and comprised a wide variety of ages and practice types. This survey ultimately highlighted the burden of iPLEDGE for American clinicians and the need for a more streamlined risk-management program. This program is deterring some US clinicians, especially those younger than 46 years, from prescribing isotretinoin and limiting patient access to an effective medication.

Cutis. 2022;110:44-47.

Isotretinoin is the most effective treatment of recalcitrant acne, but because of its teratogenicity and potential association with psychiatric adverse effects, it has been heavily regulated by the US Food and Drug Administration (FDA) through the iPLEDGE program since 2006.^{1,2} To manage the risk of teratogenicity associated with isotretinoin, various pregnancy prevention programs have been developed, but none of these programs have demonstrated a zero fetal exposure rate. The FDA reported 122 isotretinoin-exposed pregnancies during the first year iPLEDGE was implemented, which was a slight increase from the 120 pregnancies reported the year after the implementation of the System to Manage Accutane-Related Teratogenicity program, iPLEDGE's predecessor.³ The iPLEDGE program requires registration of all wholesalers distributing isotretinoin, all health care providers prescribing isotretinoin, all pharmacies dispensing isotretinoin, and all female and male patients prescribed isotretinoin to create a verifiable link that only enables patients who have met all criteria to pick up their prescriptions. For patients of reproductive potential, there are additional qualification criteria and monthly requirements; before receiving their prescription every month, patients of reproductive potential must undergo a urine or serum pregnancy test with negative results, and patients must be counseled by prescribers regarding the risks of the drug and verify they are using 2 methods of contraception (or practicing abstinence) each month before completing online questions that test their understanding

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The authors report no conflict of interest.

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doi:10.12788/cutis.0558

of the drug's side effects and their chosen methods of contraception.⁴ These requirements place burdens on both patients and prescribers. Studies have shown that in the 2 years after the implementation of iPLEDGE, there was a 29% decrease in isotretinoin prescriptions.¹⁻³

We conducted a survey study to see if clinicians chose not to prescribe isotretinoin to appropriate candidates specifically because of the administrative burden of iPLEDGE. Secondarily, we investigated the medications these clinicians would prescribe instead of isotretinoin.

Methods

In March 2020, we administered an anonymous online survey consisting of 12 multiple-choice questions to verified board-certified dermatologists in the United States using a social media group. The University of Rochester's (Rochester, New York) institutional review board determined that our protocol met criteria for exemption (IRB STUDY00004693).

Statistical Analysis—Primary analyses used Pearson χ^2 tests to identify significant differences among respondent groups, practice settings, age of respondents, and time spent registering patients for iPLEDGE.

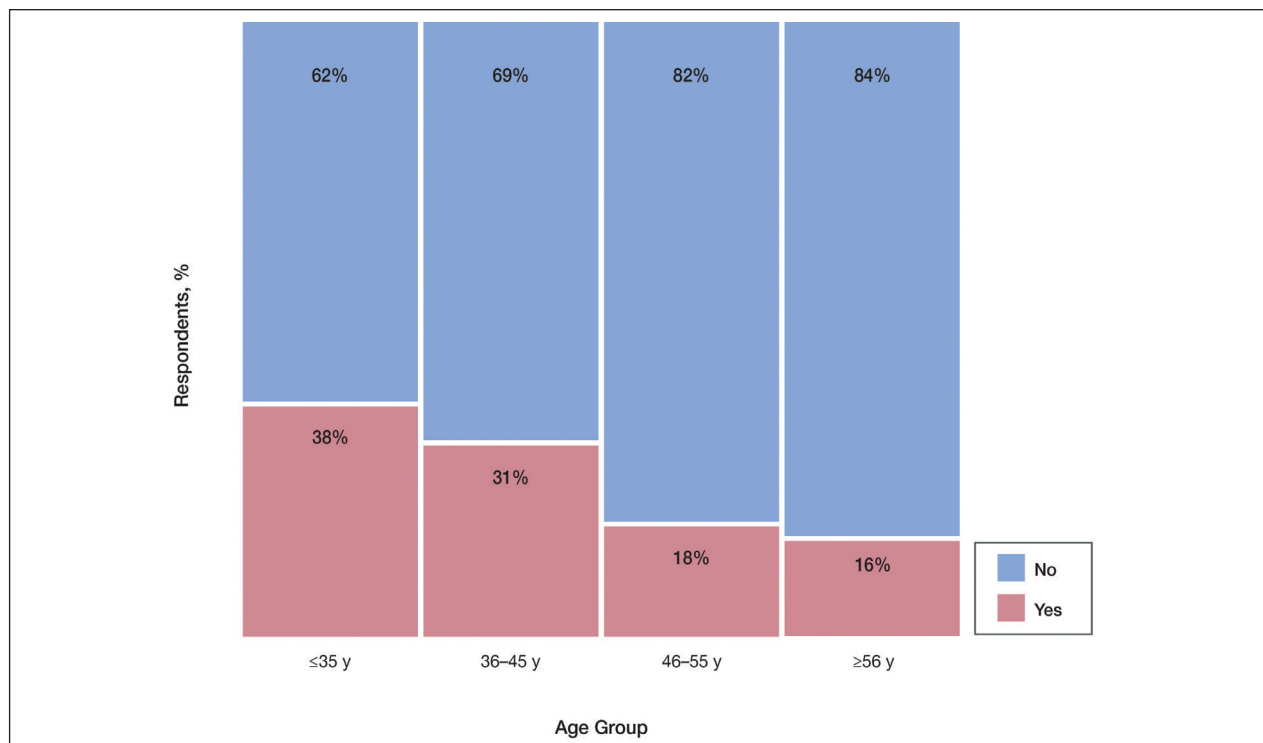
Results

Survey results from 510 respondents are summarized in the Table.

Burden of iPLEDGE—Of the respondents, 336 (65.9%) were frequent prescribers of isotretinoin, 166 (32.5%) were infrequent prescribers, and 8 (1.6%) were never prescribers. Significantly more isotretinoin prescribers estimated that their offices spend 16 to 30 minutes registering a new isotretinoin patient with the iPLEDGE program (289 [57.6%]) compared with 0 to 15 minutes (140 [27.9%]), 31 to 45 minutes (57 [11.3%]), and more than 45 minutes (16 [3.2%]) ($\chi^2_3=22.09$, $P<.0001$). Furthermore, 150 dermatologists reported sometimes not prescribing, and 2 reported never prescribing isotretinoin because of the burden of iPLEDGE.

Systemic Agents Prescribed Instead of Isotretinoin—Of the respondents, 73.0% (n=111) prescribed spironolactone to female patients and 88.8% (n=135) prescribed oral antibiotics to male patients instead of isotretinoin. Spironolactone typically is not prescribed to male patients with acne because of its feminizing side effects, such as gynecomastia.⁵ According to the American Academy of Dermatology guidelines on acne, systemic antibiotic usage should be limited to the shortest possible duration (ie, less than 3–4 months) because of potential bacterial resistance and reported associations with inflammatory bowel disease, *Clostridium difficile* infection, and candidiasis.^{6,7}

Prescriber Demographics—The frequency of not prescribing isotretinoin did not vary by practice setting



Dermatologists' isotretinoin prescribing patterns due to iPLEDGE burden by dermatologist age. The results from the question, "Have you ever not prescribed isotretinoin to patients because the iPLEDGE system is too burdensome?" are shown in this mosaic plot. This mosaic plot shows the frequency of always prescribing (blue) or at times not prescribing (red) isotretinoin because of the burden of iPLEDGE by dermatologist age.

Summary of Survey Results

Variable	Respondents, n (%)
Practice setting (N=510)	
Private solo practice	90 (17.6)
Private group practice	242 (47.5)
Multispecialty group	61 (12.0)
Hospital system owned	56 (11.0)
University affiliated	61 (12.0)
Age of respondent (N=510)	
≤35 y	159 (31.2)
36–45 y	216 (42.4)
46–55 y	85 (16.7)
≥56 y	50 (9.8)
Frequency of prescribing isotretinoin (N=510)	
Frequently (>5 patients/wk)	336 (65.9)
Infrequently (0–5 patients/wk)	166 (32.5)
Never	8 (1.6)
Ever not prescribed isotretinoin due to burden of iPLEDGE (N=510)	
Yes	150 (29.4)
No	360 (70.6)
Average time it takes to register patient on iPLEDGE (N=502)	
0–15 min	140 (27.9)
16–30 min	289 (57.6)
31–45 min	57 (11.3)
≥46 min	16 (3.2)
Is iPLEDGE effective in its current form? (N=358 ^a)	
Yes	36 (10.1)
No	322 (89.9)
Systemic agent prescribed instead of isotretinoin for female patients (N=152 ^b)	
Spironolactone	111 (73.0)
Oral antibiotics	20 (13.2)
Refer to (different) dermatologist	7 (4.6)
OCPs	7 (4.6)
Other	7 (4.6)
Systemic agent prescribed instead of isotretinoin for male patients (N=152 ^b)	
Oral antibiotics	135 (88.8)
Refer to (different) dermatologist	10 (6.6)
Topical antibiotics	1 (0.7)
Other	6 (3.9)

Abbreviation: OCP, oral contraceptive pill.

^aN=358 represents frequent and infrequent prescribers who answered no to ever not prescribing isotretinoin because of the burden of iPLEDGE.

^bN=152 represents those who do not prescribe isotretinoin because of the burden of iPLEDGE (n=150) and never prescribers (n=2) who do not prescribe for other reasons (1 reported not prescribing because of being a Mohs surgeon and 1 reported not prescribing isotretinoin because of side effects).

($\chi^2=6.44$, $P=.1689$) but did vary by age of the dermatologist ($\chi^2=15.57$, $P=.0014$). Dermatologists younger than 46 years were more likely (Figure) to report not prescribing isotretinoin because of the administrative burden of iPLEDGE. We speculate that this is because younger dermatologists are less established in their practices and therefore may have less support to complete registration without interruption of clinic workflow.

Comment

The results of our survey suggest that the administrative burden of iPLEDGE may be compelling prescribers to refrain from prescribing isotretinoin therapy to appropriate candidates when it would otherwise be the drug of choice.

Recent Changes to iPLEDGE—The FDA recently approved a modification to the iPLEDGE Risk Evaluation and Mitigation Strategy (REMS) program based on the advocacy efforts from the American Academy of Dermatology. Starting December 13, 2021, the 3 patient risk categories were consolidated into 2 gender-neutral categories: patients who can get pregnant and patients who cannot get pregnant.⁸ The iPLEDGE website was transitioned to a new system, and all iPLEDGE REMS users had to update their iPLEDGE accounts. After the implementation of the modified program, user access issues arose, leading to delayed treatment when patients, providers, and pharmacists were all locked out of the online system; users also experienced long hold times with the call center.⁸ This change highlights the ongoing critical need for a streamlined program that increases patient access to isotretinoin while maintaining safety.

Study Limitations—The main limitation of this study was the inability to calculate a true response rate to our survey. We distributed the survey via social media to maintain anonymity of the respondents. We could not track how many saw the link to compare with the number of respondents. Therefore, the only way we could calculate a response rate was with the total number of members in the group, which fluctuated around 4000 at the time we administered the survey. We calculated that we would need at least 351 responses to have a 5% margin of error at 95% confidence for our results to be generalizable and significant. We ultimately received 510 responses, which gave us a 4.05% margin of error at 95% confidence and an estimated 12.7% response rate. Since some members of the group are not active and did not see the survey link, our true response rate was likely higher. Therefore, we concluded that the survey was successful, and our significant responses were representative of US dermatologists.

Suggestions to Improve iPLEDGE Process—Our survey study should facilitate further discussions on the importance of simplifying iPLEDGE. One suggestion for improving iPLEDGE is to remove the initial registration month so care is not delayed. Currently, a patient who can get pregnant must be on 2 forms of contraception for

30 days after they register as a patient before they are eligible to fill their prescription.⁴ This process is unnecessarily long and arduous and could be eliminated as long as the patient has already been on an effective form of contraception and has a negative pregnancy test on the day of registration. The need to repeat contraception comprehension questions monthly is redundant and also could be removed. Another suggestion is to remove the category of patients who cannot become pregnant from the system entirely. Isotretinoin does not appear to be associated with adverse psychiatric effects as shown through the systematic review and meta-analysis of numerous studies.⁹ If anything, the treatment of acne with isotretinoin appears to mitigate depressive symptoms. The iPLEDGE program does not manage this largely debunked idea. Because the program's sole goal is to manage the risk of isotretinoin's teratogenicity, the category of those who cannot become pregnant should not be included.

Conclusion

This survey highlights the burdens of iPLEDGE for dermatologists and the need for a more streamlined risk management program. The burden was felt equally among all practice types but especially by younger dermatologists (<46 years). This time-consuming program is deterring some dermatologists from prescribing isotretinoin and ultimately limiting patient access to an effective medication.

Acknowledgment—The authors thank all of the responding clinicians who provided insight into the impact of iPLEDGE on their isotretinoin prescribing patterns.

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