Virtual Mentor
American Medical Association Journal of Ethics
August 2006, Volume 8, Number 8: 524-528.

Policy forum
iPLEDGE: a report from the front lines of dermatologic practice
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March 1, 2006 marked an historic turning point in the practice of dermatology in the United States. On this date, the iPLEDGE program—a mandatory program for managing the risk of birth defects linked to isotretinoin—replaced a voluntary predecessor initiative notable for its reliance upon a yellow sticker placed on prescriptions to indicate the patient was qualified to receive the medication.

In retrospect, the timing of the program launch was unfortunate. Most U.S. dermatologists were in San Francisco, Calif., attending their annual scientific meeting during the first week of March. At the meeting, a technical assistance desk staffed by employees of Covance, Inc. (a vendor selected by the isotretinoin manufacturers to design and operate the iPLEDGE program) was mobbed by concerned dermatologists seeking help for themselves and on behalf of their patients.

Nearly six months later, iPLEDGE remains a source of concern for dermatologists, their patients, pharmacists, lawmakers, FDA officials, the drug companies sponsoring the program and Covance. This article provides basic information on the iPLEDGE program and why it was created and a summary of the professionalism and ethical issues that make iPLEDGE a very hot topic of debate today.

iPLEDGE basics
The iPLEDGE program is not the only mandatory risk management program for drugs approved by the U.S. Food and Drug Administration. It is, however, the largest such program established to date and for this reason is being monitored closely by all concerned stakeholders, including dermatologists. Dermatologists account for approximately 85 to 90 percent of isotretinoin prescriptions, making them the specialists most directly impacted by the new program.

How iPLEDGE works
It is essential to know that this program is mandatory for prescribers, patients, pharmacies and wholesalers/distributors, in effect, all stakeholders in the distribution loop for this medication. No exceptions are permitted; obtaining this medication outside of the iPLEDGE program is prohibited, although it is possible to obtain it from numerous online “Internet drug stores.” The goal of the program is to prevent fetal exposure to isotretinoin, a known teratogen. To achieve this goal, the program tracks all isotretinoin transactions. This is a monumental undertaking since

isotretinoin is more widely prescribed than other medications that are subject to mandatory risk management programs. According to unofficial reports by Covance, at least 95,000 patients were registered with iPLEDGE in the first month after the program launch. By contrast, approximately 65,000 patients were registered in the STEPS program for thalidomide (on which iPLEDGE is modeled) between 2001 and 2004, according to testimony presented to the FDA in February 2004.

Before they can prescribe isotretinoin, physicians must register and then activate their status in the iPLEDGE system; this two-step process initially confused many prescribers and caused delays in their ability to prescribe isotretinoin. All isotretinoin patients—females of childbearing potential, females not of childbearing potential and males—must register with the program. There are no exceptions for age, gender or off-label or sporadic use of the medication for maintenance therapy. All patients receive counseling during monthly office visits on birth defects, adverse psychiatric events and basic safety precautions such as not sharing medication and taking the medication as prescribed. The counseling and other aspects of the visit are confirmed with iPLEDGE by dermatologists or their staff by computer or phone call. Notification of the office visit triggers a 7-day window in which the patient must pick up the prescription. Patients who fail to pick up the prescription during this 7-day window are barred from obtaining a new prescription and in effect "locked out" until the next office visit which must take place 30 days after the previous office visit. The 7-day window for picking up the prescription, the subsequent 23-day "lockout" and the 30-day gap between office visits are controversial aspects of the program which are unworkable in practice, create burdens for patients and their prescribers, and ultimately disrupt therapy for many patients across the nation.

Females of childbearing potential are subject to additional, mandatory requirements. Before she receives her first month's supply of pills, a woman in this category must obtain a negative diagnostic pregnancy test and a negative confirmatory pregnancy test in synch with her menstrual cycle and must have been on a primary and secondary form of birth control for 30 days. Abstinence is a recognized form of contraception. A negative pregnancy test, contraceptive counseling (in addition to the counseling applicable to all patients) and passing a quiz on program basics are mandatory for being given a "green light" to receive each month's supply of medication. After a female of childbearing potential completes her course of therapy, she must get a pregnancy test, continue her chosen birth control for 30 days after taking the last isotretinoin pill, obtain a final pregnancy test one month after taking her last pill and furnish that result to iPLEDGE. Pregnancy testing must be conducted by a certified laboratory.

The iPLEDGE program collects this sensitive health information on all female patients of child-bearing potential, keeping it confidential yet following up with prescribers and patients directly in cases, for example, of a positive pregnancy test result. In such cases, therapy is discontinued immediately. Subject to her consent, the pregnant patient is interviewed by teratology experts to determine the root cause of pregnancy. While the program does not provide information on options for handling

the pregnancy, the pregnancy registry will track the case. If there is a live birth, the infant is tracked for two years. Elective and spontaneous terminations of pregnancy are also recorded. At this time there is no publicly available data on the incidence of pregnancy since iPLEDGE was launched.

The previous paragraphs offer a cursory overview of salient iPLEDGE program features for patients and their prescribers. A detailed explanation of program requirements can be obtained by visiting the iPLEDGE Web site [1].

Why iPLEDGE was created

The program exists because a small number of women became pregnant while taking isotretinoin. Since 1988, voluntary initiatives that became more elaborate over time did not produce a noticeable change in the pregnancy rate for women taking this medication. The caveat with any assessment of the pre-iPLEDGE pregnancy rate is, of course, that the available statistics are the result of voluntary reporting and therefore incomplete and of doubtful accuracy or utility. Regulatory concern with the safety aspects of isotretinoin therapy culminated with a joint meeting in 2004 of the FDA's advisory committees—the Dermatologic Drugs and the Drug Safety and Risk Management—at which the framework for today's iPLEDGE was approved. The four drug companies that manufacture the medication (Roche Laboratories, Inc., Mylan Pharmaceuticals, Inc., Barr Laboratories, Inc. and Ranbaxy Laboratories, Inc.) formed the Isotretinoin Products Manufacturing Group (IPMG) that sponsors iPLEDGE and ultimately selected Covance to design and operate the program. In August 2005, the FDA approved the program design and timetable sponsored by the IPMG. At the request of the American Academy of Dermatology (AAD) and pharmacy groups, the original effective date of December 31, 2005 was pushed back to March 1, 2006. To no avail, the AAD requested additional time and pilot testing of the program when it became apparent during the transition period that there were significant concerns about the design and performance of the program.

Professionalism issues

Reports from dermatologists and their patients indicate that the design and performance of iPLEDGE leads to disruptions in therapy. A list of concerns presented by dermatologists is available at the AAD Web site [2]. The overriding issue is that the program has forced dermatologists to alter the way they practice medicine in the conduct of isotretinoin therapy without regard to their training, expertise or the safety and effectiveness with which they handled isotretinoin cases before the advent of iPLEDGE. The administrative burdens of the program have proven to be difficult for many practices, but particularly so for solo and small practices, for non-electronic practices and for practices with few isotretinoin patients. Indeed, a number of dermatologists no longer prescribe isotretinoin as a result of the iPLEDGE program, thereby limiting patient access to the treatment. In these ways, the program compromises the patient-physician relationship and the practice of medicine.

Ethical considerations

Laying aside persistent disagreements over the necessity of iPLEDGE, many serious ethical issues remain and will certainly be debated over the upcoming months and years. Putting isotretinoin—but not all teratogens—into a mandatory, restricted distribution program is arguably selective and discriminatory—and especially so in the absence of reliable pregnancy rate data for this particular medication. Access to isotretinoin is limited by iPLEDGE, in some cases for patients qualified to take the medication but discouraged by system errors and the performance of the program in general or by a scarcity of dermatologists in their community who are willing to prescribe the medication. Is this a desirable or appropriate situation? Finally, the crux of the matter is patient responsibility. In a free and open democratic society such as ours, great responsibility comes with great liberty. The availability of this valuable, effective medication means that females of childbearing potential must take personal responsibility for avoiding pregnancy while taking this medication. The fairness of subjecting female patients who are not of child-bearing potential and male patients to the burden of this risk management program is questionable since fetal exposure is not and never will be an issue with these patients. Is it fair or right that all patients who need this medication should be forced into iPLEDGE because of the handful of women known to have become pregnant on this medication?

Looking down the road

Metrics data to evaluate the iPLEDGE program are expected to be publicized later this year. Meanwhile, the AAD is conducting a survey of its members to learn more about the impact of the program on the practice of dermatology. Survey results will be released by September 2006. The survey and comments and suggestions from dermatologists and their patients are helping the academy with its ongoing effort to improve iPLEDGE so it is more workable and less burdensome for patients and their prescribers. For more information on the AAD's actions in response to the iPLEDGE program, readers are invited to visit the AAD Web site [2].

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Additional resources

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