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Review Article

Pregnancy prevention programs for medications used in dermatology

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ABSTRACT

Certain drugs used in dermatology carry a high risk of teratogenicity after maternal as well as paternal exposure. The birth of an offspring with impairments or disabilities is an emotionally distressing situation for parents, often resulting in lifelong liability for the family as well as the society. An obligation to prevent such pregnancies exposed to teratogenic agents has resulted in the development of pregnancy prevention programs. United States Food and Drug Administration in cooperation with drug manufacturers has developed a Risk Evaluation and Mitigation Strategies for a biologic or a drug to ensure that its benefit outweighs the risk. These complex but comprehensive programs were established to ensure that fetal exposure to teratogenic agents does not occur by controlling their prescription and usage. This article will review the organization, application and ethical issues raised by the mandatory standardized drug distribution programs for drugs used in dermatology, namely, thalidomide, isotretinoin, and acitretin.

Keywords: Pregnancy prevention programs, Risk evaluation and mitigation strategies, Isotretinoin, Thalidomide, Acitretin

INTRODUCTION

The use of medications during pregnancy for dermatological diseases is common despite the knowledge that developing fetus inside the mother's womb can potentially be affected by any medication given to the mother during pregnancy.[1] The need for medications that have unique effectiveness but with known teratogenicity and an obligation to prevent pregnancies exposed to such medications have led to the establishment of various pregnancy prevention programs (PPPs).

Despite documented teratogenic effects, unplanned pregnancies do occur in females using agents classified as pregnancy category X or D.[2] A ban on these drugs would have been the simplest solution to avoid embryopathy, but it would be a grave injustice to male patients and female patients of non-reproductive age group when an effective alternative does not exist. The Food and Drug Administration (FDA) Amendment Act of 2007 enabled the United States FDA (US FDA) in cooperation with drug manufacturers to require a Risk Evaluation and Mitigation Strategies (REMS) for a biologic or a drug to ensure that its benefit outweighs the risk.[3] The FDA has developed the REMS program for thalidomide, isotretinoin, and acitretin, all with a high risk of embryopathy [Table 1].[4-7] The goal of these programs is to combat drug-associated teratogenicity by controlling access to the drug, educating patients, prescribers, and pharmacists about serious risks and safe-use conditions of the drug, and monitoring compliance.[5-7]

Table 1: Drug-associated embryopathy, FDA approved indications, and REMS program for each drug.

Drug	Drug associated embryopathy	FDA approved indications	REMS
Thalidomide	Limb defects (upper limb more than lower limb): Phocomelia, amelia, polydactyly, radial dysplasia, triphalangeal thumb, prominent and sharp acromioclavicular joint, hypoplastic or absent hip joint and pubic bone Eye and ear defects: Microphthalmia, anophthalmos, poor vision, lacrimation, coloboma, strabismus, anotia, microtia, deafness Facial damage: Enlarged capillary hemangioma, facial palsy, facial asymmetry, irregular teeth numbers/spacing, small jaw, cleft palate, cleft lip and small nose Internal organ defects: Malformations of the heart (pulmonary stenosis and patent ductus arteriosus), kidneys (horseshoe, hypoplastic, rotated and ectopic malformations), genitals (absence of the testes, testicular abnormalities, hypospadias in males, malformations of the uterus and reproductive tract defects in females), and bowel (anorectal stenosis, intestinal atresia, pyloric stenosis and inguinal hernia) Nerve and CNS defects: Facial palsies, cranial nerve conduction problems, an increased incidence of autism and epilepsy in later life Vertebral anomalies: Irregular vertebral spacing, fusion of vertebrae particularly in the lower spinal column and progressive kyphosis	Cutaneous manifestations of moderate to severe ENL-acute treatment, maintenance therapy for prevention and suppression of recurrence (16 July 1998). Thalidomide is not indicated as monotherapy for ENL in the presence of moderate to severe neuritis. Multiple myeloma in combination with dexamethasone (25 May 2006)	Thalomid REMS program, formerly known as the system for thalidomide education and prescribing safety program
Isotretinoin	External abnormalities: Skull abnormality; ear abnormalities (anotia, micropinna, small or absent external auditory canals); eye abnormalities (microphthalmia); facial dysmorphia; cleft palate Internal abnormalities: CNS abnormalities including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit; cardiovascular abnormalities; thymus gland abnormalities; parathyroid hormone deficiencies Cases of IQ scores <85 with or without other abnormalities	Severe recalcitrant nodulocystic acne (May 1992)	iPLEDGE program
Acitretin	Absent hand/wrist, clubfoot, gastrointestinal malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle, premature birth	Severe forms of psoriasis	Do your pregnancy prevention actively required during and after treatment

ENL: Erythema nodosum leprosum, CNS: Central nervous system, FDA: Food and Drug Administration, REMS: Risk Evaluation and Mitigation Strategies, IQ: Intelligence Quotient

ISOTRETINOIN

Isotretinoin is a systemic retinoid which has revolutionized the treatment of acne. Approved by the US FDA in 1982 for the treatment of severe recalcitrant nodular acne, it has also acquired various off label indications.[8] However, its use is restricted by its side effect profile, most notorious being teratogenicity. It is estimated that 20% of isotretinoin-exposed pregnancies result in spontaneous abortion and there is a risk of birth defects in 18–28% of live births.[9]

The first PPP associated with isotretinoin was by the manufacturer (Roche) and consisted of patient education brochures that described risks of isotretinoin, including teratogenicity. PPP was strengthened in 1988 which necessitated women to use two methods of contraception and have monthly pregnancy tests. With PPP in place, a total of 1995 isotretinoin-exposed pregnancies were reported from 1982 to 2000.[10] Therefore, a new program System to Manage Accutane-Related Teratogenicity (SMART) was instituted in 2002 by the US FDA advisory committee where it was required to have informed consent and two consecutive pregnancy tests with negative results before starting treatment. On every prescription, a yellow sticker was pasted to verify compliance with the SMART program. The drawback was that the program did not include verification of compliance by physicians and pharmacists. Furthermore,

generic isotretinoin compounds were introduced in the market in 2002. The exposed pregnancy rates did not substantially decrease; while 127 pregnancies exposed to isotretinoin were reported a year before SMART, a total of 120 exposed pregnancies were reported in the first year following it.[11] This led the US FDA to form a more stringent REMS program, namely, iPLEDGE. The key difference between iPLEDGE and previous programs is the use of a centralized system to register patients, prescribers, and pharmacists and verify compliance with program requirements.[12] The requirements and monitoring of the system are summarized in Figure 1 and Table 2.[3,5,6]

A recent study by Tkachenko *et al.* has shown that after implementation of iPLEDGE, the exposed pregnancies remained high for years, started decreasing consistently

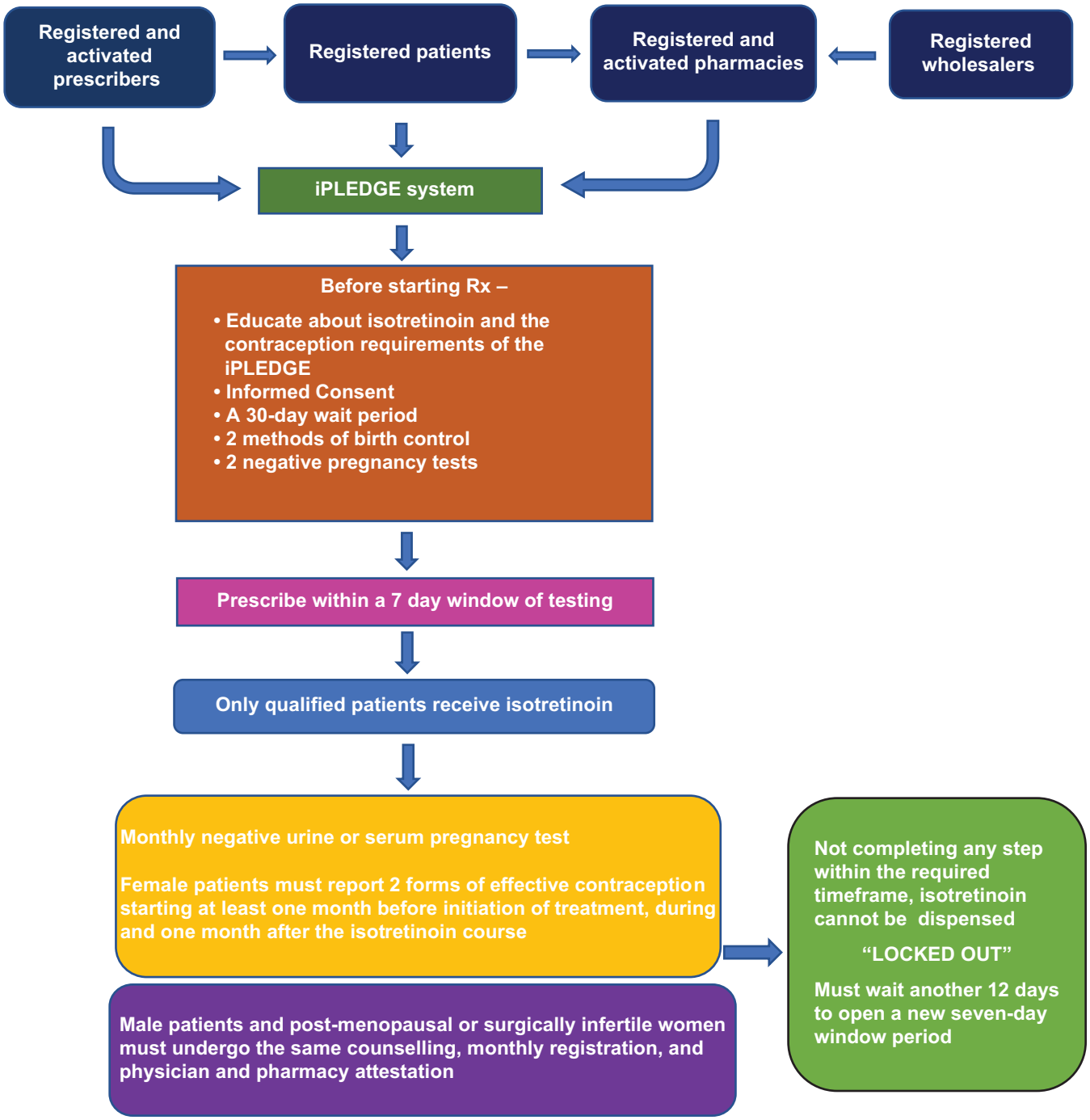

Figure 1: Schedule and monitoring requirements of iPLEDGE program.

Table 2: Contraceptive methods to be practiced and pregnancy testing requirements as per the PPP.

Methods of contraception[#]			
Primary (must choose at least one from the list)	**Secondary (must choose 1 from this list to use with primary method)**	**Unacceptable methods**	**Emergency contraception (after unprotected sexual intercourse)**
Birth control pills (but not progestin-only "minipills") Birth control patch IUD-copper bearing or progesterone releasing Injected, implanted, or inserted hormonal birth control products Tubal ligation Partner's vasectomy	Diaphragm with spermicide Cervical cap with spermicide Condom with or without spermicide Vaginal sponge (contains spermicide)	Progesterone-only "mini-pills" IUD progesterone T Female condoms Natural family planning (rhythm method) or breastfeeding Fertility awareness Withdrawal Cervical shield	Emergency Contraception Pills (ECPs) within 72 hours Insertion of Cu T 380A within 5 days
Pregnancy testing and contraceptive requirements while on the drug			
Isotretinoin Two urine/blood pregnancy tests with a sensitivity of at least 25 mlU/ml from an approved lab have to be negative to start the drug. The first test is done when the patient decides to take isotretinoin. The second test is to be done during the first 5 days of the menstrual period right before starting isotretinoin. The interval between the two tests must be at least 19 days. Patient must use two effective forms of birth control together all the time for at least 1 month before taking the second test. Thereafter monthly testing up to 1 month after discontinuation of the drug. Women of reproductive age group must use two forms of birth control together (at least one primary method) correctly all the time for 1 month before starting isotretinoin, while taking, and for 1 month after the last dose.			
Thalidomide Two negative pregnancy tests sensitive to at least 50 mIU/mL must be obtained before initiating therapy, even if continuous abstinence is the chosen method of birth control. The first test should be performed within 10–14 days and the second test within 24 h before prescription and then weekly during the 1st month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles up to 1 month after cessation of therapy. Women of child bearing potential must agree to use two forms of contraception at the same time, including one highly effective method (primary) and one physical barrier method (secondary). It is to be practiced at least 4 weeks before initiation of therapy, during therapy and for at least 4 weeks following discontinuation. As there is evidence of presence of thalidomide in the semen of men receiving the drug, it is mandatory for males receiving thalidomide to use a latex/synthetic condom during any sexual contact with females of reproductive age group while taking the drug and for up to 4 weeks after discontinuation of the drug even if they have undergone a successful vasectomy. Furthermore, they should not donate sperms.			
Acitretin Therapy cannot begin until pregnancy has been ruled out by negative results from two pregnancy tests with a sensitivity of at least 25 mIU/Ml. The first test should be done at the time the patient decides to pursue therapy. The second test should be done during the first 5 days of the menstruation immediately preceding the beginning of therapy. If the patient has amenorrhea, the pregnancy test should be done at least 11 days after the last act of unprotected sexual intercourse (without using two effective forms of contraception simultaneously). They must have a pregnancy test each month before receiving the next month's prescription and every 3 months for 3 years after discontinuation. Females of reproductive age group must choose two effective forms of contraception (at least one primary method) to be used simultaneously for at least 1 month before initiation of therapy, during therapy, and for at least 3 years after discontinuing therapy, as there is evidence that acitretin can be re-esterified to etretinate in the presence of alcohol which has very long half-life. Therefore, females of reproductive potential must not ingest ethanol during treatment and for 2 months after cessation of treatment.			

[#]As an alternative to contraception, females have the right to abstain continuously from heterosexual intercourse. Females who have documented menopause (no menses for at least 24 consecutive months) or surgical sterility (hysterectomy or bilateral oophorectomy) are exempted from contraception.
IUD: Intrauterine device, PPP: Pregnancy prevention program

after 2008, and reached a plateau by 2011.[13] Abortions both spontaneous and therapeutic as well as fetal defects have decreased. As suggested by the authors, the fall was not necessarily due to iPLEDGE implementation but may have been due to a general decrease in unplanned teenage pregnancies and improved contraception education and usage. Reporting fatigue could have been another reason for the long delay in the fall. Although there is a reduction in isotretinoin exposed pregnancies, it still occurs at unacceptable levels.

THALIDOMIDE

Thalidomide was released in 1957 as a non-addictive, non-barbiturate sedative by a German pharmaceutical company. It was marketed and advertised as a completely safe drug in 46 countries, under different names. The drug was found to be an effective anti-emetic and was used extensively to treat morning sickness in pregnant women between 1957 and 1961.[14] It was withdrawn from the market in 1961 after two independent clinicians, Lenz[15] in Germany and McBride[16] in Australia confirmed thalidomide to be the cause of the largest human-made medical disaster in history, an epidemic of phocomelia affecting over 10,000 infants.[17] Thalidomide never reached the US market then, as a FDA physician, Frances Kelsey did not approve the drug licensing despite the pressure to do so due to concerns about the reports of peripheral neuropathy in patients taking the drug. Dr. Kelsey was subsequently awarded the president's award for averting an epidemic of thalidomide induced birth defects in the US.[4,14]

In 1965, thalidomide was found to be very effective in treating erythema nodosum leprosum by Sheskin due to its anti-inflammatory and immunomodulatory action.[18] Furthermore, studies indicated its effect on vascular and neural tissue. Today thalidomide is recognized around the world as a promising treatment option for a broad range of other conditions.[19] Since the approval of thalidomide in 1998,[20] drug manufacturer Celgene had developed and operated a mandatory PPP, namely, the System for Thalidomide Education and Prescribing Safety[21,22] currently known as Thalomid REMS which was approved by the US FDA. The program regulates prescription, dispensing, and use of the drug and requires registration by prescribers, pharmacies, and patients.

Thalidomide causes damage to the forming embryo in a short time sensitive window, also known as the "critical period," which extends between days 20 and days 36 after fertilization (34–50 days after last menstrual cycle).[4,23] Even a single dose of 50 mg or 25 mg/day of the drug for two days was shown to cause characteristic birth defects.[24] The cardinal goal of the mandatory REMS is the prevention of fetal exposure of the drug in females of reproductive age group as well as female partners of male patients.

A prescriber intending to prescribe the drug must contact Celgene to request a folder that contains all the necessary materials to participate in the program and to enroll a patient and must register by completing prescriber registration cards. During the first patient visit, the use of thalidomide therapy versus alternatives is determined and the patient is given visual aids, written material and verbal counseling regarding benefits, risks, and contraceptive measures to be practiced. The patient (or parent or legal guardian in case of minor) and prescriber have to sign written informed consent, a copy of which is kept by the prescriber, the patient, and give an additional copy to the pharmacist along with the prescription. Before writing a prescription, the patient must complete a confidential survey form that ensures compliance with contraception, pregnancy testing, and drug therapy.

Female patients either receive contraceptive counseling by the prescribing physician or through referral to a gynecologist. Contraceptive measures to be followed and pregnancy testing schedule while on the drug are described in Table 2. Once all the requirements are satisfied, the prescriber can issue a written prescription to a pharmacist registered in the program. No more than 28 days' supply of thalidomide can be prescribed and no automatic refills or telephonic issue of the prescription can be done. Subsequent refills require a new prescription. Furthermore, pharmacists should not repackage the thalidomide capsule and should accept any unused drug by the patients. For female patients in the reproductive age group, no more than seven days' supply of drugs should be provided in the first four weeks, coinciding with weekly pregnancy testing requirements. All prescriptions should be filled in the seven day window period.[5]

If pregnancy occurs during drug intake, the drug is immediately discontinued, and a report is issued to Celgene and the FDA. During each visit, the patient has to complete the follow-up mandatory survey form which tracks compliance with the program on a monthly basis for female patients and on a three-month basis for male patients. Both FDA and Celgene will monitor data from the registry and are prepared to make necessary modification to the program to ensure its effectiveness.

Between September 1998 and December 2004, approximately 124,000 patients were registered with the STEPS program out of which 43% were female patients and 5% were females in the reproductive age group.[22] Out of the 6000 female patients of childbearing potential, 72 females had positive pregnancy test results, 69 were false positive, and 1 became pregnant while on the drug which resulted in a miscarriage though therapy was discontinued and two were determined to be pregnant before they received the drug. Furthermore, teratogen information service has recorded three new cases of thalidomide teratogenicity in Brazil since 2005.[25] Alarmingly, these cases were not registered through a systematic surveillance system.

ACITRETIN

Acitretin is a retinoid approved by the FDA for the management of severe forms of psoriasis in adults. It can cause severe birth defects during treatment and for up to three years after a patient stops the drug.[7] Hence, in females of reproductive age group, the drug is reserved for non-pregnant

patients who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Do your pregnancy prevention actively required during and after treatment program is intended for women of childbearing potential to help avoid pregnancy during this time.[7]

After discussing any questions or concerns with the prescriber and reading the program brochure, the patient has to undergo a self-evaluation exercise to test understanding of some of the most important aspects of the program. If any question goes wrong, the patient has to review the brochure again and make sure she understood. Other treatment options should be used if the patient is not willing or able to take seriously the responsibility for pregnancy prevention and actively follow all recommendations.

It is essential for the prescriber to rule out pregnancy before treatment begins and to fully inform the patient about effective contraception [Table 2]. Initiation of treatment should start within seven days of the specimen collection if the second pregnancy test is negative and the drug should be limited to a month's supply. To receive the initial prescription patient must sign an informed consent form along with her prescriber. A 24-h, toll-free, automated birth control counseling line has been set up for giving birth control information. The prescriber can provide a contraception counseling referral form if required and a contraception counselor is provided free of charge.

While taking acitretin, the patient will be asked to participate in a brief voluntary and confidential survey once every three months and two times a year for three years after stopping the drug. The short questionnaire is about the use of acitretin, pregnancy prevention and assesses the understanding of the risks associated with drug usage.

Males taking acitretin should not donate blood during and for at least three years following therapy as women of childbearing potential must not receive blood with the drug.[7] Based on available information, it appears that the small amounts of acitretin in semen (1/200,000 of a single 25 mg capsule)[7] of men taking the drug pose little, if any, the risk to an unborn child. Furthermore, a prospective study of ten men taking acitretin found no impairment in semen parameters during or after a 12-week regimen.[26]

THE PPP SCHEDULE FOR EACH DRUG HAS BEEN SUMMARIZED IN TABLE 3[5-7]

Challenges to be addressed[27]

The program requires the patients to be literate and able to perform the survey procedures. It also requires significant electronic and telecommunication interaction for patients, prescribers, pharmacies, and drug manufacturers with the system making it resource and labor intensive. Any failure in the process (a vacation, computer data entry error, and change of prescriber) or an exception to the seven days window time results in a refusal to dispense the drug. These highly centralized programs inadvertently interrupt normal patient-clinician relationship and raise important concerns regarding the convenience of medical care.

Substantial intrusion into personal privacy is another major concern. Patients have to register, take monthly pregnancy tests and document contraceptive methods used at many levels. Many unmarried females, including females younger than 18 years who engage in sexual relationships without parental approval are required to reveal information regarding their sexual activity as parental consent is required for the use of drug and contraception in females younger than 18 years.

Perception and use of contraceptives vary widely among different ethnic, socioeconomic, and religious groups. Abstinence is not considered reliable for previously sexually active females in these programs, as there are reports of many cases wherein females were unsuccessful in maintaining abstinence and delivered children with birth defects. Moreover, inconsistent use of contraception and lack of compliance with provisions of the program have resulted in a number of elective termination of exposed pregnancies and in birth of infants with malformations.[28] To promote patient acceptance and motivation to use contraceptives, sufficient education must be provided by the health-care professionals underscoring the scientific rationale for the need for contraception.

Another complaint is regarding gender inequality. Although males are obligated to participate, they have fewer requirements in terms of monthly pregnancy/comprehension tests and contraception. Moreover, their prescription window is 30 days rather than seven days as it is with females of reproductive age group.[5,6] Enrollment of transgender for the program is another issue, as there are no specific instructions. Transgender men, even if they are on testosterone, may still be of childbearing potential and have to be classified as females for the sake of the program that compromises their right to self-identity.[29]

Apart from the challenges mentioned, we would like to highlight other issues faced in a country like India, where these teratogenic drugs are available in the market with no stringent programs to regulate them. Effective counseling regarding adverse effects and contraception by treating physicians is a time-consuming process, which is difficult to achieve in a country like ours with heavy patient load especially in a government setup. Moreover, hesitancy of our patients to discuss their sexual activities with the physicians and reluctance to practice contraception makes the process even more difficult. Although manufacturers have taken

Table 3: Pregnancy prevention program schedule for each drug.

ISOTRETINOIN ACETRETIN THALIDOMIDE	1 month before Rx	Before Rx	During Rx	1 month after Rx	2 months after Rx	3 years after Rx
Two forms of birth control						
Two negative pregnancy test						
Ongoing pregnancy tests	Each month before prescription and after 1 month of the last dose Each month before prescription, every 3 months for 3 years after stopping Weekly first 4 weeks, repeated every month thereafter in regular cycles and 2 weekly in irregular cycles					
Confidential survey						
No blood donation						
No lactation						
No alcohol						
Sign informed consent						

care to include appropriate warnings on labels and details in package insert regarding teratogenic potential of the drugs, our patients may have limited ability to comprehend these instructions written usually in English. Easy availability of teratogenic drugs coupled with inadequate health services often lead to self-medication and sharing of pills. In a country where the basic health care of the people is not met, implementation of such centralized PPPs is unlikely to occur in near future. To prevent grave consequences, we suggest that the treating physician should take ample time to counsel and educate the patient especially regarding pregnancy testing and contraception, take written informed consent before starting the medication, reinforce the information by giving print outs in regional language and keep them under regular follow-up. Furthermore, government should ensure safe dispensing practices by pharmacists and consider components of these mandatory programs as a model for regulation of known teratogens.

CONCLUSION

Standardized drug distribution system is indeed a double-edged sword, too much flexibility in the program might lead to unmonitored off-label use, noncompliance resulting in embryopathy, and too stringent control may result in physicians unwilling to prescribe the drug, patients unwilling to take the drugs through legitimate channels resulting in unregulated black market sources. Furthermore, these drugs are used in countries where there is no such stringent control. Hence, we recommend the approval of similar programs in all countries where these drugs are used.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest.

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