



# Manage & Prevent **Isotretinoin Side Effects**

This guide will help you anticipate and prevent or minimize side effects that your patients can develop as a result of isotretinoin therapy.

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Viewed by some as a “miracle therapy,” isotretinoin is a widely used medication for patients with refractory moderate to severe acne vulgaris. The drug has been the subject of public scrutiny for some time concerning potential side effects, including depression and birth defects. While the iPledge program effectively addresses many of these concerns, some patients and many parents still express concerns about the drug’s safety.

When considering isotretinoin therapy, it is important for physicians to explain to patients and parents that with proper monitoring and compliance, isotretinoin is a safe, effective treatment. Solid patient education is the foundation of therapy. Included in this education should be an overview of potential side effects associated with isotretinoin therapy. This article will review these side effects and offer simple measures that patients can take to help prevent or manage them.

## **Side Effects Guide**

**Birth Defects.** Before beginning isotretinoin therapy, women of childbearing age must be absolutely certain they are not pregnant and do not become pregnant while on the drug or in the one month following completion of treatment. It is imperative that patients know that isotretinoin likely will cause severe birth defects in a child conceived during therapy or in the month following therapy. Large follow-up studies have shown that after one month of completion of therapy, there is no increased risk of birth defects compared to women who have never taken the drug.

Although iPledge registration may be viewed as a laborious process, it should serve to reinforce and augment your efforts in guiding patients through a successful course of isotretinoin therapy. This includes fully informing them about the risk to the fetus if the patient were to become pregnant and the need for regular laboratory pregnancy testing. Per the iPledge program, sexually active women of child-bearing age must use two approved

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forms of contraception, one primary and one secondary, for the one month before, during, and for one month following therapy. Women may instead choose complete abstinence for this time frame. Some physicians insist all female patients of child bearing potential take an oral contraceptive during this time, even if not sexually active. Importantly, all patients, men and women, must be aware of the pregnancy issue, as iPledge requires all users of the drug to be reminded during each office visit not to share the drug with anyone and not to donate blood during treatment or in the month following treatment.

**Photosensitivity.** Most patients report that they sunburn more easily during isotretinoin treatment. Physicians should caution patients not to sunbathe or use artificial tanning parlors—a good message for all patients. Prior to anticipated sun exposure, patients should apply a broad spectrum sunscreen with SPF 30 or higher such as Neutrogena Ultra Sheer™ and a lip balm that contains sunscreen (see Dry Lips below), and wear sun protective clothing. Use of a sun umbrella while at the pool or beach and avoidance of excessive sun exposure during peak sun hours of 10am to 3pm are advisable.

Sunburn treatment may include use of cool tap water compresses for 10 minutes a few times a day and aspirin (or if allergic to aspirin, choose acetaminophen) in manufacturer-recommended doses. If the sunburn blisters, patients should seek medical care. Biafine Topical Emulsion (OrthoDermatologics) may help soothe and heal a sunburn.

**Cheilitis.** Most individuals develop mild nuisance chapping of the lips while on isotretinoin. This is one of the most common effects of the drug. Occasionally the lips become more inflamed, prompting patients to seek aid. To prevent chapping, suggest 10 or more applications daily of a lip balm with sun protection such as ChapStick Ultra 30 or Blistex Ultra Protection. If chapping persists, consider Vaseline or Aquaphor Healing Ointment. Another option is for the patient to hold a warm, moist washcloth between the lips for five minutes several times a day, followed by applications of the lip balm.

For more severe inflammation, patients may use OTC hydrocortisone ointment 1% or a low potency prescription corticosteroid ointment of your choice two to three times daily for a few days at a time in addition to the preceding measures. It is important not to use the corticosteroid ointments for more than a few days at a time due to potential side effects from their overuse.

**Xerosis/Asteatotic Eczematous Dermatitis.** Dry skin and asteatotic eczematous dermatitis also are fairly common during isotretinoin treatment, especially on the face, arms and hands. Rarely, impetiginization, peeling of the palms

and soles, or paronychia may develop. Patients with a tendency to overbathe should be reminded that this behavior is counterproductive. I suggest that patients not take more than one comfortably warm (not hot) bath or shower per day unless absolutely necessary. Mild soaps, such as Dove®, Oil of Olay®, or Purpose® Gentle Cleansing Bar, or non-soap cleansers such as Cetaphil® Gentle Skin Cleanser or Aquanil® Cleansing Lotion used sparingly also are helpful in minimizing dryness. Most people require soap only to the axillae, underwear areas, and feet, in addition to a normal amount of hand washing and shampooing.

After the shower, recommend application of a good moisturizing lotion such as Lacticare® or CeraVe® Lotion. Triple Cream® is an excellent hand cream and Neutrogena Healthy Defense Daily Moisturizer™ SPF 30 is an excellent moisturizer/sunscreen for the face. Additional measures to combat dryness include a humidifier for the bedroom during cold weather, and keeping the bedroom window open a crack at night. Since topical acne medications may add to dryness, discontinuing all other acne medications while on isotretinoin is advisable.

If eczematous dermatitis develops, patients may try an OTC hydrocortisone cream or ointment 1% for brief periods or may need a low to mid potency prescription corticosteroid cream, which usually quickly controls and eliminates the rash. Prescription topical or oral anti-staph/strep antibiotics ointments may be needed for the rare circumstance where infection develops. OTC antibiotic ointments generally are not effective in treating bacterial infection.

**Epistaxis.** Patients may occasionally experience nosebleeds due to dryness of the nasal mucous membranes with consequent blood vessel fragility. Vaseline applied twice daily to the nasal mucosa and OTC Ocean® Saline Nasal Spray may help prevent this problem. Patients should be reminded that applying pressure or packing the nose will help stop the nosebleed. If the bleeding is not readily stopped, medical attention should be sought.

**Acne Flaring.** While mild worsening of acne occurs occasionally while on isotretinoin, severe flaring (acne fulminans) also is possible, albeit rare. Explain to patients that usually it will take up to two months before they start to see improvement with isotretinoin therapy. To avert worsening, it is helpful to start patients on a low dose (0.5mg/kg/day or lower) and gradually increase the dose to the target of typically about 1mg/kg/day during follow-up visits. Importantly, communication with patients on this matter is essential. Occasionally, a limited tapering systemic corticosteroid course may be necessary to control a severe flare.

**Xerophthalmia.** Eye dryness typically is mild, but can occur. Occasionally the dryness causes slightly blurry vision or

irritation of the eyes. In these instances, contact lenses, especially hard lenses, may be more difficult to wear. For patients experiencing eye dryness or irritation, artificial tears, such as Celluvisc or HypoTears, may help. Ophthalmic consultation may be warranted if symptoms do not abate.

**Musculoskeletal Symptoms.** Myalgias or arthralgias occur in about 15 percent of isotretinoin users. Usually they are mild and tolerable; occasionally they are more severe. Patients may partake in any physical activity they can tolerate, but if pain is severe, isotretinoin may need to be discontinued or the dose lowered. Athletes who are isotretinoin candidates and are playing contact sports may be best served by using the agent during the off-season.

**Alopecia.** Inform patients that hair thinning occurs in about 10 percent of isotretinoin users. Usually it is mild and not noticeable to others and it very rarely persists. Rarely, discontinuation of isotretinoin treatment is necessitated by thinning of the hair. I have advised therapy discontinuation most often as a result of the patient's request rather than due to absolute necessity.

**Nyctalopia.** Decreased night vision occurs in about five percent of isotretinoin users. Caution patients to be careful when driving at night or to avoid driving at night if the condition becomes severe.

**Skin sensitivity/scarring.** It is important that patients avoid wax epilation ("waxing") and non-ablative laser resurfacing during and for six months after treatment, due to the risk of scarring. Moreover, they should avoid ablative laser resurfacing, dermabrasion, and acne scar revisions during and for at least 12 months after treatment.

**Myelosuppression.** The occasional development of anemia, leukopenia or thrombocytopenia typically is detected with routine complete blood counts.<sup>1</sup> Inform patients that the changes are minimal and are usually of no consequence, as long as the patient is closely monitored. In the unlikely event of marked suppression, physicians may choose to adjust treatment or stop it altogether.

**Hyperlipidemia.** Increased triglyceride and cholesterol levels are fairly common and are detected with routine fasting lipid profiles. They occur most often in individuals who have diabetes mellitus, are overweight, or have a personal or family history of high triglycerides or cholesterol. Elevations are usually mild and of no consequence and will normalize within a month or two after finishing treatment. Rarely, marked hypertriglyceridemia develops, with acute pancreatitis being a potential complication.

Signs and symptoms of pancreatitis include upper abdominal pain, pain in the mid-back, nausea, vomiting, fever, jaundice, and icterus. Inform patients that, with proper monitoring, pancreatitis is completely avoidable. If triglyceride levels are elevated, you may adjust therapy accordingly. A low triglyc-

eride diet may be helpful for patients, so it is useful to provide a low triglyceride diet list.

If needed, one of the statins, such as Zocor (simvastatin, Merck) or Lipitor (atorvastatin, Pfizer), may help control these levels.

**Hepatotoxicity.** This is an occasional side effect, most often detected with routine hepatic panel monitoring. Usually the elevated liver enzyme levels are mild and require no changes in therapy. If significantly out of range, dose adjustment or discontinuation of isotretinoin may be necessary. Due to overlapping side effects between isotretinoin and vitamin A, the FDA warns against taking any supplemental vitamin A, even the low dose in multivitamins, when taking isotretinoin. With appropriate laboratory monitoring and response, risk to the liver is negligible.

Most multivitamins contain vitamin A or beta-carotene in the range of 3,500 IU (70 percent DV in a popular brand-name product) up to 5,000 IU in one specialty organic formulation, according to offerings at drugstore.com. If patients wish to continue or start a multivitamin, ebA Multivitamin Supplement® (everything but "A"®) is a multivitamin that does not contain vitamin A.

Make sure to ask your patients about any prior liver problems, such as viral or alcoholic hepatitis or cirrhosis. Request a list of all medications patients are currently taking, with particular attention to any potentially hepatotoxic medications. Patients should avoid excessive alcohol ingestion during treatment, so be open in speaking with patients to ensure they are aware of proper limits.

**Mood Changes.** Patients may experience depression or other psychiatric disorders during isotretinoin therapy, though the link between isotretinoin and depression remains controversial.<sup>6</sup> There have been rare reports of suicide during isotretinoin therapy, but they have occurred less frequently than would be expected in the general population. Thus, there does not seem to be a statistical correlation between isotretinoin therapy and suicide. Nevertheless, it is important to address any history of psychiatric illness, suicidal ideations or attempts while considering isotretinoin therapy. If relevant, it is advisable to involve the primary care physician and/or psychiatrist in the decision-making process.

**Pseudotumor Cerebri.** Fewer than one percent of isotretinoin users develop elevated intracerebral pressure. Patients should know to contact you if they experience headaches, nausea/vomiting, and or blurred vision that seem out of the ordinary or do not go away within a day or two. Be sure to review with your patients any prescription and over-the-counter medications they are taking before providing isotretinoin. As per FDA-approved Prescribing Information, antibiotics in the tetracycline family and any supplemental vitamin A, including vitamin A in multivitamins, are contraindicated while on isotretinoin. Again,

a vitamin A-free multivitamin may be taken if the patient wishes to continue a multivitamin during therapy.

Pseudotumor Cerebri resolves spontaneously if detected early and isotretinoin is stopped. If such symptoms are ignored or not reported, the condition can slowly worsen and potentially become life-threatening. Neurologic consultation is prudent if there is significant concern. Fundoscopic examination for papilledema and occasionally an MRI scan may be necessary for further evaluation.

**Inflammatory Bowel Disease.** Fewer than one percent of patients taking isotretinoin develop inflammatory bowel disease.<sup>8</sup> Before starting therapy, ask if the patient has ever had blood in the stool, any unaccounted GI symptoms or a history of ulcerative colitis or Crohn's disease. If bleeding from the rectum, bloody diarrhea or any persistent unusual GI symptoms develop during treatment, patients must contact their physicians immediately.

**Hyperglycemia.** Occasionally, people with diabetes mellitus will notice their blood sugar levels are more difficult to control while on isotretinoin. For patients with diabetes, monitoring serum glucose closely is essential. Request that they contact you and their primary care physician or endocrinologist if they have difficulty controlling their levels so that their treatment regimen may be adjusted accordingly.

There are other side effects too rare to mention here. These are listed in the isotretinoin Prescribing Information.

## Patient Take-Home

The take home message for patients is that isotretinoin side effects can be minimized and largely prevented with proper education, careful compliance, and appropriate monitoring and

management. Thus, when considering and subsequently initiating therapy, reassure patients that isotretinoin in appropriate dosage and duration is both safe and effective under your medical supervision. Hopefully, these measures will aid in achieving a smooth course of therapy and offer great improvement or cure for your acne patients. ■ ☑

*Dr. Stierstorfer is a developer of ebA multivitamins, which is available online at [www.ebAMultivitamin.com](http://www.ebAMultivitamin.com). He has no other relevant disclosures.*

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## New Insights on the Psychological Effects of Isotretinoin

In a recent study (*Int J Dermatol* 48(1):41-6), researchers assigned 78 acne patients either to isotretinoin treatment or to topical treatment, evaluating their psychological status at baseline, second and fourth months of treatment. All patients were required to complete the Dermatology Life Quality Index (DLQI), the Hospital Anxiety and Depression (HAD) scale, and the Beck Depression Inventory (BDI). At the baseline, the two groups showed no significant differences in DLQI, BDI, HAD-A, HAD-D and total HAD scores. However, at the end of the second month, quality of life was more impaired in the topical treatment group compared to the isotretinoin group, but there were no differences between the two groups in terms of BDI, HAD-A, HAD-D, and total HAD scores. At the end of fourth months, quality of life and all psychological test scores had improved more in the isotretinoin group compared to topical treatment group, indicating that there is no increase in depressive and anxiety symptoms associated with isotretinoin treatment compared to topical therapy. Instead, researchers suggest that successful treatment of acne seems to improve both depressive and anxiety symptoms and improve quality of life.