ELSEVIER

Seminars in Cutaneous Medicine and Surgery

Preventing and Managing the Side Effects of Isotretinoin

Megan Brelsford, DO, LT, MC, USN,* and Trisha Clarke Beute, MD, LCDR, MC, USN†

Isotretinoin (13-*cis*-retinoic acid) is widely used for the treatment of severe acne as well as for disorders of conification, for psoriasis, and for skin cancer prevention. As a member of the retinoid family, it has a wide spectrum of side effects, including reproductive, cutaneous, ocular, neurological, musculoskeletal, and hepatic. As long as patients are able to tolerate these side effects, it can be a very effective treatment option. This article examines both the most common and the most concerning side effects as well as ways in which providers and patients may best manage them to be able to benefit from isotretinoin treatment.

Semin Cutan Med Surg 27:197-206 © 2008 Elsevier Inc. All rights reserved.

Isotretinoin, or 13-*cis*-retinoic acid, has been approved by the Food and Drug Administration for the treatment of severe nodulo-cystic acne since 1982. The sebaceous gland is particularly sensitive to this retinoid, which has been proven to be unique in its ability to create a lasting remission in the majority of acne patients. Most acne patients are treated for a short course, approximately 6 months, at low doses of 0.5 to 2 mg/kg/d. The total cumulative dose for a full course is 120-150 mg/kg. Isotretinoin is also used off-label for the treatment of disorders of cornification, rosacea, Gram-negative folliculitis, chemoprevention of skin neoplasms, psoriasis, myelodysplastic syndromes, and for hidradenitis suppurativa. In many of these indications, the courses of treatment are longer than in acne patients, and the cumulative dosage is significantly greater.

Although an effective and generally well-tolerated medication, isotretinoin also has a broad side effect profile. Many of the effects, especially those that are mucocutaneous, are fairly predictable and dose related. Isotretinoin and its side effects have received considerable public attention based on recent Food and Drug Administration scrutiny and from case reports associating it with depression and suicide. Most of the common side effects rarely necessitate the discontinuation of treatment and most spontaneously resolve shortly after cessation of treatment. This review will place an emphasis on the most common and the most concerning side effects.

Mechanism of Action

The exact mechanism of isotretinoin is not known. It is believed that 13-*cis*-retinoic acid exerts its action by isomerization to all-*trans*-retinoic acid, which then interacts with the retinoid receptors. It is the only acne medication that affects all 4 pathogenic factors of acne. Isotretinoin is comedolytic, reduces the sebaceous gland size (up to 90%), and decreases sebum production, which in turn inhibits *Propionibacterium acnes* and its ability to elicit inflammation. During the course of isotretinoin therapy, the pustular lesions generally clear first and the comedones are the last to resolve. Lesions on the face and upper arms tend to respond faster to isotretinoin than lesions on the trunk.

Teratogenicity

The most concerning side effects are teratogenicity and an increase in the rate of spontaneous abortion. Estimates of pregnancies that end in spontaneous abortions or congenital malformations are varied. A recent large population-based study of pregnancies to women who were taking isotretinoin during a 28-year period found that 84% of patients that became pregnant elected to terminate the pregnancy. This percentage is a greater one than previously reported. Of those pregnancies that were not electively terminated, estimates of

*Naval Medical Center; Portsmouth, Va.

†Department of Dermatology, Naval Medical Center Portsmouth, Portsmouth, VA.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

Reprint requests and correspondence: Trisha Clarke Beute, MD, LCDR, MC, USN, Department of Dermatology, Naval Medical Center Portsmouth, 620 John Paul Jones Circle, Portsmouth, VA 23708. E-mail: Trisha.Beute@med.navy.mil

1085-5629/08/$-see front matter
doi:10.1016/j.sder.2008.07.002

spontaneous abortions ranged from 3% to 20%.[1,2] Of those pregnancies that result in live births, approximately 48% to 82% of the children are healthy at birth.[3] There is not enough data to determine whether these infants progress to develop abnormalities. In one study, the authors followed children for 7 years after birth and found no incidence of further abnormalities.[2]

However, abnormalities in mental function have been reported in exposed infants with no gross malformations. It has been estimated that mental retardation may occur in approximately 30% of these children and impaired neuropsychological function in approximately 6%.[1] Of those pregnancies that result in live births, 18% to 47% have characteristic congenital malformations,[1,3] which is similar to the teratogenic syndrome associated with hypervitaminosis A. This characteristic pattern involves craniofacial, central nervous system, cardiovascular, and thymic abnormalities.[4] Craniofacial abnormalities include ear defects, dysmorphism, cleft palate, depressed nasal bridge, and hypertelorism. Central nervous system abnormalities include hydrocephalus, microcephaly, facial nerve palsy, and cortical and cerebellar defects. Cardiovascular abnormalities include tetralogy of Fallot, transposition of the great vessels, septal defects, and aortic arch hypoplasia. Thymic abnormalities include ectopis, hypoplasia, and aplasia. Other abnormalities reported include spina bifida and limb reduction.

There is no safe dose at any time during pregnancy,[3] and there have been various programs in place over the years to reduce pregnancy rates. The current and most recent is the iPLEDGE program, which requires the physician to enter a negative pregnancy result into the computer system before the pharmacist can dispense isotretinoin. The iPLEDGE program also requires that all women physically capable of bearing children, including those with a tubal ligation, should be on 2 forms of birth control. Examples of acceptable forms of contraception include tubal sterilization, vasectomy, intrauterine device (except a progesterone intrauterine device), hormonal oral contraception, condoms, diaphragm, cervical cap, and vaginal sponge with spermicide. Micro-dosed progesterone (mini-pill) contraception may be ineffective while using isotretinoin and should be avoided as a form of birth control during treatment. One study investigated the pharmacokinetics of ethinyl estradiol and norethindrone (ortho novum 7/7/7 / Ortho-McNeil, Raritan, NJ) in patients also taking isotretinoin at 1 mg/kg/d. There were small but statistically insignificant changes in ethinyl estradiol and norethindrone concentrations.[5]

The iPLEDGE program does allow the patient and provider to agree on the use of abstinence as a primary form of contraception. Given the potential consequences of a pregnancy while on isotretinoin, it is advised that the provider feel very comfortable in the maturity of a patient that desires to use this as their form of birth control. In the case that the patient is a young woman, it is important to obtain a sexual history while the parent/guardian is not in the examination room. Oftentimes a patient will falsely claim abstinence in the presence of a parent. It is critical that patients contemplating isotretinoin use give a reliable sexual history.

Before starting treatment, there must be at least 2 negative pregnancy tests that are sensitive to 25 mIU/mL and they must be spaced 30 days apart. At least one of the tests must be a serum test, rather than a urine test. The first test may be performed during a physician visit, but the second must be performed in a certified laboratory.[6] The second test must be during the first 5 days of menstruation and after the patient has used 2 forms of contraception for at least 1 month. All female patients should return to a certified laboratory once a month during treatment with isotretinoin to continue to demonstrate a negative pregnancy test. Management by pregnancy testing and effective contraception should be continued until at least 1 month after cessation of therapy.

Isotretinoin is cleared from the circulation in 1 month, and birth control measures can then be discontinued if a patient wishes to become pregnant.[6,7] The teratogenic risks of isotretinoin can be passed through blood transfusion to a pregnant woman so patients may not donate blood until 1 month after cessation of treatment.[6] Isotretinoin is also transmitted in breast milk, and women who are breastfeeding should not be taking isotretinoin.[8] Isotretinoin does not have long-term effects on fertility, and there have been no cases of retinoid malformations in children of men on isotretinoin.[8]

Despite the extensive counseling through both written materials, computer-driven quizzes, and patient counseling by a health care provider, there are still pregnancies that occur while a patient is taking isotretinoin. Predictors of pregnancy during isotretinoin treatment are lower socioeconomic level and high levels of health care usage.[2] Should a patient have a known or suspected failure in their 2 forms of contraception, they should discontinue isotretinoin immediately and, if desired, seek emergency contraception. Plan B (Duramed) and Preven (Gynetics) are the 2 FDA-approved forms of emergency contraception available both over-the-counter and through a health care provider. The risk of pregnancy decreases by approximately 75% if the first dose of emergency contraception is taken within 72 hours of intercourse and the second dose within 12 hours thereafter.[7] Whenever there is any question of possible pregnancy, the patient should undergo a pregnancy test. If it is negative but there is still a high suspicion of pregnancy, the test should be repeated.

Should the patient become pregnant, she should be referred for reproductive counseling and iPLEDGE should be notified. If the patient proceeds with the pregnancy, potential structural malformations are monitored by performing alpha-fetoprotein testing at 16 to 19 weeks of gestation as well as an ultrasound scan and echocardiography at 20 to 21 weeks of gestation.[1] In utero interventions may be possible.

The current iPLEDGE program does allow a patient to restart isotretinoin after having an unplanned pregnancy while on the medication. They are required to re-enroll and restart the process with 2 new negative pregnancy tests 30 days apart while using 2 forms of birth control. Having demonstrated unreliability in maintaining 2 forms of birth control despite the education involved in the iPLEDGE program, a second course of isotretinoin would not be advised.

Mucocutaneous Side Effects

Mucocutaneous events are by far the most common[9] isotretinoin side effects. A study of 2 safety trials[9] revealed that the most common adverse mucocutaneous side effects that patients complained about were cheilitis, chapped lips, dry skin, redness or rash, peeling, dermatitis, itching, epistaxis, mucosal dryness, and dry or irritated eyes. These side effects are often dose dependent, and it has been proposed that dividing the dosing into twice daily might decrease them. Cheilitis (Figure 1) is almost universal in patients on isotretinoin and it should be considered a treatment failure or an indication of noncompliance if it does not occur. Frequent application of lip balm or petrolatum can provide relief. Dry nasal mucosa and epistaxis occurs in approximately two-thirds of patients, and petrolatum may be applied to the nares as well. Generalized xerosis and pruritus occur in almost half of all patients, most commonly in those prone to atopy before treatment. Patients should be advised to liberally apply emollients and avoid triggers for pruritus and xerosis. Desquamation can occur in some patients but is not common.[10]

Many patients will also experience an initial worsening of their acne in the first month. If the patient does experience an initial flare, it will resolve with further treatment. An initial flare of acne can be avoided by starting patients at lower doses of isotretinoin during their first month of treatment. Less commonly, isotretinoin can induce acne fulminans. These cases are rare but, if they occur, treatment should be stopped or the dose decreased and systemic steroids initiated. One report found that a patient with acne fulminans was successfully treated with dapsone without using steroids.[11] Isotretinoin may be restarted at a very low dose after the episode is resolved and increased slowly.

Staphylococcal infections are increased in patients on isotretinoin therapy and topical antibiotics may decrease bacterial colonization.[12] There have not been any data on whether the carriage of methicillin-resistant *Staphylococcus aureus* has increased. Less commonly, patients may have stimulation of granulation tissue, leading to pyogenic granuloma eruptions in acne lesions, areas of trauma, and in nail folds (Figure 2). In most cases, these lesions resolve with cessation of therapy, but they may also necessitate the use of oral steroids or silver nitrate if they become fulminant.[13,14]

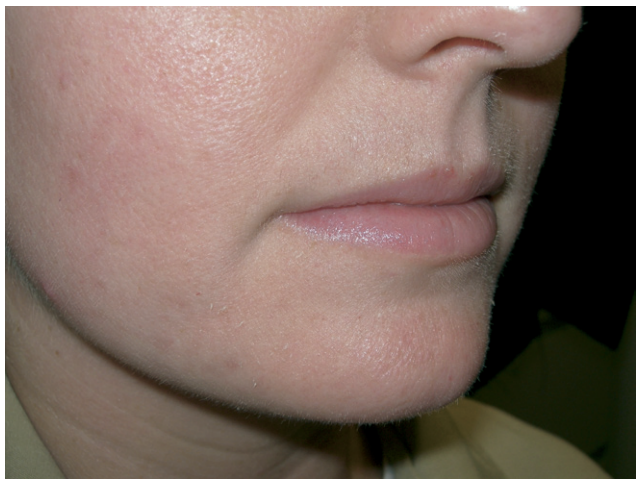

Figure 1 Mucocutaneous xerosis and cheilitis associated with isotretinoin.

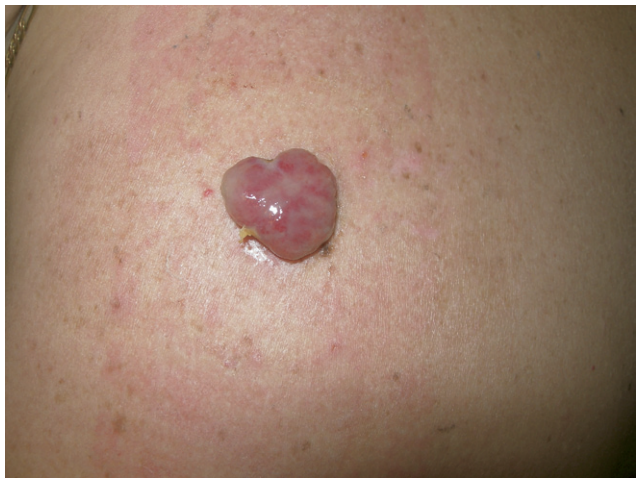

Figure 2 Pyogenic granuloma associated with isotretinoin.

Other types of mucocutaneous effects include diffuse alopecia and increased nail brittleness, most cases completely resolving within 2 months after ceasing treatment.[10] Skin atrophy and fragility often occur during treatment and, therefore, the patient should avoid dermabrasion and waxing while taking isotretinoin. Some authors recommend withholding any unnecessary skin procedure (ie, chemical peels, laser treatments) until 6 months after cessation of treatment to reduce the risk of scarring. The regular use of a lotion with ultraviolet protection should be used to prevent further skin irritation and most mucocutaneous side effects can be improved by the use of dexpanthenol cream, a vitamin B5 analog.[15]

There is anecdotal evidence that oral vitamin E (alpha-tocopherol) can ameliorate the side effects of isotretinoin.[16] Although used commonly with isotretinoin, the current literature is scant and conflicting. A small study addressing the use of vitamin E in older patients on high-dose (3 mg/kg/d) isotretinoin for the treatment of myelodysplastic syndromes suggests a favorable affect on the mucocutaneous side effects of chelitis, hyperkeratosis, and mucositis.[17] Vitamin E was taken at doses of 800 IU or greater, as compared with the recommended daily allowance of 30 IU. Vitamin E was as effective at 800 IU a day as it was at greater doses. However, a recent double-blinded, placebo-controlled study with 800 IU a day of vitamin E in patients on lower doses of isotretinoin (1 mg/kg) failed to demonstrate a significant difference in mucocutaneous side effects.[18]

The risks of prescribing vitamin E are minimal, and toxicity is rare. There are a few patient populations in which vitamin E usage may cause concern. It can prolong the prothrombin time in patients deficient in vitamin K and should not be used in patients that are anticoagulated. A recent meta-analysis suggests increases in mortality and heart failure with long term use of doses as low as 400 IU in patients with

chronic disease.[19] In patients older than 55 years of age with a history of vascular disease and diabetes mellitus, there also appears to be an increase in the risk of heart failure.[20] A study of patients with lung cancer suggests that vitamin E increases the cancer risk in those that smoke.[21] Finally, there is evidence that it may decrease the protective effect on HDL of some lipid-lowering agents and cause increases in triglycerides and cholesterol if taken with vitamin C and beta carotene.[22] Overall, if used in the main patient population taking isotretinoin (adolescents and young adults with acne), it is unlikely to cause problems. On the basis of the work of Besa and coworkers, a maximum dose of 800 IU a day is recommended. Interactions between vitamin E and isotretinoin have not been evaluated.[17]

Lipid and Hepatic Effects

Isotretinoin, like the other retinoids, is known to affect serum lipid levels. Estimates of the incidences of hypertriglyceridemia have varied from 25% to 44%.[23] It also affects cholesterol and low-density lipoprotein levels, with increases in approximately 30% of patients.[23] Of those with increased total cholesterol and triglycerides, high-density lipoprotein cholesterol was decreased in 20% to 25%.[24] Recent larger studies demonstrated that the lipid levels rarely elevate over double the upper limit of normal and are rarely significant enough to require cessation of therapy.[23,25] The most significant lipid elevations were observed in patients who already had elevated baseline laboratory values.[26] There was no correlation between the severity of laboratory value abnormalities and the dosage of isotretinoin. Patients who are overweight or who have increased baseline triglyceride levels are at greater risk for hypertriglyceridemia during treatment, but normal baseline triglyceride levels do not rule out the possibility of developing abnormalities.[9,23] Triglyceride elevations are most common in the first 2 months of treatment and levels rarely rise in the remainder of treatment.[26,27] Levels often return to baseline levels within 1 month of cessation of isotretinoin.[9]

Elevated serum triglyceride levels greater than 1000 mol/l are associated with a greater risk of pancreatitis. Despite the common occurrences of increased triglycerides with isotretinoin, there are few reported cases of pancreatitis, and some are confounded by concomitant administration of another medication known to cause pancreatitis.[28] Although isotretinoin should be used with caution in patients with a personal or family history of hypertriglyceridemia or pancreatitis, the chance of a patient developing pancreatitis is exceedingly rare. Medications that can cause pancreatitis should be avoided (Table 1).

Isotretinoin has been known to cause increased serum levels of liver enzymes in approximately 15% to 20% of patients. These levels usually normalize within a few weeks despite continuation of the medication[9] and are usually insignificant.[23,25,26] It is rare to develop changes in liver function if it has not presented within the first 2 months.[27] If pretreatment liver function tests are normal, the risk of hepatic disease is low, but again, does not preclude elevations.[23] Hepatitis has been associated with isotretinoin but studies have not found a causal relationship with chronic liver toxicity.[9]

Patients with a personal or family history of cardiac disease, pancreatitis, hypertriglyceridemia, hyperlipidemia, liver disease, or diabetes should be monitored closely and those with baseline laboratory values that are abnormal should have an evaluation before starting isotretinoin. If isotretinoin is used in high risk patients, close laboratory monitoring is needed (Table 2). The pharmaceutical insert to isotretinoin advises monitoring fasting serum lipid levels before, during, and after cessation of isotretinoin treatment and to conduct laboratory testing every 1 to 2 weeks at the beginning of therapy until the lipid response to isotretinoin has been established. On the basis of the aforementioned information, it appears that this level of testing is unlikely to be necessary unless the patient has a concerning history or elevated baseline values.

Before initiation of treatment with isotretinoin, patients should maintain a well-balanced diet low in cholesterol and fat with minimal alcohol consumption. The same measures are recommended for prevention of elevating liver and lipid laboratory values. Isotretinoin does not affect the overall risk for cardiac disease in young healthy patients, even in those experiencing significant lipid abnormalities during isotretinoin treatment.[29] However, those that do have elevations appear to be at greater risk for the development of metabolic syndrome later in life.[30]

Dietary supplementation has proven to decrease several of the side effects of isotretinoin. One study found that the use of fish oil (2.6 g of eicosapentaenoic acid and 2.4 g of docosahexaenoic acid, for 8 weeks) reduced triglycerides by 70% and cholesterol by 45% whereas high-density lipoprotein levels remained unaffected.[31] Cottonseed and soy protein have been found to reduce retinoid induced hypertriglyceridemia in an animal models without affecting treatment efficacy or the isotretinoin serum levels.[32-34] An animal model also found that replacing half of dietary casein with soy protein isolates[35] decreased levels of triglycerides and cholesterol. Vitamin E has been shown to improve the incidence of cholesterol and triglyceride elevation.[18] The use of dietary supplements may be a simple way of treating lipid side effects while allowing the patient to remain on an effective dose of isotretinoin.

Prescription drugs may be beneficial for patients when diet modification and supplementation is not enough to effectively treat or manage the effects of isotretinoin. Prescription omega-3-acid ethyl esters (Lovaza, GlaxoSmithKline, Middlesex, UK) have been effective for treatment of hypertriglyceridemia[36] and may potentially be useful for isotretinoin patients. The recommended dosage for effective triglyceride reduction is 2 to 4 g/d.[37] In patients with triglyceride levels >500 mg/dL, 4 g/d of omega-3 fatty acids have been shown to lower triglycerides by 45% and low-density lipoprotein cholesterol by 50%.[37] Prescription omega-3 fatty acids provide the benefit of ensuring consistent quality and purity by FDA standards as compared with over-the-counter options.

Fibrates (gemfibrozil at 300 to 600 mg twice daily, or fenofibrate at 200 mg capsule daily) and Niacin (starting at

Table 1 Medications to Avoid While Taking Isotretinoin*

Category	Medication
Medications that increase risk for vitamin A toxicity	Vitamin A
	Other members of retinoid family
Topical drying agents	Retin A
	Benzoyl peroxide
	Salicylic acid/glycolic acid
Medications associated with pseudotumor cerebri†	Cimetidine
	Corticosteroids
	Cyclosporine
	Danazol
	Levonorgestrel implant
	Levothyroxine
	Lithium
	Nalidixic acid
	Nitrofurantoin
	Pancreatin
	Recombinant growth hormone
	Tamoxifen
	Tetracycline/minocycline
	Trimethoprim-sulfamethoxazole
Medications that interfere with oral contraceptive pills	Rifampin
	St John's Wort
Birth control methods that are less effective when used with isotretinoin	Progesterone only mini-pill, progesterone intrauterine device‡
Medications that increase risk of bone loss	Phenytoin
	Corticosteroids
Medications that increase risk for liver toxicity§	Acetaminophen
	Benoxaprofen
	Duloxetine
	ETOH
	Felbamate
	INH
	Interferon beta-1a
	Kava Kava
	Nonsteroidal antiinflammatory drugs
	Phenytoin
	Phenelzine
	Propylthiouracil
	Sertraline
	Telithromycin
	Tienilic acid
	Tolcapone
	Trovafloxacin
	Zileuton
Medications associated with pancreatitis¶	Aminosalicylic acid compounds
	Azathioprine
	Corticosteroids
	Didanosine
	Estrogens
	Furosemides
	Octreotide
	Pentamidine
	Sulfonamides
	Sulindac
	Tetracycline
	Mercaptopurine
	Methyldopa
	Valproic acid

*There are many medications that patients should avoid while taking isotretinoin. Providers should be aware of these medications and review the mediation profile for each patient before initiation of treatment.

†Goodwin, J. Pseudotumor Cerebri, eMedicine. December 8, 2006.

‡Accutane product insert, Roche.

§Mehta N, Ozick L. Drug-Induced Hepatotoxicity. eMedicine, March 28, 2008.

¶Gardner TB, Berk BS, Yakshe P. Pancreatitis, Acute, eMedicine. July 20, 2006.

500 mg daily increasing by 500 mg monthly to 2000 mg daily) are both effective agents for controlling triglyceride levels and should also be an option considered to treat hypertriglyceridemia.[37] Statins, such as atorvastatin 10 to 80 mg daily or simvastatin 20 to 80 mg daily, are effective in reducing cholesterol but can potentially cause elevated transaminases, myopathy, or rhabdomyolysis.[38] The use of statins in isotretinoin patients with already known liver abnormalities or muscular side effects would not be advised. Prescription omega-3-acid ethyl esters may be used in combination with statins and fibrates for improved efficacy.[36] Finally, if lipids are not well controlled despite treatment, isotretinoin should be discontinued in high-risk patients.

Gastrointestinal Effects

Based only on anecdotal case reports, there is a possible association between isotretinoin therapy and both the development of new-onset inflammatory bowel disease and flares of preexisting disease.[39,40] These include the development of symptoms in both patients on isotretinoin therapy and in the years after therapy. Because the cause of inflammatory bowel disease is not known, it is difficult to know what level of concern to place on reports of patients who develop symptoms that are not temporally related to the course of isotretinoin. Some cases demonstrate remission and flares of inflammatory bowel disease on de-challenge and re-challenge.[39] However, patients with known ulcerative colitis have been treated successfully with isotretinoin without exacerbation of their condition,[40,41] and it appears that, at least in some European countries, the majority of patients with inflammatory bowel disease have not been exposed to isotretinoin.[42] The establishment of causality is clouded by the vagueness of the initial symptoms of inflammatory bowel disease and the fact that the average age of onset is during the young adult years. Further studies are needed before any definitive correlation between isotretinoin and inflammatory bowel disease can be assumed. Isotretinoin has been reported to cause nausea, diarrhea, and abdominal pain but this is uncommon.[10] If patients develop gastrointestinal symptoms, the medication should be stopped and an evaluation started. If there is a

Table 2 Guidelines for Laboratory and Radiological Studies*†‡§: Effective Prevention and Management of the Side Effects of Isotretinoin Include Obtaining Pretreatment Baseline and Regular Posttreatment Continuous Monitoring of Laboratory and Radiological Studies (These Studies Can Be Used to Optimize Treatment)

Radiological studies
Short-term therapy
Unnecessary unless symptomatic
Long-term therapy (>1 year):
Consider baseline plain films of spine and feet
Consider annual plain films of spine and feet
Repeat films at any time if symptomatic
Children
Consider baseline plain films of spine, feet, and evaluation of growth plates
Annual evaluation
Laboratory studies
HCG: in compliance with iPLEDGE program
Short-term therapy
Lipids: Baseline before therapy, repeat at 4 weeks and 8 weeks. If initial or 4 week or 8 week test elevated, then evaluate monthly. If elevated but cholesterol <300 mg/dL and triglycerides <400 mg/dL, institute diet modifications and consider lipid-lowering agent if not improving. If above these values, consider discontinuation of medication.
Hepatic panel: Baseline before therapy, repeat at 4 weeks and 8 weeks. If initial test elevated investigate possible causes and if isotretinoin is started continue to check monthly. If elevations <2 to 3× normal develop during therapy discuss habit modification such as avoidance of alcohol. If >2 to 3× normal discontinue medication.
CBC: Baseline before therapy. If initial test abnormal investigate possible causes and if isotretinoin is started continue to check monthly. If initial test normal repeat if abnormality is found or suspected.
Long-term therapy
Lipids: Same as short-term therapy. If normal after 4- and 8-week evaluations, continue to check periodically.
Hepatic panel: Same as short term therapy. If normal after 4- and 8-week evaluations, continue to check periodically
CBC: Baseline before therapy. If initial test abnormal investigate possible causes and if isotretinoin is started continue to check monthly. If initial test normal repeat if abnormality is found or suspected.
Other exams
Pilots and patients that rely on their night vision may consider baseline ophthalmology exam and retinal studies.

*Zane LT, Leyden WA, Marqueling AL, et al: A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. Arch Dermatol 142:1016-1022, 2006.

†Altman RS, Altman LJ, Altman JS: A proposed set of new guidelines for routine blood tests during isotretinoin therapy for acne vulgaris. Dermatology 204:232-235, 2002.

‡Ertam, Barth JH, MacDonald-Hull SP, Mark J, et al: Is it necessary to have routine blood tests in patients treated with isotretinoin? J Dermatol Ther 17:214-216, 2006.

§Barth JH, MacDonald-Hull SP, Mark J, et al: Isotretinoin therapy for acne vulgaris: A re-evaluation of the need for measurements of plasma lipids and liver function tests. Br J Dermatol 129:704-707, 1993.

family history of inflammatory bowel disease or concerning gastrointestinal symptoms before the initiation of therapy, evaluation by a gastroenterologist is advised.

Ocular Side Effects

Isotretinoin may cause several ocular side effects. One of the most commonly reported is sicca (dry eyes), which can be related to both atrophy of the meibomian glands[43] and changes in the tear film.[44] In rare instances, this complication may be irreversible. Patients experiencing sicca should stop wearing contact lenses and use wetting drops to avoid further complications. Many of the other ocular side effects, such as discomfort, keratitis, blepharoconjunctivitis, poor tolerance of contact lenses, increase in *S. aureus* colonization,[45] and photophobia.[46] are secondary to the sicca.

The most concerning ocular side effects are the loss of dark adaptation and the loss of color vision. Changes in color vision, and most cases of night blindness, resolve with cessation of the medication. There are rare cases of irreversible night vision loss,[47-49] which appear to be idiosyncratic and not related to cumulative dose as it has been reported at both low-dose as well as high-dose therapy.[48,49] The mechanism for the loss of night vision is likely related to the inhibition of ocular retinol dehydrogenases which decreases the amount of the visual chromophore 11-*cis*-retinal.[50] Isotretinoin can also cause corneal opacities but these do not usually affect vision.

Overall, the vast majority of ocular conditions will resolve with discontinuation of isotretinoin. It is not usually necessary to stop isotretinoin due to ocular side effects, although a decreased daily dose may be necessary. To decrease ocular risks, prospective patients should be verbally screened for preexisting problems with night vision, sicca, blepharoconjunctivitis and color vision. Those with preexisting problems may not be ideal candidates for isotretinoin treatment.[44] During treatment, the development of changes in night vision, changes in color vision, onset of headaches accompanied by visual disturbances, and significant dry eyes should prompt a referral to ophthalmology and cessation of therapy. Patients

with uveitis should wear ultraviolet protection lenses as isotretinoin is photosensitizing.[44] Patients with occupations that depend on their night vision will need a careful discussion of the low, but possible, risk of irreversible changes in their night vision. If treatment with isotretinoin is started, it may be prudent to have these patients screened by an ophthalmologist before treatment and at periodic intervals. Patients on a short course (less than one year) are not likely to need visual evaluation. Those on chronic or long term therapy should have an annual eye examination.[44]

Other than careful screening, there is currently no preventative therapy for the majority of ocular complications. Patients with sicca should use saline wetting drops or stop wearing contact lenses. Because it has been postulated that isotretinoin binds to the same ocular photoreceptor as vitamin A and thus decreases night vision by competitive inhibition, it has been suggested that vitamin A supplements may be helpful in patients that have experienced visual changes or that pretreatment with vitamin A could reduce the risk of these side effects.[51] There is currently no proof for this mechanism of action and, as the result of concern for hypervitaminosis A, this is not supported.

Bone and Muscle

The most common bone effects of isotretinoin are hyperostotic changes resembling diffuse idiopathic skeletal hyperostosis and calcifications of tendons and ligaments.[52] Hyperostotic changes affect all people, regardless of retinoid exposure, as they age. In retinoid-treated populations, hyperostosis occurs more commonly with increasing age, greater doses, and longer courses of treatment. The spine and feet are the most frequently involved areas earlier in treatment. Those hyperostoses that appear the earliest become the largest over time.[53] In the typical acne patients treated for short durations (especially at low doses of 0.5 mg/kg/d),[54] hyperostoses are not clinically significant. After 5 years of treatment, hyperostotic changes are present in the majority of patients on isotretinoin but they are still most commonly asymptomatic.[52,55] Appendicular, or extremity, hyperostosis occurs later and to a lesser extent. With the exception of one case report,[56] there have been no occurrences in patients on short courses of treatment. In older populations or in patients that are on chronic, long-term therapy, periodic x-rays may be advised, especially if the patient is symptomatic. If hyperostoses are found but are not asymptomatic, except perhaps in the case of involvement of the posterior longitudinal ligament, it is unlikely to cause the patient problems with continued therapy. Bisphosphonates have not been found to benefit retinoid bone changes but surgical removal can be successful.[52]

Other retinoid bone effects such as premature epiphysial closure and osteoporotic changes are less of a concern with isotretinoin than with other members of the retinoid family. Isotretinoin can cause premature epiphysial closure but most case reports are associated with high doses and long time periods[52]; in the short-term treatment of the acne population, this side effect is of little concern. There is little scientific support for osteoporosis associated with isotretinoin, nor is there support for reduced gains in bone mass in adolescents on isotretinoin.[57-59] To date, however, the largest study on bone mass and isotretinoin has been of approximately 200 patients, and this sample size may not be large enough to detect a small change in bone mass.

Myalgias (such as lower back pain and arthralgias) may be commonly experienced while on isotretinoin and have been reported in up to 50% of patients,[9] especially with increased exercise. They are rarely severe and can be managed with antiinflammatories. If pain is severe or not responsive to antiinflammatory drugs, the medication should be discontinued. Approximately 15% to 50% of isotretinoin patients with myalgias have been found to have elevated levels of creatine phosphokinase (CPK). CPK is not pathognomonic to isotretinoin induced myalgias and management by obtaining CPK levels is not indicated unless there is severe muscular pain.[60]

Neurological Effects

The current patient insert for isotretinoin warns that it may cause "depression, psychosis, suicide ideation and attempts."[61] The evidence for this association consists primarily of case reports and adverse event reports that stress a temporal relationship between isotretinoin use and the onset of depressive symptoms. The utility of these reports to demonstrate causality of depressive disorder and suicidality is poor because they are difficult to compare, provide little data on the dosages and patient risk factors, and do not distinguish between depressive symptoms and depressive disorder. Some are confounded by potentially important risk factors for suicide that were unrecognized and unrelated to isotretinoin, such as the presence of a gun in the home[62,63] and the use of lysergic acid diethylamide (ie, LSD) and cannabis.[64] Of these case reports, only a very few have demonstrated resolution of the symptoms with discontinuation of isotretinoin and then recurrence with rechallenge.

Review of the data is further clouded by the risk factors for suicide inherent in the young population that is most often prescribed isotretinoin. The adolescent age group has a high rate of suicide and poor impulse control. Acne patients in general appear to have greater rates of depression and anxiety.[65,66] A retrospective study comparing isotretinoin users to age- and sex-matched controls showed that isotretinoin users had a greater rate of depression at initiation of therapy.[67] Recent reviews of the literature on depression in acne patients with use of isotretinoin as well as cohort and population-based studies concluded that the current literature does not support a causal relationship between isotretinoin and depression.[62,63,67-71] Indeed, it appears that treatment with isotretinoin may actually decrease rates of depression[66,72] in patients, especially those with facial acne, experience less depressive symptoms after treatment with isotretinoin.[68,71,73] On the basis of estimates from 1998 US rate of suicides, the number of suicides expected from 1982 to 2000 for the number and ages of patients on isotretinoin, is much greater than that reported for isotretinoin adverse events

Table 3 Recommended Guidelines for History Screening*

Screening Category	History Screening Profile
Teratogenicity	Previous contraception failure on isotretinoin
	Contraception use and history
Laboratory abnormalities	Personal or family history of pancreatitis
	Personal or family history of hyperlipidemia
	Anemia
	Diet and exercise routine
	Alcohol use
Drug interactions	Prescribed medications
	Herbal medications or supplements
Neuropsychological	Depression or depressive symptoms
	Psychiatric disorder
	History of violence
	Substance abuse
	Headaches
Ocular	Night blindness
	Occupation
	Contact lens use
	Sicca
Gastrointestinal	Inflammatory bowel disease

*Providers should perform a thorough screening through a detailed history to optimize management of care during treatment with isotretinoin. This table represents the basic topics that should be covered during this process.

(400 versus 37).[70] The rate of suicides in this population is also well below the background rate expected based on census data.[67]

Other reported psychological effects include irritability, mood lability, and anger. Again, given the patient population that most often receives isotretinoin, it is difficult to establish causality. If patients are demonstrating any of these symptoms a decrease in dose or discontinuation may be appropriate.

Although retinoid receptors are present in the brain and retinoids have been shown to effect the dopamine systems, there is also no explained biological mechanism to support an association between isotretinoin and depressive symptoms. A recent study demonstrated decreased metabolism in the orbitofrontal cortex on positron emission tomography, a region of the brain that has been associated with depressive symptoms, of patients taking 1 mg/kg of isotretinoin for 4 months. The clinical importance of this is uncertain as the sample size was very small and patients did not demonstrate depressive symptoms but they did demonstrate headaches.[74]

It is prudent to screen all isotretinoin patients for depressive symptoms before the start of therapy, especially in light of the increase in depressive symptoms in this population. Should depressive symptoms be found, they should be evaluated by a mental health professional. However, as long as they are being monitored and close tracking is provided while on the medication, there is no data that exists to deny isotretinoin to patients with a history of depression.

The evidence for causality is much stronger for intracranial hypertension, or pseudotumor cerebri. New onset of severe headaches and visual changes, especially in the first 2 to 3 months of treatment, should raise concern. Other symptoms can include nausea, vomiting, diplopia, and pulsatile tinnitus. Concomitant use of other medications known to cause pseudotumor cerebri, such as the tetracyclines (Table 2), should be avoided, although the majority of reported cases were patients taking only isotretinoin.[75] Patients with a history of medication-induced pseudotumor cerebri from common acne medications may not necessarily develop it again with isotretinoin.[76] Patients with concerning symptoms should be referred to both ophthalmology and neurology for examination, lumbar puncture, and possible magnetic resonance imaging. Isotretinoin should be stopped and treatment with acetazolamide or steroids should be considered.[75]

Hematologic

Thrombocytopenia and neutropenia have been reported as complications of treatment, but they are rare.[25] Other than a baseline complete blood count to check for preexisting abnormalities, no monitoring is needed unless abnormalities are found or expected.[23]

Table 4 Isotretinoin Side Effect Management*

Side Effect Category	Management Recommendations
Teratogenicity	Routine pregnancy testing
	Two forms of reliable contraception
Lab abnormalities	Diet and exercise
	Prescreen personal and family history
	Baseline labs values
	Routine screening labs
	Treatment of abnormalities with diet supplements or prescription medications
Psychiatric	Prescreen personal and family history
	Routine screening history
	Treatment of depression or psychiatric disorder
Mucocutaneous	Sunblock use
	Lip balm, emollient use
	Avoidance of laser treatments, dermabraision, waxing, or chemical peels
Ocular	Wetting drops
	Sunglass use

*Shown are general guidelines for management of the side effects of isotretinoin. Routine follow-up evaluations are critical for prudent care. Patients should be well equipped with the knowledge of the side-effect profile and know how to prevent or improve these effects.

Long-Term Side Effects/Efficacy

Various studies have investigated the risk factors for poor response or the need for a second course. The most important factor seems to be the dosage, with patients receiving a cumulative dosage of <120 mg/kg experiencing greater rates of relapse (82% versus 30%).[77] In keeping with this, current dosage recommendations are >120 mg/kg to 150 mg/kg total. The greater the severity of acne at the onset of therapy and the longer the length of time that the acne has been present also correlates with a greater risk for relapse.[77,78] Truncal acne appears to be more resistant than facial. Those patients that do relapse most commonly do so in the first year and rarely after the third year post treatment.[77] The side effects were not worsened with successive courses and there does not appear to be evidence of tolerance, thus allowing multiple courses to be given if necessary.

Conclusion

Overall, isotretinoin in a very well-tolerated medication. The most common side effects include mucocutaneous events and myalgias. Long-term side effects are infrequent, occurring in less than 10% of the patient population, and they are usually mild, requiring little to no treatment.[79] With both proper screening and preventative measures (Tables 3 and 4), isotretinoin remains a valuable tool in the treatment of acne.

References

1. Sladden MJ, Harman KE: What is the chance of a normal pregnancy in a woman whose fetus has been exposed to isotretinoin? Arch Derm 143:1187-1188, 2007
2. Berard A, Azoulay L, Koren G, et al: Isotretinoin, pregnancies, abortions and birth defects: A population-based perspective. Br J Clin Pharm 63:196-205, 2007
3. Dai WS, LaBraico JM, Stern RS: Epidemiology of isotretinoin exposure during pregnancy. J Am Acad Dermatol 26:599-606, 1992
4. Lammer EJ, Chen DT, Hoar RM: Retinoic Acid Embryopathy. N Engl J Med 313:837-841, 1985
5. Hendrix CW, Jackson KA, Whitmore E, et al: The effects of isotretinoin on the pharmacokinetics and pharmacodynamics of ethinyl estradiol and norethindrone. Clin Pharmacol Ther 75:464-475, 2004
6. The Guide to Best Practices for the iPLEDGE Program, iPLEDGE program, 2 December 2007
7. Goldsmith LA, Bolognia JL, Callen JP, et al: American Academy of Dermatology Consensus Conference on the Safe and Optimal Use of Isotretinoin: Summary and recommendations. J Am Acad Dermatol 50:900-906, 2004
8. Wolverton SE, Patton TJ, Zirwas MJ: Systemic retinoids, in Wolverton SE (ed): Comprehensive Dermatologic Therapy (ed 2). Philadelphia, PA, Saunders, 2007, pp 275-300
9. McLane J: Analysis of common side effects of isotretinoin. Am Acad Dermatol 45:S188-S194, 2001
10. Ellis CN, Krach KJ: Uses and Complications of isotretinoin therapy. J Am Acad Dermatol 45:S150-S157, 2001
11. Tan BB, Lear JT, Smith AG: Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. Clin Exp Dermatol 22:26-27, 1997
12. Leyden JJ, James WD: *Staphylococcus aureus* infection as a complication of isotretinoin therapy. Arch Dermatol 123:606-608, 1987
13. Exner JH, Dahod S, Pochi PE: Pyogenic granuloma-like acne lesions during isotretinoin therapy. Arch Dermatol 119:808-811, 1983
14. Lane PR, Hogan DJ: Granulomatous lesions appearing during isotretinoin therapy. Can Med Assoc J 130:550, 1984
15. Romiti R, Romiti N: Dexpanthenol cream significantly improves mucocutaneous side effects associated with isotretinoin therapy. Pediatr Dermatol 19:368, 2002
16. Lebwohl M: Clinical pearl: Vitamin E (alpha-tocopherol), 800 IU daily may reduce retinoid toxicity. J Am Acad Dermatol 41:260, 1999
17. Besa EC, Abrahm JL, Bartholomew MJ, et al: Treatment with 13-*cis*-retinoic acid in transfusion dependent patients with myelodysplastic syndrome and decreased toxicity with addition of alpha-tocopherol. Am J Med 89:739-747, 1990
18. Strauss JS, Gottlieb AB, Jones T, et al: Concomitant administration of vitamin E does not change the side effects of isotretinoin as used in acne vulgaris: A randomized trial. J Am Acad Dermatol 43:777-784, 2000
19. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al: Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 142:37-46, 2005
20. Lonn E, Bosch J, Yusuf S, et al: HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. JAMA 293:1338-1347, 2005
21. Slatore C, Littman AJ, Au DH, et al: Long term use of supplemental multivitamins vitamin C, vitamin E and folate does not reduce the risk of lung cancer. Am J Respir Crit Care Med 177:524-530, 2008
22. Brown BG, Zhao XQ, Chait A, et al: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 345:1583-1592, 2001
23. Zane LT, Leyden WA, Marqueling AL, et al: A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. Arch Dermatol 142:1016-1022, 2006
24. Bickers DR, Saurat J: Isotretinoin: A state of the art conference. J Am Acad Dermatol 45:S125-S128, 2001
25. Ertam, Barth JH, MacDonald-Hull SP, et al: Is it necessary to have routine blood tests in patients treated with isotretinoin? J Dermatol Treat 17:214-216, 2006
26. Barth JH, MacDonald-Hull SP, Mark J, et al: Isotretinoin therapy for acne vulgaris: A re-evaluation of the need for the measurements of plasma lipids and liver function tests. Br J Dermatol 129:704-707, 1993
27. Altman RS, Altman LJ, Altman JS: A proposed set of new guidelines for routine blood tests during isotretinoin therapy for acne vulgaris. Dermatology 204:232-235, 2002
28. Flynn WJ, Freeman PG, Wickboldt LG: Pancreatitis associated with isotretinoin – induced hypertriglyceridemia. Ann Intern Med 107:63. 1987
29. Lestringant GC, Frossard PM, Agarwal M, et al: Variations in lipid and lipoprotein levels during isotretinoin treatment for acne vulgaris with special emphasis of HDL-cholesterol. Int J Dermatol 3:859-862, 1997
30. Rodondi N, Darioli R, Ramelet A: High risk for hyperlipidemia and the metabolic syndrome after an episode of hypertriglyceridemia during 13-*cis*-retinoic acid therapy for acne: A pharmacogenetic study. Ann Intern Med 136:582-589, 2002
31. Marsden JR: Effect of dietary fish oil on hyperlipidaemia due to isotretinoin and etretinate. Hum Toxicol 6:219-222, 1987
32. Radcliffe JD, Glass AC: Dietary cottonseed protein can reduce the severity of retinoid-induced hypertriglyceridemia. Cancer Detect Prev 18:401-406, 1994
33. Radcliffe JD, Czaika-Narins DM: A Comparison of the effectiveness of soy protein isolate and fish oil for reducing the severity of retinoid-induced hypertriglyceridemia. Nutr Biochem 15:163-168, 2004
34. Radcliffe JD, Imrhan VL, Hsueh AM: The use of soy protein isolate to reduce the severity of 13-*cis* retinoic acid-induced hypertriglyceridemia. Cancer Detect Prev 22:526-532, 1998
35. Radcliffe JD, Czajka-Narins DM: Partial replacement of dietary casein with soy protein isolate can reduce the severity of retinoid-induced hypertriglyceridemia. Plant Foods Hum Nutr 52:97-108, 1998
36. Bays HE, Tighe AP, Sadovsky R, et al: Prescription omega-3 fatty acids and their lipid effects: Physiologic mechanisms of action and clinical implications. Expert Rev Cardiovasc Ther 6:391-409, 2008

37. McKenney JM, Sica D: Role of prescription omega-3 fatty acids in the treatment of hypertriglyceridemia. Pharmacotherapy 27:715-728, 2007
38. Armitage J: The safety of statins in clinical practice. Lancet 24;370: 1781-1790, 2007
39. Reddy D, Siegel CA, Sands BE, et al: Possible association between isotretinoin and inflammatory bowel disease. Am J Gastroenterol 101: 1569-1573, 2006
40. Godfrey KM, James MP: Treatment of severe acne with isotretinoin in patients with inflammatory bowel disease. Br J Dermatol 123:635-636, 1990
41. Schleicher S: Oral isotretinoin and inflammatory bowel disease. J Am Acad Dermatol 13:834-835, 1985
42. Guslandi M: Isotretinoin and inflammatory bowel disease. Am J Gastroenterol 102:1546-1547, 2007
43. Mathers WD, Shields WJ, Sachder MS, et al: Meibomian gland morphology and tear osmolarity: changes with accutane therapy. Cornea 10:286-290, 1991
44. Fraunfelder FT, Fraunfelder FW, Edwards R: Ocular side effects possibly associated with isotretinoin usage. Am J Ophthalmol 132:299-305, 2001
45. Bozkurt B, Irkec MT, Atakan N, et al: Lacrimal function and ocular complications in patients treated with systemic isotretinoin. Eur J Ophthalmol 12:173-176, 2002
46. Fraunfelder FW: Ocular side effects associated with isotretinoin. Drugs Today 40:23-27, 2004
47. Maclean H, Wright M, Choi D, et al: Abnormal night vision with isotretinoin therapy for acne. Clin Exp Dermatol 20:86, 1995
48. Mollan SP, Woodcock M, Siddiqi R, et al: Does the use of isotretinoin rule out a career in flying? Br J Ophthalmol 113:305-212, 2006
49. Halpagi P, Grigg J, Klistorner A, et al: Night blindness following low dose isotretinoin. J Eur Acad Dermatol Venereol 22:893-894, 2007
50. Law WC, Rando RR: The molecular basis of retinoic acid induced night blindness. Biochem Biophys Res Commun 161:825-829, 1989
51. Danby FW: Night blindness. Vitamin A deficiency, and isotretinoin psychotoxicity. Dermatol Online J 9:30, 2003
52. DiGiovanna JJ: Isotretinoin effects on bone. J Am Acad Dermatol 45: S176-S182, 2001
53. Pennes DR, Martel W, Ellis CN, et al: Evolution of Skeletal hyperostoses caused by 13-*cis*-retinoic acid therapy. AJR Am J Roentgenol 151:967-973, 1988
54. Carey BM, Parkin GJS, Cunliffe WJ, et al: Skeletal Toxicity with isotretinoin therapy: A clinico-radiological evaluation. Br J Dermatol 119:609-614, 1988
55. Tangrea JA, Kilcoyne RF, Taylor PR, et al: Skeletal hyperostosis in patients receiving chronic, very-low-dose isotretinoin. Arch Dermatol 128:921-925, 1992
56. Stitik TP, Nadler SF, Foye PM, et al: Greater trochanter enthesopathy: An example of "short course retinoid enthesopathy": a case report. Am J Physical Med Rehab 78:571-576, 1999
57. Kocijancic M: 13-cis-Retinoic acid and bone density. Int J Dermatol 34:733-734, 1995
58. Margolis DJ, Attie M, Leyden JJ: Effects of isotretinoin on bone mineralization during routine therapy with isotretinoin for acne vulgaris. Arch Dermatol 132:769-774, 1996
59. DiGiovanna JJ, Langman CB, Tschen EH, et al: Effect of a single course of isotretinoin therapy on bone mineral density in adolescent patients with severe. Recalcitrant, nodular acne. J Am Acad Dermatol 51:709-717, 2004
60. Kaymak Y: Creatine phosphokinase values during isotretinoin treatment for acne. Int J Dermatol 47:398-401, 2008
61. Roche Pharmaceuticals: Accutane: Isotretinoin. Roche Laboratories Inc. (pharmaceutical insert information). Available at http://www.rocheusa.com/products/accutane/pi.pdf. Accessed October 2007
62. Jacobs DG, Deutsch NL, Brewer M: Suicide, depression, and isotretinoin: Is there a causal link? J Am Acad Dermatol 45:S168-S175, 2001
63. Strahan JE, Raimer S: Isotretinoin and the controversy of psychiatric adverse effects. Int J Dermatol 45:789-799, 2006
64. Kovacs So, Mallory SB: Mood changes associated with isotretinoin and substance abuse. Pediatr Dermatol 13:350, 1996
65. Yazici K, Baz K, Yazici AE, et al: Disease specific quality of life is associated with anxiety and depression in patients with acne. J Eur Acad Dermatol Venereol 18:435-439, 2004
66. Kellett SC, Gawkrodger DJ: The psychological and emotional impact of acne and the effect of treatment with isotretinoin. Br J Dermatol 140: 273-282, 1999
67. Hull PR, D'Aracy C: Acne, depression and suicide. Dermatol Clin 23: 665-674, 2005
68. Chia CY, Lane W, Chibnall J, et al: Isotretinoin therapy and mood changes in adolescents with moderate to severe acne. Arch Dermatol 141:557-560, 2005
69. Cohen J, Adams S, Patten S: No association found between patients receiving isotretinoin for acne and the development of depression in a canadian prospective cohort. Can J Clin Pharmacol 14:e227-e233, 2007
70. Wysowski DK, Pitts M, Beitz J: An analysis of reports of depression and suicide in patients treated with isotretinoin. J Am Acad Dermatol 45: 515-519, 2001
71. Marqueling AL, Zane LT: Depression and suicidal behavior in acne patients treated with isotretinoin: A systemic review. Semin Cutan Med Surg 24:92-102, 2005
72. Gupta MA, Gupta AK, Schork NJ, et al: Psychiatric aspects of the treatment of mild to moderate facial acne. Some preliminary observations. Int J Dermatol 29:719-721, 1990
73. Rubinow DR, Peck GL, Squillace KM, et al: Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. J Am Acad Dermatol 17:25-32, 1987
74. Bremner JD, Fani N, Ashraf A, et al: Functional brain imaging alterations in acne patients treated with isotretinoin. Am J Psychiatry 162: 983-991, 2005
75. Fraunfelder FW, Fraunfelder FT, Corbett JJ: Isotretinoin-associated intracranial hypertension. Ophthalmology 111:1248-1250, 2004
76. Bettoli V, Borghi A, Ferroni M, et al: Pseudotumor cerebri does not appear during oral isotretinoin therapy after a previous episode with minocycline for acne: Report of a case. J Am Acad Dermatol 52:P21, 2005
77. Layton AM, Knaggs H, Taylor J, et al: Isotretinoin for acne vulgaris—10 years later a safe and successful treatment. Br J Dermatol 129:292-296, 1993
78. Stainforth JM, Layton AM, Taylor JP, et al: Isotretinoin for the treatment of acne vulgaris: Which factors may predict the need for more than one course? Br J Dermatol 129:297-301, 1993
79. Goulden V, Layton AM, Cunliffe WJ: Long-term safety of isotretinoin as a treatment for acne vulgaris. Br J Dermatol 131:360-363, 1994