

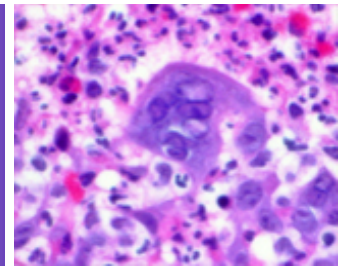


eLITERATURE REVIEW

eMedicalDermatology Review

Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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October 2011: Volume 3, Issue 1

Welcome to Volume 3 of eMedicalDermatology Review

As we begin Volume 3, we want to welcome back our returning subscribers, say hello to our newly registered clinicians, and thank the more than 3700 of you receiving this issue for your involvement in this program. In Volume 3, we'll continue to provide you with current, clinically relevant data important to helping you improve outcomes in your patients, delivered via 6 bi-monthly newsletters and 6 case-based podcasts. Topics scheduled for this volume include: infantile hemangiomas, urticaria, UV therapy beyond psoriasis, laser derm surgery and controversies in biologic therapy for psoriasis.

Isotretinoin Updates

In this Issue...

Severe nodulocystic acne often requires treatment with isotretinoin, a drug that carries with it many side effects. Of note, depression is a concern in patients taking isotretinoin, and other adverse events such as xerosis and cheilitis are extremely common and may be dose-related. While isotretinoin is extremely effective, some patients require multiple courses of therapy.

In this issue, we review updates on isotretinoin treatment dosages, regimens, and the relationship to depression.

LEARNING OBJECTIVES

After participating in this activity the participant will demonstrate the ability to:

- Identify various isotretinoin dosing regimens for the treatment of acne vulgaris
- Describe common adverse events associated with isotretinoin and their relationship to dosage
- Discuss how new research on isotretinoin will affect physicians' treatment paradigms

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October 11, 2011

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October 10, 2013

Next Issue

November 8, 2011

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Guest Faculty Disclosures

Joshua Zeichner, MD has disclosed that he has received grants for clinical research and is a consultant to CORIA Laboratories. He also disclosed that he has worked as a consultant for and received honorarium from Galderma Laboratories, Ortho Dermatologics, PreCision Dermatology, as well as a grant for research from Medicis Pharmaceutical Corp.

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COMMENTARY

Severe nodulocystic acne is a skin disease characterized by erythema, inflammation, nodules, cysts, and scarring. Patients run the risk of permanent scarring of the skin after the active lesions resolve. Moreover, the disease has a psychological impact and can interfere with the patient's quality of life.¹ Aggressive treatment may be used to quickly and effectively treat the skin and help avoid permanent scarring. Oral isotretinoin has become the gold standard in treating these severe acne cases.²

The pathogenesis of acne is multi-factorial. Isotretinoin addresses several of these pathogenic factors, which explains its therapeutic effect. Isotretinoin reverses follicular hyperkeratosis, decreases sebum production, suppresses proliferation of *P. acnes*, and helps reduce inflammation.³ In addition, unlike other acne medications, isotretinoin is capable of inducing a long-term suppression of sebaceous gland activity.⁴

The approved dosage of isotretinoin is between 0.5 - 2.0 mg/kg/day, usually given over a 20 week course. However, variable dosing regimens are used.⁵ Most experts treat patients at a dose of 0.5 mg/kg/day for the first month and increase the dose to 1.0 mg/kg/day for the duration of therapy. Treatment usually lasts around 20 weeks, although longer courses may be used for more severe cases.² In addition, in some severe cases, concurrent use of oral prednisone (0.5 – 1.0 mg/kg/day for 2-6 weeks) may be administered to reduce the risk of a severe exacerbation after initiating oral isotretinoin.⁶ Evidence-based

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recommendations are lacking, although several clinical trials have been published evaluating high dose, low dose, and intermittent dosing regimens.^{7, 8}

While oral isotretinoin is extremely efficacious in treating acne, it carries with it many side effects. Most commonly, patients commonly develop xerosis and cheilitis. A recent study has shown these side effects to be dose-dependent and to occur significantly more frequently in patients on higher doses of isotretinoin.⁹ Other potential side effects include headache, hyperlipidemia, alopecia, myalgia, fatigue, and visual disturbances.¹⁰

Pseudotumor cerebri is another documented adverse event from isotretinoin.⁹ Concurrent use of tetracycline antibiotics and isotretinoin should be avoided, as tetracycline class antibiotics carry their own risk of pseudotumor cerebri.¹¹

Isotretinoin has been associated with depression, and suicidal ideation was added to the drug's label in 1998. Studies evaluating the association with depression have shown mixed results. In November 2010, the American Academy of Dermatology (AAD) issued a position statement on the issue. "A correlation between isotretinoin use and depression/anxiety symptoms has been suggested but an evidence-based causal relationship has not been established. Other studies give evidence that treatment of acne with isotretinoin was accompanied by improvement of both depressive and anxiety symptoms, as well as improved quality of life of patients with acne."¹²

Isotretinoin is a teratogen, and prescriptions have become regulated because the significant risk for birth defects in pregnant women exposed to the drug.¹³ The iPLEDGE distribution program is a risk management program regulated by the United States Food and Drug Administration. To be enrolled, female patients of childbearing potential must demonstrate two negative pregnancy tests. In addition, they must use two forms of birth control. Male patients must also be registered into the system. All parties involved in isotretinoin distribution, including physicians and pharmacists, are obligated to abide by the iPLEDGE regulations.

Since the 1980's, isotretinoin has been questionably linked to inflammatory bowel disease (IBD)^{14,15}, although clinical trials evaluating this association have shown conflicting results. In 2009, Bernstein and colleagues published a case-control study of patients diagnosed with inflammatory bowel disease within the Canadian health care system. The group found no correlation between isotretinoin and ulcerative colitis or Crohn's disease.¹⁶ A 2010 large case-controlled study did find an association between isotretinoin and ulcerative colitis, but not Crohn's disease.¹⁷ Despite these data, there are reports in the literature of patients with both Crohn's disease¹⁸ and ulcerative colitis¹⁹ treated with isotretinoin without exacerbation of their disease.

In the November 2010 updated isotretinoin position statement, the AAD published the following comment on the potential association of isotretinoin and IBD. "Current evidence is insufficient to prove either an association or a causal relationship between isotretinoin use and inflammatory bowel disease (IBD) in the general population. While some recent studies have suggested such a relationship further studies are required to conclusively determine if the association or causal relationship exists and/or whether IBD risk may be linked to the presence of severe acne itself...The Association concludes that the prescription of isotretinoin for severe nodular acne continues to be appropriate as long as prescribing physicians are aware of the issues related to isotretinoin use, including IBD or psychiatric disturbance, and educate their patients about these and other potential risks. Physicians also should monitor their patients for any indication of IBD and depressive symptoms."¹²

Isotretinoin has revolutionized the way dermatologists treat acne and is the drug of choice for patients with severe, nodulocystic disease. Current research continues to improve our understanding of how to maximize treatment outcomes while minimizing potential adverse events.

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VARIABLE DOSING REGIMENS FOR ISOTRETINOIN

Lee JW, Yoo KH, Park KY, et al. **Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study**. *Br J Dermatol*. 2011 Jun; 164(6): 1369-75.



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Isotretinoin has been traditionally dosed to obtain a total cumulative dose of 120-150 mg/kg. However, various dosing regimens have been used to obtain this cumulative dose: many prescribers employ a low-dose regimen (<0.5 mg/kg/day) over longer periods of time in an attempt to minimize dose related side effects, such as skin dryness and cheilitis, while others may start out at a low dose for the first month, then raise the dose to a conventional 1.0 mg/kg/day regimen. Moreover, there are those who believe that an intermittent treatment regimen is best. Patients may receive variable pulsed therapies, ranging from every other day, once weekly, or one week per month. There is a paucity of evidence-based data comparing these different regimens.

In this study, the authors directly evaluated efficacy and safety of 3 different dosing regimens in South Korea. The first group was treated using traditional doses of isotretinoin (0.5-1.0 mg/kg/day), the second with low doses (0.25 -0.4 mg/kg/day), and the third with intermittent doses (0.5-0.7 mg/kg/day, for one week per month).

Sixty patients with moderate acne were randomized 1:1:1 into one of the 3 groups. Patients were evaluated every 4 weeks for a 24 week treatment period, with an additional visit 1 year post-treatment. Efficacy measurements included a global severity assessment as well as inflammatory and noninflammatory lesion counts. Safety measurements included blood work at each visit, recording of adverse events, and a patient satisfaction survey at the end of treatment.

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The investigators found a statistically significant difference in all efficacy scores of both the high and low dose continuous regimens compared to the intermittent treatment group ($p=0.001$ and $p=0.044$, respectively). However, there was no significant difference in these efficacy scores between the high and low dose groups. Patient satisfaction was highest in the low dose regimen group, followed by the intermittent treatment group. Patients in the conventional dose group were the least satisfied in the study. However, there was no statistical significance in the satisfaction rating between the continuous therapy groups. Adverse events, such as skin irritation, were most common in the conventional dose, continuous therapy group. At the one year follow-up visit, the investigators found no statistically significant difference in relapse rate between the continuous therapy groups (13% in the conventional dosing group and 18% in the low-dose group). There was a significant difference between both the conventional and low-dose groups compared to the intermittent therapy group (56%), $p=0.002$ and $p=0.015$, respectively.

Based on their findings, the authors concluded that conventional and low-dose dosing regimens are equally efficacious. Intermittent treatment, on the other hand, is less efficacious than either of the continuous dose regimens. Based on satisfaction scores and prevalence of adverse events, the investigators concluded that the low-dose, continuous therapy group was the recommended regimen.

This study offers excellent, evidence-based data on which treatment recommendations can be made. The only limitation of the study, however, is the small sample size used. Larger numbers of patients must be evaluated, especially when assessing the small percentage of patients who relapse.

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Coloe J, Du H, Morrell DS. **Could higher doses of isotretinoin reduce the frequency of treatment failure in patients with acne?** *J Am Acad Dermatol.* 2011 Aug; 65(2): 422-3.

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Several studies over the past decade have concluded that lower cumulative doses of isotretinoin may increase the rate of acne relapse. The authors of this research letter attempted to answer the question of whether higher cumulative doses of isotretinoin are associated with lower relapse and/or re-treatment rates. In this case, *acne relapse* is defined as a worsening of acne after conclusion of therapy, requiring treatment. *Re-treatment* is defined as a relapse severe enough to necessitate an additional course of isotretinoin.

The investigators performed a retrospective chart review evaluating 102 patients treated with isotretinoin for at least 4 months consecutively, and who were followed for at least one year. Of these, 45.1% experienced a relapse after treatment, and 15.7% required re-treatment.

There was no statistical significance in patients who relapsed and those who did not in terms of cumulative isotretinoin dose, treatment duration, and dose during the last treatment month. However, there was a statistically significant difference between the patients who required a re-treatment and those who did not, $p=0.009$. Patients who received a cumulative dose greater than 218.8 mg/kg were less likely to require a second course of isotretinoin compared to patients who received lower doses. Moreover, female patients had a 4.1 times greater risk of requiring a re-treatment.

The authors concluded that treating patients with higher doses may lead to less severe recurrences and a lower need for an additional course of isotretinoin.

There were a few limitations to this chart review. First, the sample size was relatively small. Second, the severity of adverse events was not graded, so no associations between dose and adverse events could be made. Finally, there was a significantly longer follow-up time for the patients requiring re-treatment compared to those who did not, $p=0.011$.

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DOSE-RELATED ISOTRETINOIN ADVERSE EVENTS

Rademaker M. **Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin.** *Australasian J Dermatol.* 2010 Nov; 51(4):248-53

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Many dermatologists choose to prescribe isotretinoin at low doses over extended periods of time to minimize side effects that are likely dose-related. However, much of this data is anecdotal and pooled expert opinion. In this study, the investigators performed a retrospective review evaluating adverse events and their relation to isotretinoin dosage.

A private dermatology practice in New Zealand provided 1,743 patient charts for evaluation. Treatment doses were divided into the following ranges: very low (≤ 0.25 mg/kg/day), low (0.26–0.50 mg/kg/day), medium (0.51–0.75 mg/kg/day), and high (0.76–1.0 mg/kg/day). "Excellent" or "skin clear" efficacy was observed in >90% of patients in all treatment groups.

The most common side effects observed in all isotretinoin-treated patients were cheilitis, eczema, and mood changes. Each of these was found to be dose dependent. Overall, cheilitis developed in 78.4% of patients, and both eczema and tiredness occurred in 12.1% of patients. Eighteen-point-five percent of patients reported no side effects, the majority of whom were taking very low doses of isotretinoin.

The largest difference in adverse events were observed when comparing very low dose and high dose isotretinoin. When taken at high doses, 96.4% of patients developed cheilitis. On the other hand, only 47.1% of patients develop cheilitis when taking low dose isotretinoin. Similarly, eczema was observed in 15.8% of patients on high dose isotretinoin, as compared to only 7.3% on the lower dosed regimen. Finally, tiredness developed in 17.9% of patients in the high dose group versus 5.5% in the low dose group.

Isotretinoin has been associated with depression and suicidal ideation, with depression being added to the drug's prescribing information over a decade ago. Many studies have evaluated this association, giving mixed results. In this study, there were no recorded instances of suicidal ideation or attempted suicide. Mood change was reported in 7.1% of all patients, which dropped to 4.5% and 4.7% in the very low and low dose groups. Most cases of mood change were preceded by tiredness, and were self-reported as mild in severity. Mood change and tiredness lead to discontinuation of therapy in a small number of patients, 13 and 12 patients respectively. All of the patients recovered, and 8 of the 13 patients with mood changes were successfully re-treated with isotretinoin in the future.

The main limitation of the study stemmed from the fact that it was retrospective. Long-term patient follow up was not addressed, and less common adverse events may have been under-reported as they were not specifically asked about.

Based on their findings, the authors concluded that isotretinoin has a low side effect profile when prescribed at lower doses. Moreover, with the exception of 2 pregnancies due to failure of contraception, there were no adverse events.

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LIPID ABNORMALITIES AND ISOTRETINOIN

Rodondi N, Darioli R, Ramelet AA, et al. **High risk for hyperlipidemia and the metabolic syndrome after an episode of hypertriglyceridemia during 13-cis retinoic acid therapy or acne: a pharmacogenetic study.** *Ann Intern Med.* 2002 Apr 16; 136(8): 582-9.

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Hyperlipidemia is a well-known potential side-effect associated with isotretinoin, which usually resolves after discontinuation of the drug. The mechanism of action of this phenomenon is not completely understood. Throughout the course of treatment, prescribers commonly monitor their patients with fasting lipids panels. There is no consensus on how to proceed treating these patients. The dose of isotretinoin may be decreased when triglycerides exceed a particular cutoff level, but standard guidelines have not been established.

The primary objective of this Swiss study was to assess whether isotretinoin is a trigger for the metabolic syndrome and to identify a potential genetic susceptibility to hyperlipidemia. One hundred-two patients with a significant increase in triglycerides while on isotretinoin (hyper-responders) and 100 patients who did not have an increase (non-responders) were evaluated via waist-to-hip ratio, fasting glucose, insulin, lipid levels, and ApoE genotype. These parameters were re-evaluated 4 years post-treatment. In addition, parents of the patients were evaluated.

Investigators found that both hyper- and non-responders had similar pretreatment body weights and lipid levels. However, there were significant differences uncovered at the 4 year post-treatment follow-up. Patients who were lipid hyperresponders during isotretinoin therapy were more likely to have elevations of their triglycerides and cholesterol. In addition, they demonstrated truncal obesity, as measured by an increased waist-to-hip ratio, and increased insulin levels, $p < 0.001$.

Interestingly, a genetic predisposition for hyperlipidemia was uncovered. Hyper-responders were found to have at least one parent with hypertriglyceridemia. In addition, the investigators discovered a close association with the presence of the ApoE gene. They conclude that a significant increase in triglycerides during isotretinoin therapy for acne is a risk factor for the metabolic syndrome and hypertriglyceridemia in the future. In addition, the patients' parents are at risk. Therefore, patients who have undergone isotretinoin therapy should be closely monitored by their health care providers for the metabolic syndrome.

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ISOTRETINOIN AND DEPRESSION

Sundstrom A, Alfredsson L, Sjolín-Forsberg G, et al. **Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study.** *BMJ*. 2010 Nov 11; 341: c5812.

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Suicidal ideation is listed in the prescribing information for isotretinoin, and all patients should be monitored for depression during their course of therapy. This association, however, is controversial and studies evaluating it have shown mixed results. In this Swedish retrospective, cohort study, the investigators assessed the risk of attempted

suicide before, during, and after isotretinoin treatment.

The investigators assessed 5,756 patients who received isotretinoin for severe acne. Patient records were followed from 3 years pre-treatment up to 15 years post-treatment. Attempted suicide rates were assessed by reviewing hospital discharge records for isotretinoin patients who attempted suicide. Patients ranged in age from 15-49 years old, with a total of 128 patients identified as having been admitted to the hospital for attempted suicide.

A causal relationship between isotretinoin and attempted suicide was not identified. The attempted suicide risk in severe acne patients was actually lower during the treatment period than it was during both the pre- and post-treatment period. Moreover, patients who attempted suicide before isotretinoin actually had fewer suicide attempts during treatment compared to patients who had not previously attempted suicide before treatment. Interestingly, the attempted suicide rate in severe acne patients was elevated in the year before initiation of isotretinoin therapy. This was true both for patients with first attempts

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Step 3.

Complete the post-test and course evaluation.

and multiple suicide attempts. Additionally, in the 6 month period after isotretinoin treatment, the attempted suicide risk was even higher than before treatment. Only after 3 years after isotretinoin therapy did the attempted suicide risk lower to that of the general population.

Collectively, these findings support the argument that a history of depression in patients with severe acne should not automatically prevent them from being treated with isotretinoin. Independent of the questionable link between isotretinoin and depression, acne itself has a significant psychosocial impact and can influence patients' quality of life. All patients with severe acne must be carefully monitored before, during, and after treatment for depressive symptoms.

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Step 4.
Print out your certificate.

PHYSICIAN
POST-TEST

NURSE
POST-TEST

