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ABOUT THE AUTHOR

Vincent Richer, MD, FRCPC

Dr. Vincent Richer practices medical and cosmetic dermatology at Pacific Derm in Vancouver. He holds the position of Clinical Associate Professor at the University of British Columbia's Department of Dermatology and Skin Science. He trained at Université de Montréal in Medicine and Dermatology and completed a fellowship in Photobiology and Cutaneous Laser Surgery at UBC.

Affiliations: Dermatologist, Pacific Derm
Clinical Associate Professor, University of British Columbia Department of Dermatology and Skin Science, Vancouver, British Columbia

Safety and Monitoring Update on Isotretinoin

Vincent Richer, MD, FRCPC

Introduction

Canadian dermatologists frequently encounter fear and misconceptions of isotretinoin among patients and the general public. In contrast, few medications in dermatology have been as transformative: since its introduction, isotretinoin has dramatically changed the treatment of acne through its potential for providing long-term remission (**Figure 1**). Initial consultations in which isotretinoin is proposed are often lengthy and emotionally charged, with substantial discussion devoted to drug safety, treatment monitoring, and risk-mitigation strategies. This article provides an evidence-based update on select safety concerns surrounding isotretinoin, including well-established and serious risks, concerns that have been confidently refuted, and some less common issues frequently raised by patients based on their own research.

Pregnancy and Teratogenicity

Unlike some of the more controversial concerns surrounding isotretinoin, its teratogenic effects are unequivocal and remain the single most critical safety consideration when prescribing this medication to women of childbearing potential.

In Canada, 3.1 pregnancies per 1,000 female isotretinoin users were reported between 1996 and 2011.[1] In the United States, isotretinoin use is tightly regulated via iPLEDGE, a mandatory United States-Food and Drug Administration safety program designed to prevent fetal exposure to isotretinoin. Despite this, 3,347 isotretinoin-exposed pregnancies were reported in the United States from 2006–2020.[2]

With this in mind, prescribing isotretinoin requires disclosure of this risk, discussion about sexual activity and the potential for pregnancy, establishment of appropriate contraception, routine urine pregnancy testing, and clear

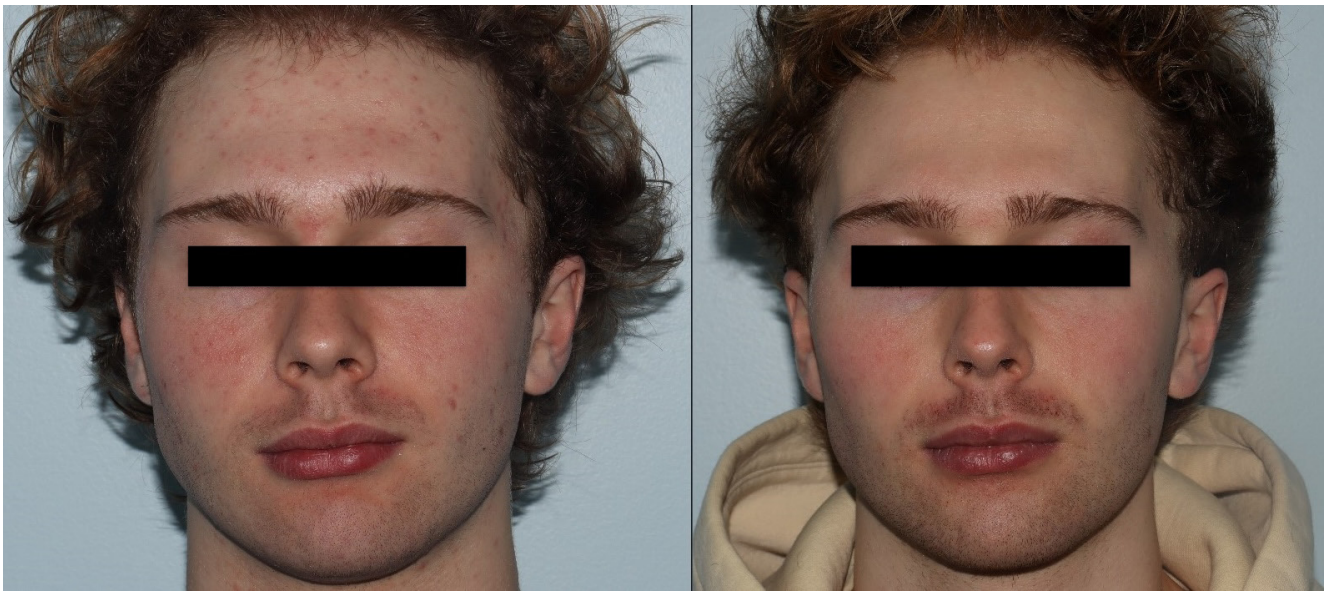

Figure 1. Moderate persistent acne that was insufficiently responsive to topical treatments in an adult patient treated with isotretinoin. The potential for long-term remission with isotretinoin treatment coupled with an improved understanding of its safety profile has allowed for an expansion of its clinical indications in the Canadian practice landscape; *courtesy of Vincent Richer, MD, FRCPC*.

counselling about the indication for a medical abortion in the event of a pregnancy during treatment. A key challenge is achieving an appropriate balance between the safe use of the treatment and maintaining access without imposing unnecessary regulatory burdens.

Depression and Mental Health

A possible link between isotretinoin and depression remains one of the most emotionally charged issues in dermatology. Historically, case reports and anecdotal experiences raised concerns that isotretinoin might directly trigger depression, anxiety, or suicidal ideation. These concerns led to the introduction of black box warnings and the recommendation for extensive psychiatric screening protocols.

The challenge in interpreting this link is that patients with severe acne causing scars were being treated with isotretinoin, a condition that is itself strongly associated with depression, social withdrawal, anxiety, and reduced quality of life.[3] Treatment of acne with multiple modalities has been demonstrated to improve quality of life and reduce depression scores. Large retrospective cohort studies and meta-analyses have failed to demonstrate a causal relationship between isotretinoin and depression in the general population. In fact, many reports suggest a positive impact on quality of life and mental health in patients who complete treatment with isotretinoin.[4] However, these findings are counter-balanced by adverse event reporting databases that continue to collect individual cases of mood disorders, including suicidal ideation, during treatment.

This nuance is best addressed directly in discussions with patients. Current evidence does not suggest that isotretinoin universally increases depression risk, however, some individuals may experience idiosyncratic mood changes during treatment. Notably, acne itself is a major confounding factor. Rather, many dermatologists have observed improvements in psychological well-being and self-confidence among their patients during treatment.

Inflammatory Bowel Disease

The possible association between isotretinoin and inflammatory bowel disease (IBD) has been debated for years; however, this controversy is one that has been more clearly refuted. Early

observational studies and class action lawsuits amplified public concern, leading many patients to believe that isotretinoin directly causes IBD.

The association between IBD and isotretinoin does not persist when controlling for factors such as antibiotic use, acne severity, and oral contraceptive use.[4] It is unclear if prolonged antibiotic use in the context of acne treatment may induce gut microbiome dysbiosis and affect IBD development risk. Furthermore, severe acne and inflammatory disorders may share underlying immune or genetic predispositions independent of isotretinoin exposure. These variables have been confirmed as confounders in large cohort analyses. For example, the TriNetX network study compared more than 81,000 exposed patients with 1.9 million controls and reported very reassuring hazard ratios (HR): IBD overall (HR: 0.88, 95% confidence interval [CI]: 0.49–1.57), ulcerative colitis5 (HR: 1.05, 95% CI: 0.78–1.41), and Crohn's disease (HR: 0.69, 95% CI: 0.51–0.94).

In light of such reassuring datasets, most experts do not consider isotretinoin a proven cause of IBD.

Peanut Allergy and Isotretinoin

Canadian dermatologists may be surprised to note that peanut allergy is mentioned as a contra-indication to treatment with isotretinoin in the British and European product monographs. However, isotretinoin formulations contain no peanut protein; this labelling stems from historical concerns of cross-reactivity between peanuts and soy, as both are legumes. Isotretinoin is often formulated in refined soybean oil, which is considered safe not only for patients with peanut allergy but is also considered generally safe for patients with soy allergy. Patients with clinical and prick-test positive peanut allergy have been successfully and safely treated with isotretinoin.[6]

Premature Closure of Epiphyseal Plates

Premature epiphyseal plate closure is a rare but important theoretical concern associated with systemic retinoids, and is likely to be a concern for the parents of children who have not yet reached full growth, especially if their anticipated height may be below average.

Although isolated case reports exist in the literature, usually in the context of high-dose treatment in oncology, clinically significant growth disturbances from standard acne dosing remain exceptionally uncommon. A recent publication analyzed insurance data from 2005–2021 and used patients treated with antibiotics as the control group.[7] While a reduced height velocity was observed during treatment with isotretinoin, there was no difference in the final adult height between the groups.

Overall, current evidence does not support widespread concern regarding growth impairment with typical isotretinoin treatment courses used for acne in preadolescents—a population in whom severe acne may have the greatest long-term psychosocial and scarring consequences.

Diminished Night Vision

One of the other considerations during isotretinoin treatment is diminished night vision. Though this effect is rarely reported by patients, it is thought to be potentially problematic for pilot performance.[8] The Federal Aviation Agency recommends restricting the use of isotretinoin to >2 weeks before flying; otherwise a medical exam or clearance is required to fly. This constitutes another factor to consider when weighing the risks and benefits of treatment, particularly for student pilots.

Laboratory Monitoring

While routine monthly pregnancy tests continue to be recommended during isotretinoin treatment, laboratory monitoring of liver enzymes, lipids, and other parameters has come under significant scrutiny in recent years. The intensive monitoring schedule highlighted in the original Accutane© monograph (every 1–2 weeks initially!) had already been challenged in clinical practice prior to systematic reviews, meta-analyses, and letters to the editor began calling for reduced laboratory monitoring more than a decade ago.[9]

Laboratory changes from baseline were overwhelmingly not clinically relevant, and

usually emerge within 8 weeks of the initiation of treatment.[10] In the absence of liver disease or metabolic syndrome, it has been recommended to assess liver enzymes and lipids at baseline and again at 8 weeks, with further follow-up on any identified abnormalities only. Routine complete blood count (CBC) monitoring is no longer recommended in the absence of preexisting abnormalities.

Recent articles extend this discussion further in the pediatric population, suggesting that decisions regarding laboratory monitoring should be customized to the individual given the rarity of severe side effects and the lack of evidence of preventable adverse outcomes. In a pediatric outpatient clinic study, 165 patients underwent 708 laboratory tests; all laboratory abnormalities were attributed to preexisting baseline findings or non-fasting samples.[11]

Furthermore, new evidence highlights that laboratory monitoring practices may reflect gender bias. Female patients are more likely to undergo more CBC, liver function, and lipid laboratory testing, likely due to these tests being ordered simultaneously with pregnancy testing as part of standing orders, rather than requested based on clinical indications.[12] Authors also emphasize that urine pregnancy tests are preferred over serum testing, both to reduce health care costs and to avoid the risk of false-positive results in the context of anti-heterophile antibodies.

Isotretinoin in the Era of Modern Medicine: Telemedicine and Artificial Intelligence

Although the application and practicality of telemedicine in dermatology has been limited in scope, acne is one of the conditions that can be treated reliably via remote care. A recent study[13] examined the rate of incomplete isotretinoin courses delivered via telemedicine and compared them to with those from in-person adult and pediatric clinics. While 27% of telemedicine-treated courses were incomplete, higher rates were observed in in-person adult (37%) and in-person pediatric (49%) clinics. These findings suggest that telemedicine is well-suited to providing ongoing access to isotretinoin.

Lastly, patients are increasingly turning to artificial intelligence (AI) chatbots for medical information. When evaluated systematically and compared, commonly used AI chatbots provided accurate information, with ChatGPT and Gemini outperforming Copilot.[14] However, all systems scored comparatively poorly on readability, highlighting the need for future AI models to better account for the limited health literacy of the general public.

Conclusion

One of the challenges with prescribing isotretinoin is that it exists at the intersection of dermatology, medicine, psychology, internet culture, and historical controversy. Patients often arrive having encountered alarming information online—some of which is legitimate, while other concerns are disproportionately amplified beyond what the evidence supports. The clinician's responsibility is not to oversimplify in either direction, but to engage in a balanced and nuanced discussion of risks and benefits with our patients. Isotretinoin remains one of our most valuable tools—not because it is risk-free, but because its long-term benefits are well established and its risks are well defined and manageable.

Correspondence

Vincent Richer, MD, FRCPC
Email: vincent.richer@ubc.ca

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