American Journal of Clinical Dermatology (2020) 21:411–419
https://doi.org/10.1007/s40257-020-00508-0

THERAPY IN PRACTICE

Optimizing Isotretinoin Treatment of Acne: Update on Current Recommendations for Monitoring, Dosing, Safety, Adverse Effects, Compliance, and Outcomes

Megan N. Landis[1,2]

Published online: 27 February 2020

Abstract
Acne vulgaris is the most common skin disease treated by dermatologists. It can be severe and result in permanent scars. Isotretinoin is the most effective treatment for acne and has the potential for long-term clearance. Prescribing and monitoring protocols can vary widely among prescribers. Recent studies, reports, and consensus statements help shed light on optimizing the use of isotretinoin for acne. A recent literature review is summarized in this article to help the practitioner optimize isotretinoin use for acne. The article outlines the advantages and disadvantages of standard, high-dose, and low-dose isotretinoin regimens; discusses the current status of controversies surrounding isotretinoin (including depression/suicide, pregnancy, and inflammatory bowel disease); reviews monitoring recommendations and treatment for hypertriglyceridemia and elevated transaminase levels; and discusses common adverse effects seen with isotretinoin, along with their treatment and prevention.

1 Introduction

Acne vulgaris is one of the most common diseases encountered by dermatologists, affecting approximately 80% of the population at some point during their lives [1]. Oral isotretinoin has been available since 1982 and has resulted in significant improvement in the lives of numerous acne patients. Despite its unparalleled efficacy, isotretinoin continues to have controversies surrounding it, most of which are based on scant data, opinion, or anecdote; however, the potential array of adverse effects and potential risk of birth defects must be taken into consideration. Recent large-scale reviews have helped shed light on pregnancy risk and prevention, mental health disorders, and inflammatory bowel disease (IBD). The controversies surrounding isotretinoin have limited and restricted its use due to unplanned pregnancies and misinformation leading to unwarranted fears among parents, guardians, and patients who could benefit from the

Key Points

Isotretinoin monitoring recommendations for otherwise healthy patients include the baseline lipid profile, and liver profile (including alanine aminotransferase and aspartate aminotransferase) at baseline and around month 2, or when peak daily dose is achieved. However, γ-glutamyltransferase may be more indicative of liver injury. Creatine kinase may be monitored in physically active patients.

High, low, and low intermittent dosing regimens have been reported to be well tolerated and with varying degrees of efficacy. The standard dosing regimen (achieving a cumulative dose of 120–150 mg/kg) is associated with some recurrences but there are limitations of previous studies. The current recommendation based on consensus is to treat until the acne is clear, and continue for 1 more month. Patients with more severe disease may require higher cumulative doses.

Patient counseling, use of patient-independent contraception, and limiting the 'use' of abstinence to previously sexually inactive women only may decrease fetal exposure to isotretinoin.

✉ Megan N. Landis
meganlandis08@yahoo.com

[1] Department of Medicine (Dermatology), University of Louisville School of Medicine, Louisville, KY, USA

[2] The Dermatology and Skin Cancer Center of Southern Indiana, Corydon, IN, USA

medication. Isotretinoin has been life-changing for numerous patients and is currently the only treatment available to have a long-term potentially curative effect on acne. Acne can produce significant scarring, both physical and psychological, but early and effective acne treatment can prevent these problems.

Recent advances and studies are helping to clarify ideal dosing regimens and ideal cumulative threshold dosing. Additionally, recent reviews and recommendations help support more standardized laboratory evaluations.

The aim of this article was to review what is new in dosing and adherence when using isotretinoin to treat acne vulgaris. The article will discuss safety, potential adverse effects and how to manage them, and laboratory monitoring to help practitioners optimize their use of oral isotretinoin in treating patients with acne.

2 Methods

The information provided herein is a summary of recently published studies and guidelines gathered by a review of the current literature regarding isotretinoin and acne. When the author's clinical experience is considered, it is noted.

3 Indications

Oral isotretinoin is indicated for patients with severe and/or treatment-resistant acne vulgaris. It is the most effective acne treatment currently available and the first-line treatment for patients with severe cystic, nodular, or other actively scaring acne [2]; however, all acne lesions, not only cysts and nodules, have the potential to result in permanent scars. Thus, when first-line treatments are ineffective for patients with moderate acne, isotretinoin may be considered. The recommendations from the American Academy of Dermatology guidelines, as well as other organizations around the world, is to limit the use of oral antibiotics to minimize and avoid the development of antibiotic-resistant bacteria [3]. Systemic antibiotics can be used for the acute management of acne, but then discontinued after 3–4 months whenever possible, with the goal of maintaining improvement with topical therapy such as a topical retinoid and/or topical antimicrobial agent. When unable to sustain skin clearance of acne, isotretinoin may be considered. Early and aggressive acne treatment can prevent permanent scarring of the skin. Oral isotretinoin is the most effective treatment of acne vulgaris, and the best option to potentially have long-term sustained clearance.

4 Potential Adverse Effects and Their Management

With the exception of its teratogenic effects, the adverse effects of isotretinoin are generally mucocutaneous, dose-dependent, and reversible with discontinuation of the medication [4, 5].

4.1 Mucocutaneous Adverse Effects

The most common adverse effects resemble symptoms of hypervitaminosis A, including dryness of lips, skin, and eyes. It is helpful to emphasize to patients the importance of gentle skin care, including the avoidance of other topical acne treatments that may be irritating while taking isotretinoin. A non-soap, gentle cleanser, and generous gentle emollient application can help prevent xerosis and skin irritation while taking isotretinoin.

Dryness of lips occurs in nearly all patients (90–100%) [6]; frequent and generous applications of petroleum jelly or a similar emollient can help minimize dryness. When severe, hydrocortisone 1% balm is available over-the-counter.

Dryness of nasal and oral mucosa occurs in 30–50% of patients. Moisturizing with petroleum jelly or saline products to the nares is generally effective.

Dry eyes and blepharoconjunctivitis occurs in approximately 14% of patients and can typically be controlled with ocular lubricants [7]. These adverse effects are common but are dose-dependent, manageable, and transient, improving and/or resolving with dose decreases and/or cessation of therapy [4, 5, 8].

4.2 Systemic Adverse Effects

Headaches are commonly reported in patients taking isotretinoin but at rates similar to the general population and not extreme in intensity or duration. However, while rare, headaches also occur in more serious conditions, including pseudotumor cerebri, and may need to be evaluated if persistent, severe, and/or associated with vision changes or vomiting [5].

Joint and muscle aches are reported in approximately 15% of patients and can typically be monitored and treated with a non-steroidal anti-inflammatory drug or aspirin if needed [5, 8].

4.3 Depression

The concern and controversy over the potential association with depression and suicide is based on uncommonly reported cases [9, 10]. Additionally, acne itself causes depression, anxiety, and other psychological issues [11–13].

Multiple studies have found no causative effect between isotretinoin and depression; however, these studies are epidemiologic and cannot exclude an idiosyncratic adverse reaction in an individual [14–19]. Several studies have shown improvement in anxiety and depression following isotretinoin treatment for acne [20–22].

Nonetheless, reports of depression and suicide while taking isotretinoin do exist [9, 23]. The patient's overall health and well-being is most important and there is a high baseline rate of anxiety, depression, suicide, and suicidal ideation in young adults (the population most commonly affected by acne requiring isotretinoin treatment).

A meta-analysis of 31 controlled studies found no evidence of increased depression or suicide rates during isotretinoin treatment [24]. Depression scores improved with acne treatment; however, with possible idiosyncratic individual reactions to isotretinoin and the overall high risk of depression and suicide in adolescents and young adults, it is important to screen patients for depression and mood issues before and during the course of isotretinoin. If patients have a history of or active depression, they can often be co-managed with their mental health provider. If mood issues arise while taking isotretinoin, the medication can be stopped while mental health issues are addressed [25]. Open communication between the isotretinoin prescriber, the patient and family, and the mental health care provider is key.

4.4 Pregnancy

Isotretinoin is a teratogen that was initially documented following its 1982 release, with several reports of congenital malformations [26]. Three different risk management programs have been implemented since that time, with each program being more restrictive but no more effective in preventing the approximately 150 pregnancy exposures that occur yearly [27, 28]. The iPledge program, currently in place in the US, was established in 2006 and requires women of childbearing potential to abstain or to commit to using two forms of contraception for the duration of the course of therapy and for at least 30 days after completion of the isotretinoin course. Patients must have two negative pregnancy tests 1 month apart before starting isotretinoin, and monthly thereafter. Approximately one-third of women admitted to non-compliance with contraception practices [28]. Increased use of patient-independent contraception and limiting the 'use' of abstinence to previously sexually inactive women only may decrease fetal exposure to isotretinoin [28]. Contraceptive education is required, especially patients' understanding of the relative effectiveness of various forms of birth control (i.e. that no single form of birth control is 100% effective), which proves the need for two forms of contraception [29].

4.5 Inflammatory Bowel Disease

The association between IBD (including both Crohn's Disease and ulcerative colitis) continues to be proven to be controversial and with little evidence. While some studies showed a possible association [30, 31], more recent larger studies have shown no association between isotretinoin and IBD [32–35].

5 Laboratory Monitoring and Interpretation

In the past, laboratory monitoring for patients taking isotretinoin varied widely among prescribers, at times being obtained monthly; however, a recent series has helped to standardize monitoring. For healthy patients, it is recommended to perform liver function tests (typically alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and lipid profile (ideally fasting) at baseline and at month two (or when peak dosing is achieved) [36]. Further testing may be considered if fasting values are significantly abnormal or their medical or family history indicates a higher risk [37].

The most common laboratory abnormality seen in patients taking isotretinoin is elevation of triglycerides, which normalizes to patient's own baseline following cessation or completion of the isotretinoin treatment course [38, 39]. Elevations in triglyceride levels during short courses of isotretinoin typical for the treatment of acne are a marker of atherosclerosis risk, not a cause of it [40–43]. The importance of noting triglyceride elevation during the treatment course is to note the potential increased atherosclerosis risk later in life; prolonged and continuous use of isotretinoin in patients with underlying lipid disorders is not recommended [44]. The short-term concern and reason triglycerides are monitored while taking isotretinoin is concern for the development of hypertriglyceride-induced pancreatitis, which is extremely rare, with only four reports in nearly 40 years [40].

When triglycerides are elevated, it can be helpful to repeat the test and be certain the patient was fasting. For moderate elevations (300–500 mg/dL) of triglycerides, recommendations include weight reduction, increased physical activity, and a low-fat, low-carbohydrate, low-alcohol diet. Recent reports found that omega-3 fatty acid supplements may be a useful adjunct to manage triglyceride levels in patients taking isotretinoin, especially those with elevated triglyceride levels at baseline [45–48].

When triglyceride levels are over 500 mg/dL, the isotretinoin dose can be decreased, in addition to the lifestyle and diet changes previously mentioned. If the triglyceride levels remain elevated, treatment with a lipid-lowering agent may be required (such as a fibric acid derivative, niacin, or statin). Triglyceride elevations > 800 to 1000 mg/dL can cause

pancreatitis and isotretinoin may need to be stopped until lipids are better managed. Pancreatitis rarely develops while taking isotretinoin; it occurs idiosyncratically more commonly than due to hypertriglyceridemia. While it is a rare complication, patients should be aware of the symptoms of pancreatitis [40]. Lipid elevations are reversible upon cessation of isotretinoin; however, it has been shown that these patients often have lipid issues later in life (independent of isotretinoin) [42].

Liver function tests traditionally often refer to ALT and AST when monitoring isotretinoin patients; however, these markers are also present in muscle tissue and red blood cells and correlate more with creatine kinase (CK) levels. This suggests elevated AST and ALT may correlate more with muscle than liver tissue [49]. γ-Glutamyltransferase (GGT) may be more specific for liver injury during isotretinoin therapy.

One may consider checking serum CK levels, especially in physically active patients. Some experts recommend checking baseline CK levels in all patients, and regular monitoring in those with baseline abnormalities and/or athletes engaging in strenuous physical activity [49, 50]. There is no current consensus on this but at least one documented death from rhabdomyolysis has been reported (CK levels over five times the normal value) [51]. Patients who have CK levels approaching or exceeding five times the reference value may discontinue or reduce strenuous physical activity or isotretinoin dosage until the CK level approaches their individual baseline pre-isotretinoin level [50] (see Table 1 for a summary of laboratory monitoring recommendations).

6 Dosing

Isotretinoin is often initiated at a dose of approximately 0.5 mg/kg/day when treating severe acne, to minimize severe flaring at the start of treatment. The dose is then increased toward 1 mg/kg/day, as tolerated by the patient, as adverse effects (especially cheilitis and xerosis) often increase with higher doses [8] (see Fig. 1 for an isotretinoin prescribing checklist). Patients with very severe acne at baseline may require starting at an even lower dose of isotretinoin with or without concomitant oral corticosteroids to prevent a severe flare and increased risk of scarring, also known as pseudo acne fulminans [3]. One recommended protocol is to start prednisone 0.5–1.0 mg/kg/day for 4–6 weeks, then gradually decrease the dose. Oral isotretinoin can be continued at 0.5 mg/kg/day and increased gradually, while the prednisone is tapered [52, 53].

After the introduction of isotretinoin, a target dose range of 120–150 mg/kg over a 4- to 6-month time period was recommended to improve remission rates and decrease recurrences [54, 55]; however, a systematic literature review [56] found the cumulative dose target range was based on studies that were not designed to evaluate the role of cumulative dose on relapse rates [57]. Another retrospective chart review of over 1400 patients treated with isotretinoin found 22% required a second course of therapy (follow-up time ranging from 12 months to 5 years), and neither the daily nor the cumulative dose had an effect on the relapse rate as long as treatment was continued for at least 2 months after the complete resolution of acne lesions [57]. The 2018 consensus statement from the Global Alliance to Improve Outcomes in Acne agreed and concluded that a good target for isotretinoin dosing recommends treating until the acne is completely clear and continue for 1 more month [25]. Based on the author's anecdotal evidence, especially in seeing different prescribing habits and approaches, the two targets (120–150 mg/kg vs. treating until clear and then continuing for an additional month) often end up resulting in the same endpoint. Patients with more recalcitrant disease may require higher cumulative doses to clear their skin [58].

Table 1 Management of laboratory abnormalities

Laboratory abnormality	Treatment
Elevated triglycerides	
300–500 mg/dL	Weight reduction; exercise; low fat, low carb, low alcohol diet. Consider omega-3 supplement [48, 76]
> 500 mg/dL	Action recommended. Decrease isotretinoin dose. Consider omega-3 supplement. Consider a lipid-lowering agent (fibric acid derivative, statin, or niacin). Monitor lipids more frequently [37]
> 800 to 1000 mg/dL	Can cause pancreatitis [77]. Consider stopping isotretinoin until lipids are controlled
Transaminase elevation	
Two to threefold increase	Consider a dose decrease. Recheck in 2 weeks. May need to stop isotretinoin if no improvement [78]
A more than threefold increase	Immediate cessation of therapy [79]
Creatine kinase[a]	
Levels approaching or exceeding five times the reference value	± Discontinue or reduce strenuous physical activity or isotretinoin dosage until the creatine kinase level approaches the individual baseline pre-isotretinoin level [49]

[a]Consider in physically active patients, at baseline. May monitor regularly in those with baseline abnormalities and/or athletes engaging in strenuous physical activity

Pretreatment:

- ☐ *Pregnancy Test*
- ☐ *Confirm two forms of contraception OR abstinence*
- ☐ *Enroll in iPledge system (United States)*

- ☐ Lipid Profile (ideally fasting)
- ☐ Liver Function Tests (LFTs), (+/- Gamma-glutamyltransferase (GGT))[2]

- ☐ (+/-CK)[1]

Month 1 (Treatment Start):

- ☐ *Pregnancy Test*
- ☐ Lipids (if not previously obtained, ideally fasting)
- ☐ LFTs (+/-GGT)[2](if not previously obtained),
- ☐ (+/-CK)[1]
- ☐ Start isotretinoin: 0.5mg/kg/day (or lower to prevent flare in severe patients)

Month 2:

- ☐ *Pregnancy Test*
- ☐ (+/-CK)[1]
- ☐ Increase isotretinoin: 1mg/kg/day divided bid (if patient tolerating)

Month 3:

- ☐ *Pregnancy Test*
- ☐ Lipid Profile (ideally fasting)
- ☐ Liver Function Tests (LFTs), +/- Gamma-glutamyltransferase (GGT)[2]
- ☐ (+/-CK)[1]

Month 4 and Beyond:

- ☐ *Pregnancy Test*
- ☐ +/-lipid profile, LFTs (+/-GGT)[2], CK[1] if dose change/previous abnormalities/symptoms

One month after completion of treatment course/last dose of isotretinoin:

- ☐ *Pregnancy Test*
- ☐ Consider topical retinoid for all patients upon completion of course

Fig. 1 Isotretinoin checklist. Guidelines for female patients of childbearing potential are shown in italics. [1]Consider in physically active patients, at baseline. May monitor regularly in those with baseline abnormalities and/or athletes engaging in strenuous physical activity. [2]GGT: shown to be more indicative of liver injury versus aspartate aminotransferase and alanine aminotransferase [49]. *LFTs* liver function tests, *GGT* γ-glutamyltransferase, *CK* creatine kinase, *bid* twice daily

Several reports of alternative dosing regimens have been described. High cumulative doses of isotretinoin (> 220 mg/kg compared with < 220 mg/kg) may decrease relapse rates and the need for repeat courses of treatment [59]. Higher cumulative dosing appears to be well tolerated—only rash was more common in the higher-treatment-dose group.

Low-dose intermittent and fixed low-dose regimens of isotretinoin have been used with varying degrees of success for acne, mostly mild to moderate acne. The low-dose intermittent regimen has been proven to be well tolerated [60] and effective for treating acne and consists of 0.5 mg/kg/day for 1 week every 4 weeks for a treatment course of 6 months [61, 62]. Fixed low-dose regimens have varying protocols; 20 mg daily and 20 mg every other day can be effective in moderate acne [63, 64]. A low-dose regimen report suggested decreased frequency and severity of mucocutaneous adverse effects, and increased patient compliance [61–65]. Long-term relapse rates are unknown. This option may be suited for moderate acne but is not recommended for patients of childbearing potential [66] (see Table 2 for a summary and comparison of various proposed dosing regimens).

Table 2 Isotretinoin dosing regimen

Dosing regimen	Advantages	Disadvantages
Traditional 120–150 mg/kg cumulative dose [56, 57]	Cumulative dose target range was based on studies that were not designed to evaluate the role of cumulative dose on relapse rates [57] Well tolerated Effective Common adverse effects: dryness of skin and lips	Relapses requiring repeat isotretinoin course approximately 20% [80]
Traditional dosing with once- versus twice-daily dosing [81]	High clinical efficacy with no statistical difference between once- versus twice-daily dosing [81]	Fewer adverse effects in twice-daily dosing (dry lips, xerosis, eczema, epistaxis, back pain, headache, gastrointestinal upset, angular cheilitis [81]
Fixed low-dose isotretinoin: 20 mg/day × 6 months [64], 20 mg on alternate days × 6 months [82]	Effective in moderate acne Low adverse effects and higher patient compliance [64, 83, 84] Slightly better patient compliance and lower risk relapse at 6 months versus low-dose intermittent dosing [84]	Limited studies and limited long-term relapse data Lack of demonstrated efficacy in severe patients Outside of recommended guidelines Not appropriate for females of childbearing potential [66]
Low dose intermittent isotretinoin: 0.5 mg/kg/day for 1 week every 4 weeks for 6 months [61, 65] 0.5 mg/kg/day for the first 10 days of each month for 6 months, or 0.5 mg/kg/day every day for the first month then 0.5 mg/kg/day for the first 10 days of each month for 5 months [62]	Effective for mild to moderate acne [61, 62] Low adverse effects and high patient compliance [61, 62, 65]	Limited studies and limited long-term relapse data Less patient compliance and greater risk relapse at 6 months compared with a fixed low-dose regimen [84] Lack of demonstrated efficacy in severe patients Outside of recommended guidelines Not appropriate for females of childbearing potential [66]
High dose High cumulative doses of isotretinoin (> 220 mg/kg compared with < 220 mg/kg) [59]	Increased efficacy with a lower relapse rate (47% vs. 27% at 1 year) reported [58]. Not statistically significant when adjusted for age, sex, race, treating physician, and duration of treatment [85] May decrease relapse rates and need for repeat courses of treatment Well tolerated—only rash was more common in the higher treatment dose group [58]	Limited data Increased mucocutaneous adverse effects [58]

7 Surgical and Other Procedures

There has been concern in the past regarding isotretinoin potentially disrupting the healing process after injury or procedure; however, an observational study found that isotretinoin was not associated with the development of hypertrophic scars or keloids [67]. There is no issue with wisdom tooth extraction during a course of isotretinoin [68]. Systematic reviews have also recently found no evidence to delay cutaneous surgery or many cosmetic procedures during or immediately after completing a course of isotretinoin [69, 70]; however, it is recommended to avoid mechanical dermabrasion and fully ablative laser while taking isotretinoin [69].

8 Post-Treatment Prophylaxis

Since approximately 20% of patients have relapse of acne necessitating a second course of isotretinoin [71–74], prescribers may consider post-treatment prophylaxis with a topical retinoid, which helps maintain post-treatment clearance [75]. Given how sensitive patients' skin is during and immediately following completion of an isotretinoin course, patients may need to wait 1–2 months before gradually starting a topical retinoid regimen for maintenance.

9 Conclusions

Isotretinoin is the most effective treatment currently available for acne. Patients who are good candidates for the treatment typically do very well and are extremely satisfied. While there are potential adverse effects, with close monitoring and good patient counseling these can be monitored for and can typically be easily managed.

Compliance with Ethical Standards

Funding No sources of funding were provided for this manuscript.

Conflict of interest Megan N. Landis has served on advisory boards for Mayne and Janssen, and as an investigator for Galderma, Novartis, Pfizer, and Foamix.

References

1. Collier CN, Harper JC, Cantrell WC, Wang W, Foster KW, Elewski BE. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008;58(1):56–9.
2. Gollnick HP, Bettoli V, Lambert J, Araviiskaia E, Binic I, Dessinioti C, et al. A consensus-based practical and daily guide for the treatment of acne patients. J Eur Acad Dermatol Venereol. 2016;30(9):1480–90.
3. Greywal T, Zaenglein AL, Baldwin HE, Bhatia N, Chernoff KA, Del Rosso JQ, et al. Evidence-based recommendations for the management of acne fulminans and its variants. J Am Acad Dermatol. 2017;77(1):109–17.
4. Rademaker M. Adverse effects of isotretinoin: a retrospective review of 1743 patients started on isotretinoin. Australas J Dermatol. 2010;51(4):248–53.
5. McLane J. Analysis of common side effects of isotretinoin. J Am Acad Dermatol. 2001;45(5):S188–94.
6. Millan SB, Flowers FP, Sherertz EF. Isotretinoin. South Med J. 1987;80(4):494–9.
7. Neudorfer M, Goldshtein I, Shamai-Lubovitz O, Chodick G, Dadon Y, Shalev V. Ocular adverse effects of systemic treatment with isotretinoin. Arch Dermatol. 2012;148(7):803–8.
8. Layton A. The use of isotretinoin in acne. Dermatoendocrinol. 2009;1(3):162–9.
9. Sundström A, Alfredsson L, Sjölin-Forsberg G, Gerdén B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. BMJ. 2010;341:c5812.
10. Marqueling AL, Zand LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. Semin Cutan Med Surg. 2005;24(2):92–102.
11. Yang YC, Tu HP, Hong CH, Chang WC, Fu HC, Ho JC, et al. Female gender and acne disease are jointly and independently associated with the risk of major depression and suicide: a national population-based study. Biomed Res Int. 2014;2014:504279.
12. Halvorsen JA, Stern RS, Dalgard F, Thoresen M, Bjertness E, Lien L. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. J Invest Dermatol. 2011;131(2):363–70.
13. Rowe C, Spelman L, Oziemski M, Ryan A, Manoharan S, Wilson P, et al. Isotretinoin and mental health in adolescents: Australian consensus. Australas J Dermatol. 2014;55(2):162–7.
14. Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinion use and risk of depression, psychotic symptoms, suicide, and attempted suicide. Arch Dermatol. 2000;136(10):1231–6.
15. Nevoralová Z, Dvořáková D. Mood changes, depression and suicide risk during isotretinoin treatment: a prospective study. Int J Dermatol. 2013;52(2):163–8.
16. Rehn L, Meririnne E, Höök-Nikanne J, Isometsä E, Henriksson M. Depressive symptoms and suicidal ideation during isotretinoin treatment: a 12-week follow-up study of male Finnish military conscripts. J Eur Acad Dermatol Venereol. 2009;23(11):1294–7.
17. Bozdağ KE, Gülseren Ş, Güven F, Çam B. Evaluation of depressive symptoms in acne patients treated with isotretinoin. J Dermatolog Treat. 2009;20(5):293–6.
18. Simić D, Situm M, Letica E, Penavić JZ, Zivković MV, Tomić T. Psychological impact of therapy with isotretinoin in moderate and severe acne patients. Acta Derm Venereol. 2009;33(Suppl 2):15–9.
19. Suarez B, Serrano A, Cova Y, Baptista T. Isotretinoin was not associated with depression or anxiety: a twelve-week study. World J Psychiatry. 2016;6(1):136–42.
20. Rubinow DR, Peck GL, Squillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. J Am Acad Dermatol. 1987;17(1):25–32.
21. Hahm BJ, Min SU, Yoon MY, Shin YW, Kim JS, Jung JY, et al. Changes of psychiatric parameters and their relationships by oral isotretinoin in acne patients. J Dermatol. 2009;36(5):255–61.
22. Marron SE, Tomas-Aragones L, Boira S. Anxiety, depression, quality of life and patient satisfaction in acne patients treated with oral isotretinoin. Acta Derm Venereol. 2013;93(6):701–6.

23. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. Semin Cutan Med Surg. 2005;24(2):92–102.
24. Huang YC, Cheng YC. Isotretinoin treatment for acne and risk of depression: a systematic review and meta-analysis. J Am Acad Dermatol. 2017;76(6):1068–1076.e9.
25. Thiboutot DM, Dréno B, Abanmi A, Alexis AF, Araviiskaia E, Barona Cabal MI, et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol. 2018;78(2):S1–S23.e1.
26. Baum C. Isotretinoin and pregnancy. J Am Acad Dermatol. 1984;10(5 Pt 1):851–4.
27. Shin J, Cheetham TC, Wong L, Niu F, Kass E, Yoshinaga MA, et al. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system. J Am Acad Dermatol. 2011;65(6):1117–25.
28. Collins MK, Moreau JF, Opel D, Swan J, Prevost N, Hastings M, et al. Compliance with pregnancy prevention measures during isotretinoin therapy. J Am Acad Dermatol. 2014;70(1):55–9.
29. Werner CA, Papic MJ, Ferris LK, Lee JK, Borrero S, Prevost N, et al. Women's experiences with isotretinoin risk reduction counseling. JAMA Dermatology. 2014;150(4):366–71.
30. Crockett SD, Porter CQ, Martin CF, Sandler RS, Kappelman MD. Isotretinoin use and the risk of inflammatory bowel disease: a case-control study. Am J Gastroenterol. 2010;105(9):1986–93.
31. Dubeau M-F, Iacucci M, Beck PL, Moran GW, Kaplan GG, Ghosh S, et al. Drug-induced inflammatory bowel disease and IBD-like conditions. Inflamm Bowel Dis. 2013;19(2):445–56.
32. Alhusayen RO, Juurlink DN, Mamdani MM, Morrow RL, Shear NH, Dormuth CR. Isotretinoin use and the risk of inflammatory bowel disease: a population-based cohort study. J Invest Dermatol. 2013;133(4):907–12.
33. Etminan M, Bird ST, Delaney JA, Bressler B, Brophy JM. Isotretinoin and risk for inflammatory bowel disease: a nested case-control study and meta-analysis of published and unpublished data. JAMA Dermatol. 2013;149(2):216–20.
34. Rashtak S, Khaleghi S, Pittelkow MR, Larson JJ, Lahr BD, Murray JA. Isotretinoin exposure and risk of inflammatory bowel disease. JAMA Dermatology. 2014;150(12):1322.
35. Bernstein CN, Nugent Z, Longobardi T, Blanchard JF. Isotretinoin is not associated with inflammatory bowel disease: a population-based case-control study. Am J Gastroenterol. 2009;104(11):2774–8.
36. Hansen TJ, Lucking SM, Miller JJ, Kirby JS, Thiboutot DM, Zaenglein AL. Standardized laboratory monitoring with use of isotretinoin in acne. J Am Acad Dermatol. 2016;75(2):323–8.
37. Brelsford M, Beute TC. Preventing and managing the side effects of isotretinoin. Semin Cutan Med Surg. 2008;27(3):197–206.
38. Brzezinski P, Borowska K, Chiriac A, Smigielski J. Adverse effects of isotretinoin: a large, retrospective review. Dermatol Ther. 2017. https://doi.org/10.1111/dth.12483.
39. Rao PK, Bhat RM, Nandakishore B, Dandakeri S, Martis J, Kamath GH. Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. Indian J Dermatol. 2014;59(3):316.
40. Opel D, Kramer ON, Chevalier M, Bigby M, Albrecht J. Not every patient needs a triglyceride check, but all can get pancreatitis: a systematic review and clinical characterization of isotretinoin-associated pancreatitis. Br J Dermatol. 2017;177(4):960–6.
41. Lilley JS, Linton MF, Fazio S. Oral retinoids and plasma lipids. Dermatol Ther. 2013;26(5):404–10.
42. Rodondi N, Darioli R, Ramelet AA, Hohl D, Lenain V, Perdrix J, et al. 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. 2002;136(8):582–9.
43. Alcalay J, Landau M, Zucker A. Analysis of laboratory data in acne patients treated with isotretinoin: is there really a need to perform routine laboratory tests? J Dermatolog Treat. 2001;12(1):9–12.
44. Hanson N, Leachman S. Safety issues in isotretinoin therapy. Semin Cutan Med Surg. 2001;20(3):166–83.
45. Krishna S, Okhovat J-P, Kim J, Kim CN. Influence of ω-3 fatty acids on triglyceride levels in patients using isotretinoin. JAMA Dermatol. 2015;151(1):101.
46. The effect of omega-3 fatty acid on triglyceride levels in patients using isotretinoin. J Am Acad Dermatol. 2012;66(4):AB19.
47. Lyons F, Laker MF, Marsden JR, Manuel R, Shuster S. Effect of oral 13-cis-retinoic acid on serum lipids. Br J Dermatol. 1982;107(5):591–5.
48. Marsden JR. Effect of dietary fish oil on hyperlipidaemia due to isotretinoin and etretinate. Hum Exp Toxicol. 1987;6(3):219–22.
49. Webster GF, Webster TG, Grimes LR. Laboratory tests in patients treated with isotretinoin: occurrence of liver and muscle abnormalities and failure of AST and ALT to predict liver abnormality. Dermatol Online J. 2017;23(5):3.
50. Marson JW, Baldwin HE. New concepts, concerns, and creations in acne. Dermatol Clin. 2019;37(1):1–9.
51. Hartung B, Merk HF, Huckenbeck W, Daldrup T, Neuen-Jacob E, Ritz-Timme S. Severe generalised rhabdomyolysis with fatal outcome associated with isotretinoin. Int J Legal Med. 2012;126(6):953–6.
52. Kaminsky A. Less common methods to treat acne. Dermatology. 2003;206(1):68–73.
53. Grando LR, Leite OG, Cestari TF. Pseudo-acne fulminans associated with oral isotretinoin. An Bras Dermatol. 2014;89(4):657–9.
54. Layton AM, Cunliffe WJ. Guidelines for optimal use of isotretinoin in acne. J Am Acad Dermatol. 1992;27(6 Pt 2):S2–7.
55. Cunliffe WJ, Van de Kerkhof PCM, Caputo R, Cavicchini S, Cooper A, Fyrand OL, et al. Roaccutane treatment guidelines: results of an international survey. Dermatology. 1997;194(4):351–7.
56. Tan J, Knezevic S, Boyal S, Waterman B, Janik T. Evaluation of evidence for acne remission with oral isotretinoin cumulative dosing of 120–150 mg/kg. J Cutan Med Surg. 2016;20(1):13–20.
57. Rademaker M. Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris. Int J Dermatol. 2016;55(5):518–23.
58. Blasiak RC, Stamey CR, Burkhart CN, Lugo-Somolinos A, Morrell DS. High-dose isotretinoin treatment and the rate of retrial, relapse, and adverse effects in patients with acne vulgaris. JAMA Dermatol. 2013;149(12):1392.
59. Blasiak RC, Stamey CR, Burkhart CN, Lugo-Somolinos A, Morrell DS. High-dose isotretinoin treatment and the rate of retrial, relapse, and adverse effects in patients with acne vulgaris. JAMA Dermatol. 2013;149(12):1392.
60. Agarwal US, Besarwal RK, Bhola K. Oral isotretinoin in different dose regimens for acne vulgaris: a randomized comparative trial. Indian J Dermatol Venereol Leprol. 2011;77(6):688–94.
61. Kaymak Y, Illter N. The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. J Eur Acad Dermatol Venereol. 2006;20:1256–60.
62. Akman A, Durusoy C, Senturk M, Koc CK, Soyturk D, Alpsoy E. Treatment of acne with intermittent and conventional isotretinoin: a randomized, controlled multicenter study. Arch Dermatol Res. 2007;299(10):467–73.
63. Sardana K, Garg V. Efficacy of low-dose isotretinoin in acne vulgaris. Indian J Dermatol Venereol Leprol. 2010;76:7–13.

64. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol. 2006;54(4):644–6.
65. Kumar A, Kumar VK. Toxicity of low-dose intermittent isotretinoin in recalcitrant acne. Med J Armed Forces India. 2010;66(3):208–12.
66. Layton A. The use of isotretinoin in acne. Dermatoendocrinol. 2009;1(3):162–9.
67. Guadanhim LRS, Gonçalves RG, Bagatin E. Observational retrospective study evaluating the effects of oral isotretinoin in keloids and hypertrophic scars. Int J Dermatol. 2016;55(11):1255–8.
68. Sharma J, Thiboutot DM, Zaenglein AL. The effects of isotretinoin on wisdom tooth extraction. J Am Acad Dermatol. 2012;67(4):794–5.
69. Spring LK, Krakowski AC, Alam M, Bhatia A, Brauer J, Cohen J, et al. Isotretinoin and timing of procedural interventions. JAMA Dermatol. 2017;153(8):802.
70. Waldman A, Bolotin D, Arndt KA, Dover JS, Geronemus RG, Chapas A, et al. ASDS Guidelines Task Force. Dermatol Surg. 2017;43(10):1249–62.
71. White GM, Chen W, Yao J, Wolde-Tsadik G. Recurrence rates after the first course of isotretinoin. Arch Dermatol. 1998;134(3):376–8.
72. Layton AM, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later: a safe and succesful treatment. Br J Dermatol. 1993;108:333–43.
73. Stainforth JM, Layton AM, Taylor JP, Cunliffe WJ. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? Br J Dermatol. 1993;129(3):297–301.
74. Chivot M, Midoun H. Isotretinoin and acne—a study of relapses. Dermatology. 1990;180:240–3.
75. Truchuelo MT, Jiménez N, Mavura D, Jaén P. Assessment of the efficacy and safety of a combination of 2 topical retinoids (RetinSphere) in maintaining post-treatment response of acne to oral isotretinoin. Actas Dermo-Sifiliográficas. 2015;106(2):126–32.
76. Krishna S, Kim C, Kim J. The effect of omega-3 fatty acid on triglyceride levels in patients using isotretinoin. J Am Acad Dermatol. 2012;66(4 Suppl 1):AB19.
77. Fortson MR, Freedman SN, Webster PD 3rd. Clinical assessment of hyperlipidemic pancreatitis. Am J Gastroenterol. 1995;90(12):2134–9.
78. Roenigk HH. Liver toxicity of retinoid therapy. J Am Acad Dermatol. 1988;19(1 Pt 2):199–208.
79. Wolverton S. Comprehensive dermatologic drug therapy. 3rd ed. Saunders; 2012.
80. Rademaker M, Isotretinoin: dose, duration and relapse. What does 30 years of usage tell us? Australas J Dermatol. 2013;54(3):157–62.
81. Ahmad HM. Analysis of clinical efficacy, side effects, and laboratory changes among patients with acne vulgaris receiving single versus twice daily dose of oral isotretinoin. Dermatol Ther. 2015;28(3):151–7.
82. Sardana K, Garg VK, Sehgal VN, Mahajan S, Bhushan P. Efficacy of fixed low-dose isotretinoin (20 mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris. J Eur Acad Dermatol Venereol. 2009;23(5):556–60.
83. Mandekou-Lefaki I, Delli F, Teknetzis A, Euthimiadou R, Karakatsanis G. Low-dose schema of isotretinoin in acne vulgaris. Int J Clin Pharmacol Res. 2003;23(2–3):41–6.
84. Boyraz N, Mustak PK. Comparison of the efficacies of intermittent and continuous low-dose isotretinoin regimens in the treatment of moderate acne vulgaris. Int J Dermatol. 2013;52(10):1265–7.
85. Owen CE. Treating acne with high-dose isotretinoin. JAMA. 2014;311(20):2121.