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REVIEW

Physiological and Psychological Effects of Isotretinoin in the Treatment of Patients with Acne: A Narrative Review

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Abstract: Isotretinoin (ISO) is a powerful vitamin A derivative that offers the potential for treatment of permanent remission of acne; however, its potential side effects on both physiological and psychological aspects limit its application. This article reviews the side effects of ISO from physiological and psychological aspects in detail, to better screen the suitable population of ISO and improve the efficiency of clinical treatment. Our findings indicate that ISO may cause teratogenicity, skin reactions, ocular reactions, changes in blood indicators, and occasional acne fulminans. To optimize clinical treatment, more attention should be paid to identifying the specific conditions under which these reactions occur, how severe they are, and how they subside to alleviate patient concerns. Regarding the controversial issue of psychological side effects caused by ISO, researchers should shift their focus to the psychological problems that acne itself may cause.

Keywords: acne, isotretinoin, physiological effects, psychological effects

Introduction

Acne vulgaris (AV) is a chronic, immune-mediated, multifactorial inflammatory disease affecting the hair sebaceous gland units,[1–3] which is one of the most common skin disorder afflicting adolescents worldwide.[4,5] Isotretinoin (ISO) is a powerful vitamin A derivative, and it is the only possible treatment for permanent remission of acne. Its action mechanism is to normalize the differentiation of follicular keratinocytes by reducing the size and secretion of sebaceous glands, inhibiting the growth and inflammatory response of keratinocytes in acne.[6] ISO is the only therapy that affects all major causes of acne.[7,8] Since oral ISO was first approved by the US Food and Drug Administration (FDA) in 1982 for the treatment of severe acne,[7] oral ISO has been proven to be a major pharmacological breakthrough in the treatment of severe and recalcitrant cases with acne.[9] However, ISO has three prominent adverse reactions: (1) psychological problems, (2) inflammatory bowel disease (IBD), and (3) teratogenicity.[10] Yilmaz et al[11] reported that genotoxicity, teratogenicity, and carcinogenicity information of ISO was very limited and controversial. Nevertheless, the claims about side effects of ISO had led many patients to hesitate to use it.

The psychological side effects of ISO treatment for acne on patients are still vague, and the types of skin reactions and blood changes associated with the treatment are occasionally debated. Ko et al[12] found that the medical personnel group evaluated ISO as more neutral, while the non-medical personnel group rated ISO as more negative, based on YouTube. Due to the mysteries of ISO, this article reviews the side effects of ISO from both psychological and physiological aspects to better screen the suitable population.

Methods

A review of the literature was conducted using PubMed, with the search formula "(Acne [Title/Abstract]) AND ((Isotretinoin[Title/Abstract]) or (ISO[Title/Abstract]))" and the time limit was after 2018.

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Four hundred and seventy-four articles were initially included, and after screening the titles, abstracts, and relevant references, there were 160 articles left. Then we removed the duplicate expression, 127 articles were ultimately included in this research.

Results

Physical Effects

The incidence of adverse reactions after 3 months in patients with ISO was 40% in a Nepal study.[13] Vallerand et al[14] collected data from 11 trials meeting eligibility for review (total 760 patients randomized) and found that the rate of adverse events was twice as high in the ISO group compared to the control group across all trials. In a 2022 study by Brzezinski et al[15] of 90 adolescent participants treated with ISO for acne, 11 different adverse effects were noted during ISO treatment. Next, we begin to tease out the physical side effects of ISO treatment with the three prominent adverse effects mentioned above.

IBD

ISO has sparked many discussions about its potential association with IBD. Reddy et al[16] reviewed all of the adverse reports filed with the FDA from 1997 to 2002, and eighty-five cases of IBD associated with ISO use were reported. Das et al[17] showed that ISO caused development of IBD related macroscopical and histopathological alterations, scholars experimented with mice and found that the frequency of defecation in animals after ISO treatment increased over time, eventually leading to bloody stools.

A retrospective cohort analysis that Wright et al[18] did showed that 6-month IBD incidence among AV patients with ISO treatment was very low, even similar to AV patients without ISO (0.08% vs 0.04%). Many scholars found no evidence supporting that ISO caused IBD/ulcerative colitis.[14,19] Sakhamuru et al[20] reviewed 33 publications and found that most studies showed no significant association between the use of ISO and the development of ulcerative colitis. The Brazilian Society of Dermatology appointed eight experts from five universities to reach a consensus on the indications for ISO, and the experts agreed that there was no causal relationship between IBD and ISO.[1]

Although the incidence of IBD in patients treated with ISO is low, the consequences for an individual developing IBD may be significant.[21] Doctors can avoid providing ISO to IBD susceptible patients as much as possible by inquiring about family or personal medical history, in order to avoid serious consequences.

Pregnancy and Teratogenicity

ISO has adverse effects on the pituitary-ovarian axis, which can enhance granulosa cell apoptosis and reduce follicular reserve.[22] In the study conducted by Schaefer et al,[23] ISO was considered the most teratogenic drug after thalidomide. Even a simple capsule may cause congenital malformations within the first trimester.[24]

ISO played a role in teratogenicity.[25] Natural abortion, dysgnosia, craniofacial defects, central nervous system, and endocrine system disorders, are all potential birth defects.[26] The mean age of ISO users is approximately 24 years old,[27] which means that users are mostly women of childbearing age. According to data reported by Sladden et al,[28] in pregnancies which the fetus was exposed to ISO, the risk of spontaneous abortion and embryopathy was approximately 20% and 18% to 28%, the main abnormalities were craniofacial, thymic, cardiac, and central nervous system. Of the 19 pregnancies in which the fetuses reached a viable gestational age in the retrospective case series reported by Lammer et al,[29] 2 resulted in malformed stillborn infants and 14 in malformed liveborn infants. Of the 36 prospectively identified ISO-exposed pregnancies reported by Lammer et al,[29] 8 resulted in first-trimester spontaneous abortion, 1 in a malformed stillborn infant, and 4 in live-born infants with at least one major malformation. A report contained 151 births exposed to ISO reported by Dai et al,[24] 47% had congenital malformations. Of 94 prospectively ascertained pregnancies that ended in births, 28% had congenital malformations.[24]

Due to the teratogenic effect of ISO, both Europe and the United States had strict requirements for the prevention of pregnancy in female patients to prevent fetal abnormalities caused by ISO.[26,30,31] This means that the ISO is strictly restricted for women users and these users are required to use contraception during the time.

Acne Fulminans (AF)

AF is a severe form of inflammatory acne.[32–34] It might begin during ISO treatment and also may occur spontaneously,[35,36] primarily affecting adolescent males with pre-existing AV.[35–37] In some patients, mild cystic acne with ISO rapidly progressed to ulcerative and necrotizing acne with systemic symptoms.[33,35]

Sánchez-Velázquez et al[32] reported an acne adolescent with a history of overweight started with ISO at a dose of 0.4 mg/kg/day had worsened acne after six-week treatment with pustules, numerous painful papules, and hemorrhagic nodules crusting on the back and chest. He was diagnosed with ISO-induced AF, then he was advised to stop taking ISO and prednisone 1 mg/kg/day was initiated. ISO was reintroduced at 0.1 mg/kg/day after four weeks, however, when the patient attempted to reduce prednisone or increase ISO, he experienced multiple truncal flare ups. Finally, the adolescent achieved complete remission after being treated with apremilast monotherapy.

The possible biological mechanisms for ISO-induced AF are as follows: Short-term exposure to ISO in sebum cells increases the intracellular lipid content and the expression of sterol regulatory element-binding protein (SREBP)-1 and arachidonic synthetase 5-lipoxygenase (LOX).[8] The upregulation of SREBP-1 and 5-LOX may lead to AF because of their participation in sebum production.[38]

The reasonable treatment for ISO-induced AF with systemic symptoms is oral corticosteroids at a dose of 0.5–1 mg/kg/day for more than 4 weeks until AF subsides.[32] Researchers reported that ISO in combination with systemic steroids or other anti-inflammatory agents, adalimumab, and 5-Aminolevulinic acid photodynamic therapy (ALA-PDT) might be effective means in treating AF.[35,39,40] In terms of dose, Zaba et al[35] once suggested a pathogenic dose: 0.5–1 mg/kg/day, and the duration of treatment before the origin of AF was an average of 3 weeks (range, 1 to 7 weeks). Borghi et al[41] found that for ISO treatment of acne, the number of AF cases starting at a dose ≤0.2 mg/kg/day was smaller than the number of AF cases starting at a dose of 0.5 mg/kg/day ($P < 0.05$) during the first 4 weeks of treatment, and the efficacy was not different from therapies starting with higher doses (0.5 mg/kg/day). It had also been suggested that the presence of multiple large pimples in the first few weeks of taking ISO appeared to be a momentous risk factor for acne outbreaks.[7]

Skin Reaction

During ISO treatment of acne, more than half of the adverse events were skin diseases and related to dryness, dry skin was the most common adverse reaction, and desquamation of the skin and mucous membranes were common side effects.[13,14,30] It might be because that treatment with ISO could result in a decrease in skin hydration.[42] In the study proved by Brzezinski et al,[15] concluding 90 teenagers with acne treated with ISO, the incidence of dry lips was 100%. Chapped lips were also the adverse reaction.[38,43] However, evening primrose oil as a dietary supplement was considered safe, which could result in a significant increase in skin hydration in patients treated with ISO, and significantly ameliorate the adverse effects such as dryness, lip cracking, and peeling skin.[42] Retinoid dermatitis, burning sensation, and itching sensation were all adverse reactions caused by ISO, among the side effects of mucocutaneous, cheilitis was the most common adverse effect and dose-dependent.[38,43] Zainab et al[44] demonstrated that omega 3 could be used to prevent or manage cheilitis, xerosis or dry lips. The ISO side effects of various mucocutaneous and central nervous systems were mostly dose-related.[45] For the skin side effects of ISO, they were usually reversible, dose-dependent, predictable, and manageable.[30,46] The absence of these reactions raised the possibility of underdosing.[47]

ISO is a retinol derivative of vitamin A and has an impact on the formation of collagen.[48] In addition, ISO inhibited collagenase and gelatinase activities in stimulated fibroblasts in vitro, which affect collagen formation.[35] What is more, Retinoids are known for increasing skin vulnerability by reducing the number of tensin filaments and desmosomes attached and the secondary accumulation of amorphous material in the epidermis.[35] These may partly explain the keloid in some patients.

Ocular Reaction

ISO was also associated with ocular changes, mainly in the ocular surface. Acar et al[49] found that systemic ISO treatment effected both ocular surface parameters and corneal and meibomian glands structure in a prospective study. Dry eye disease, eyelid conjunctivitis, abnormal or atrophy of meibomian gland secretion, chalazion or stye were common

adverse reactions. Other events such as corneal opacity, photophobia, refractive changes, keratitis, impaired night vision/color vision, and papilledema were rare.[50] In addition, ISO treatment has been associated with neuro-ophthalmic abnormalities, dark adaptation and worsening color vision, cataracts, and retinal toxicity such as premacular bleeding, serous retinal detachment, vascular occlusion, and vitreous abnormalities.[30,51–53] What's more, the use of ISO could result in an increase in the area of retinal pigment epithelium-Bruch membrane complex and ellipsoid zone with short term.[54]

In the study by Shrestha et al,[13] dry eyes were one of the adverse effects after 3 months of oral ISO treatment. Nearly all dermatologists prescribed lubricant eye drops routinely for patients in ISO treatment in Egypt.[55] Villani et al[30] also found that patients might experience dry mucous membranes, such as eyes, nose, and mouth, when the dose was too high for them. This might be because systemic ISO administration altered the function and structure of meibomian glands and inhibited lipid production, resulting in rapid tear evaporation.[56,57] ISO also could cause tear film instability with Meibomian gland dysfunction and change of morphology and may cause evaporative type of dryness.[58] In addition, it altered the conjunctival epithelium, affected the morphology of goblet cells, and interfered with mucin production.[56,59] What is more, the level of the tear was associated with the use of ISO and an increase in bacterial flora in the conjunctiva.[56] After the use of artificial tears consisting of 0.2% galacto-xyloglucan and 0.4% hyaluronic acid, both symptoms and tear rupture time were improved in subjects treated with oral ISO.[56]

Compared with healthy group, acne group had higher scores on the total eyelid and meibomian gland secretion.[60] Compared with the control group, the meibomian glands, the thickening, thinning, tortuosity, and presence of ghost areas were statistically significantly more common in the AV group on the morphological evaluation.[60] This means that when exploring the side effects of ISO treatment in acne patients on the eye, the effect of acne itself needs to be excluded.

Other Reactions

Shrestha et al[13] found that adverse effects after 3 months of oral ISO treatment also included hair loss. Hair loss was a less common side effect.[61] Age, cumulative dose and duration of treatment were the factors affecting hair loss.[61] Patients who received ISO ≥0.5 mg/kg/day were more likely to have hair loss than those who received ISO <0.5 mg/kg/day (5.7% vs 3.2%).[62] Researchers reported that menstrual irregularity and hirsutism could be observed,[63,64] and ISO gradually increased the nail growth rate and thinned the nail plate over time.[65] Researchers found that ISO caused musculoskeletal side effects,[66] such as arthralgia, myalgia, back pain, and symptoms associated with spondyloarthropathy and sacroiliac arthritis,[30] but did not alter muscle strength.[67] Webster et al[68] reported that nearly half of patients on ISO develop elevated levels of creatine kinase, a proxy for potential muscle tissue damage. Pain severity is directly correlated with the cumulative dose of ISO and the increasing age.[69]

Hareedy et al[70] considered the effects of ISO on liver, kidney, and hematological function, potential oxidative stress associated with ISO treatment: ISO treatment might be associated with oxidative stress, liver and lipid abnormalities in acne patients. Hepatic dysfunction occurred in up to 15% of patients taking ISO.[71] Serum ferritin increased while serum ceruloplasmin decreased. ISO was associated with a possible positive nitrogen balance (increased protein) and elevated blood urea nitrogen and uric acid levels.

Zane et al[72] found that ISO use could cause leukopenia, neutropenia, agranulocytosis, thrombocytopenia, thrombocytosis, and other abnormalities in hematological parameters. Cosansu et al[73] found that low-density lipoprotein cholesterol, serum total cholesterol, aspartate aminotransferase levels, and triglyceride increased after ISO treatment. When the treatment in advance hemogram parameters of the patients and the values in the third month were compared, no statistically significant differences were detected in the lymphocyte count, monocyte count, platelet-to-lymphocyte ratio, and monocyte–lymphocyte ratio.[73] Inflammatory and non-inflammatory lesions were significantly reduced after 3 months of oral ISO at a dose of 0.5–0.7 mg/kg/day.[13] Besides, when other parameters were evaluated, total white blood cell counts, neutrophils, lymphocytes, monocytes, basophils, and platelets did not change from baseline, however, there was a significant decrease in mean GAGS score, total, inflammatory and non-inflammatory lesion counts, eosinophils, and absolute eosinophil count.[13] Hareedy et al[70] shared that ISO could affect immune regulation (lowering the ratio of neutrophils to lymphocytes) and was associated with blood abnormalities. What is more, ISO might have a sensitization effect.[74]

Researchers have found that ISO treatment causes significant changes in hormone levels, thyroid gland hormones decrease and pituitary thyroid-stimulating hormone levels increase, and the observed changes in hormonal levels were increased with the augment of therapy.[75]

Some scholars, such as Toossi et al[76], proposed that ISO caused low serum vitamin D levels and that there was a correlation between acne and serum vitamin D deficiency. Shrestha et al[13] put forward the opposite view, they concluded that patients with moderate to severe acne had low vitamin D levels, that no change in vitamin D levels was found after short-term treatment with oral ISO, and that there was no significant association between acne and serum vitamin D deficiency.

Psychological Effects

For a long time, many researchers harbored the idea that ISO involvement in treatment could result in psychological reactions, such as low mood, depression, anxiety, and suicide. ISO is a derivative of vitamin A and has many adverse side effects similar to those patients with high doses of vitamin A. The adult brain is sensitive to exposure to excess retinoic acid (the metabolite of the vitamin). Retinoic acid may be linked to psychological problems by observing the overlap of brain regions implicated in retinoic acid function, stress, and depression.[77] What is more, treatment with 13-cis-RA increased 5-HT1A protein and serotonin reuptake transporter protein levels, it might result in the decrease of serotonin availability at synapses.[78] Chaos in serotonin levels is closely related to depression and emotional problems.[77,79] In addition, Bremner et al[80] found that the use of ISO was associated with decreased brain metabolism in the orbitofrontal cortex, which meant the onset of mediate depression.

Studies in both animals and human show that ISO can lead to depressive behaviors.[77,78] On the contrary, some scholars found that the use of ISO was not associated with the increased risk of depression in acne patients.[81–84] Some scholars reported that patients with ISO experienced a lower risk of depression compared to those with oral antibiotics.[85–87] What's more, acne treatment appeared to improve depressive symptoms.[82]

In a retrospective cohort research conducted by Sundström et al[88] in Sweden, the risk of attempted suicide increased significantly six months after the ISO treatment, but the risk due to ISO cannot be calculated solely, because the risk has already been rising before treatment. Female gender, assessment by Consultation-Liaison Psychiatry, and absence of protective factors were linked to increased suicidality risk.[89] Psychiatric history and anxiety history were risk factors for suicide attempts in ISO users.[90,91] On the contrary, the researchers found that acne patients with suicidal ideation or attempts in the general population were 1.47 times than those taking ISO, patients taking ISO might have a lower rate (8.4/100 000 vs 11.8/100 000 in 2009; 5.6/100 000 vs 12.1/100 000 in 2010) of complete suicide than the general US population.[92,93] ISO treatment for acne may reduce suicidal behavior.[88] What is more, Sundström et al[88] indicated that if acne could not be effectively resolved, the risk of suicide would increase because of the severity of the psychological burden of acne by a retrospective cohort study.

The scholars found that psychiatric or psychosomatic symptoms were common in ISO treatment.[14] Bray et al[94] investigated whether ISO treatment resulted in changes in the concentration of key mood-related neurotransmitters, but the amount of patients who agreed to follow-up was too small to draw a conclusion, leading to speculation that it was related to mood factors. By contrast, experts in Brazil and Spain agreed that there was no evidence of a causal relationship between ISO on psychological effects.[1,90] Chen et al[95] reported that there was no increased risk of psychiatric disorders in acne patients with ISO, whatever dosage and duration of treatment were. Tapio et al[86] also obtained similar results by observing changes in mental status following ISO use in more than 30,000 cases, ISO was not independently related to exorbitant mental adverse outcomes, and the relation between increased acne severity and incidence of adverse mental results was reported. What is more, Tapio et al[86] also reported that compared with acne patients who were propensity score-matched and prescribed oral antibiotics, ISO was associated with lower rates of anxiety, sleep problems, non-fatal self-harm, and prescription of psychotropic medications. Similarly, Kridin et al[85] also reported that patients under ISO had less psychological distress,[87] lower risk of post-traumatic stress disorder, anxiety, bipolar disorder, schizophrenia, and adjustment disorder relative to those treated with oral antibiotics.

Dose Related Effects

Different doses of ISO may influence whether side effects occur. American Academy of Dermatology Guidelines (2016) gave a reference dose: ISO treatment should start at a dose of 0.5 mg/kg/day, increase to 1 mg/kg/day, and continue until a dose of 120–150 mg/kg (severe acne) is reached;[30] For patients with moderate acne, the recommended dose is 0.3–0.5 mg/kg/day. Previous studies have shown nearly the same results: to enhance response rates and prevent a recurrence, the recommended dose was 0.5–1.0 mg/kg/day for 12–16 weeks, with a recommended cumulative dose of 120 mg/kg.[96,97] European guidelines also offered dose recommendations in 2016 based on the severity and type of acne: 0.3–0.5 mg/kg for severe papulopustular and moderate nodular forms of acne and a dose of >0.5 mg/kg for conglobate acne.[98] Muqarrab et al[99] showed that conventional-dose (0.5–1.0 mg/kg/d) ISO improves the odds of preventing relapses than low-dose (0.1–0.3 mg/kg/d) in adults with mild-to-moderate AV by a meta-analysis review. Otherwise, it is vital to note that ISO at a dose of 35 mg/kg causes the most severe damage to the intestinal mucosa.[17] The dose is also an issue that cannot be ignored in pregnancy and teratogenicity, low-dose (0.25–0.4 mg/kg/day) ISO in treatment of moderate to severe acne seems to be safer on ovarian reserve.[100]

In contrast, an international consensus on acne published by the Global Alliance for Improved Outcomes did not make a specific recommendation for ISO dosage, but it only recommended continuing to use ISO for a month after the acne cleared up, regardless of the cumulative dose.[101,102] Rademaker[103] took the attitude that neither daily nor cumulative dosages influenced relapse of AV so long as treatment was continued for ≥2 months after the acne had completely resolved. Several scholars also found no difference in recurrence rates between patients taking cumulative doses >120 mg/kg and those taking less than 120 mg/kg,[102,104–106] ISO cumulative dosage higher than 120 mg/kg had nothing clinical advantage, and may increase the risk of adverse events because of the reduction of compliance.[107]

Discussion

Acne vulgaris patients often experience reduced quality of life.[108] Our previous study demonstrated that the more severe the acne severity grading, the greater impact on daily life, social activity and mental health.[109] What is more, the impact of acne on patients varied by gender: females were less tolerant of appearance blemishes, while males were more troubled by physical discomforts caused by acne.[109] However, skin lesions appear most often on the face in the female population.[110] This may lead to more serious psychological problems in this group. The above content indicated that acne seriously affects patients' lives. ISO is one of the important drugs for treating acne, the above content of this article reviewed the side effects of ISO from physiological and psychological aspects, to better screen the suitable population of ISO and improve the efficiency of clinical treatment.

For the two opposing views about psychological, we harbored the idea that the reason for the different results might be the psychological problems brought to the patients by the severe acne itself. AV and adolescence are both independent risk elements for suicide and depression.[111] Therefore, we proposed that subsequent research on the psychological effects of ISO treatment on acne must focus on the serious psychological burden associated with recalcitrant acne. In addition, it is momentous to note that the risk of depression should not be a reason to discourage the use of ISO in patients with moderate to severe acne. Before drug administration, doctors should explain the emotional problems that might be taken by ISO to patients, communicate with the patients more during the treatment, and suspend therapy if clinically momentous depression occurs.[10] In addition, early and effective treatment is vital to reduce the risk of scarring.[2,112]

Approximately 30% who regularly prescribed ISO in clinicians, had at times chosen not to prescribe ISO to patients with severe acne because of the iPLEDGE program.[113] Due to the abortion bans in some countries, it might cause dermatologists to eschew ISO use in patients of childbearing potential.[114] Because of the difficulty of accessing ISO, patients may turn to over-The-counter dietary vitamin A supplements.[115] Cook et al[116] proved that at doses of 50,000–300,000 IU daily, vitamin A probably supply a second choice for acne management when ISO is unavailable. However, vitamin A was not considered safe enough to be reused because it was easily available and could not be strictly monitored. That means there was a big security risk, the iPledge risk evaluation and mitigation strategy and other programs must actively solve workflow concerns and predict changes that threaten patient access to medication, even in changes.[115] Doctors should also do a better job of advising acne patients on medications to avoid tragedies. Vitamin D can act as an immunomodulator, regulating the proliferation and differentiation of keratinocytes and sebum cells, and

has the effect of acne lysis.[13,117,118] It seems we still need to find out more about the effects of vitamin A and vitamin D on acne. Besides, A single-blind randomized study conducted by de et al[119] found that the use of a dietary supplementation containing magnesium, phosphate, minerals and fatty acids in AV for 6 months, 100% of patients experienced complete resolution of symptoms with no reported side effects, and the lesions were more effective than ISO treatment, the pharmacological effect was faster and the long-term curative effect was better after withdrawal. Even seven years after completing treatment, there was no recurrence of AV. Piszczatoski et al[120] showed that topical clascoterone was likely an effective option for the treatment of AV without systemic side effects by a review. This suggests that there are a lot of potential drugs that academics need to explore.

A systematic treatment escalation based on disease severity, extension, and treatment response are at the core of therapeutic strategies.[121] Since the treatment which could concurrently and safely target all the pathogenic elements implicated in the appearance of acne lesions with minimal side effects did not exist now, we advocated combination therapies.[121] Ma et al[122] reported that topical antimicrobial peptides combined with low doses (0.3 mg/kg/d) of systemic ISO resulted in considerable improvement of clinical manifestations of mild-to-moderate AV than ISO monotherapy and the reduction in the acne dermatology index turned to be 74.9% with investigator global assessment score 0–1 after 12 weeks. Ye et al[123] summarized that oral ISO combined with supramolecular salicylic acid decreased response time compared to ISO monotherapy, with significantly improved global acne grading system (GAGS) score, count of lesions, and efficacy at 4–6 weeks. Skin indices of melanin, pore, erythema, and texture evaluated at week 10 were all enhanced. Oral ISO with or without supramolecular salicylic acid was effective in lesion clearance; only supramolecular salicylic acid significantly enhanced the transepidermal water loss. All the side effects were temporary and tolerable, and no adverse effects were observed. Dixit et al[124] reported that the combination of oral ISO (0.5 mg/kg/d) with salicylic-mandelic acid (20% salicylic and 10% mandelic acid) was significantly effective than the monotherapy (ISO: 0.5 mg/kg/d) by a comparative double-blind randomized single-center interventional open-label study. And this combination therapy could be used as newer therapy against adult acne without any serious side effects. Salah et al[125] suggested that oral zinc plus low-dose (0.25mg/kg/d) ISO resulted in the same satisfactory improvement as those who received the standard ISO dosage (0.5mg/kg/d) in moderate to severe AV patients with fewer side effects, and there was no difference regarding the relapse rates between both groups. Ibrahim et al[126] reported that the combining low-dose ISO (0.25 mg/kg/day) with pulsed dye laser group showed a statistically significantly greater improvement regarding all parameters, such as GAGS, Cardiff acne disability index compared with the standard higher-dose ISO (0.5 mg/kg/day) as monotherapy with less side effects. In a similar way, the ISO and 420 nm intense pulsed light combined treatment played an active role that was clinically significant from AV alleviation perspective in Chinese subjects, lightening basic skin tone and relieving erythema were other major advantages.[127]

Conclusion

In order to better screen the suitable population for ISO and improve clinical treatment efficiency, this article reviewed the side effects of ISO from both physiological and psychological perspectives. Finally, we found that teratogenicity, skin reactions, ocular reactions, changes in blood indicators, and occasional AF caused by ISO were not controversial, which meant that we should pay more attention to how to use medication to reduce these side effects, such as considering combination medication and adjusting drug dosage, in order to provide patients with a better treatment experience. For the most controversial issue of psychological problems caused by ISO, researchers should focus more on the psychological problems caused by acne itself.

Data Sharing Statement

This is a review article. All data generated or analysed during this study are included in this published article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Bagatin E, Costa CS, Rocha MADD, et al. Consensus on the use of oral isotretinoin in dermatology - Brazilian Society of Dermatology. *An Bras Dermatol*. 2020;95(Suppl 1):19–38. doi:10.1016/j.abd.2020.09.001
2. Leung AK, Barankin B, Lam JM, et al. Dermatology: how to manage acne vulgaris. *Drugs Context*. 2021;10:1–18. doi:10.7573/dic.2021-8-6
3. Acne Group, Combination of Traditional and Western Medicine Dermatology, Acne Group, Chinese Society of Dermatology, Acne Group, Chinese Dermatologist Association, Acne group, Dermatology Committee, Chinese Non-government Medical Institutions Association. Chinese Guidelines for the management of acne vulgaris: 2019 update. 国□皮肤性病学杂志*(英文) [Int J Dermatol Venereol]*. 2019;2(3):9.
4. Hollingshead N, Hodax JK, Boos MD. Management of acne in transgender and gender diverse youth Part 2: unique considerations and strategies in medical treatment. *Pediatr Dermatol*. 2022;39(6):870–875. doi:10.1111/pde.15114
5. Kaźmierska A, Bolesławska I, Jagielski P, et al. Effect of evening primrose oil supplementation on biochemical parameters and nutrition of patients treated with isotretinoin for acne vulgaris: a randomized double-blind trial. *Nutrients*. 2022;14(7):1342.
6. Park AM, Brahe C. Oral isotretinoin for acne in the US military: how accelerated courses and teledermatology can minimize the duty-limiting impacts of treatment. *Cutis*. 2022;109(2):75–78. doi:10.12788/cutis.0452
7. Layton A. The use of isotretinoin in acne. *Dermatoendocrinol*. 2009;1(3):162–169. doi:10.4161/derm.1.3.9364
8. Burney W, Bosanac SS, Nguyen C, et al. Short-term exposure of human sebocytes to 13- cis -retinoic acid induces acnegenic changes. *Br J Dermatol*. 2018;179(5):1201–1202. doi:10.1111/bjd.16837
9. Leyden JJ, Del Rosso JQ, Baum EW. The use of isotretinoin in the treatment of acne vulgaris: clinical considerations and future directions. *J Clin Aesthet Dermatol*. 2014;7(2 Suppl):S3–S21.
10. Wolverton SE, Harper JC. Important controversies associated with isotretinoin therapy for acne. *Am J Clin Dermatol*. 2013;14(2):71–76. doi:10.1007/s40257-013-0014-z
11. Yilmaz S. Toxicity, genotoxicity, and carcinogenicity of isotretinoin: a review. *Curr Mol Pharmacol*. 2022;16(1):83–90.
12. Ko BC, Haw S. Evaluation of YouTube videos about isotretinoin as treatment of acne vulgaris. *Ann Dermatol*. 2022;34(5):340–348. doi:10.5021/ad.21.143
13. Shrestha S, Agrawal S, Lamsal M. Vitamin D level in patients with moderate-to-severe acne: a case-control study combined with prospective study following oral isotretinoin treatment. *J Cosmet Dermatol*. 2022;21(10):5127–5133. doi:10.1111/jocd.14996
14. Vallerand IA, Lewinson RT, Farris MS, et al. Efficacy and adverse events of oral isotretinoin for acne: a systematic review. *Br J Dermatol*. 2018;178(1):76–85. doi:10.1111/bjd.15668
15. Brzezinski P, Wollina U, Smigielski J, et al. The use of isotretinoin in acne therapy in early childhood and its effect on the occurrence of acne symptoms later in life. Eight-year follow-up. *Postepy Dermatol Alergol*. 2022;39(4):682–687. doi:10.5114/ada.2022.118921
16. Reddy D, Siegel CA, Sands BE, et al. Possible association between isotretinoin and inflammatory bowel disease. *Am J Gastroenterol*. 2006;101(7):1569–1573. doi:10.1111/j.1572-0241.2006.00632.x
17. Das R, Khurana N, Sharma N. Development, optimization, and validation of Inflammatory Bowel Disease rat model using isotretinoin. *Chem Biol Interact*. 2022;363:110026. doi:10.1016/j.cbi.2022.110026
18. Wright S, Strunk A, Garg A. Risk of new-onset inflammatory bowel disease among patients with acne vulgaris exposed to isotretinoin. *J Am Acad Dermatol*. 2021;84(1):41–45. doi:10.1016/j.jaad.2020.07.042
19. Bendezú-García R, Hernández-Martínez Á, Patrón-Román GÓ, et al. Ulcerative colitis and isotretinoin: is there a causal relationship? *Rev Esp Enferm Dig*. 2014;106(2):150–151. doi:10.4321/S1130-01082014000200016
20. Sakhamuru S, Kambampati S, Wasim S, et al. The role of Propionibacterium acnes in the pathogenesis of sarcoidosis and ulcerative colitis: how this connection may inspire novel management of these conditions. *Cureus*. 2020;12(10):e10812. doi:10.7759/cureus.10812
21. Shale M, Kaplan GG, Panaccione R, et al. Isotretinoin and intestinal inflammation: what gastroenterologists need to know. *Gut*. 2009;58(6):737–741. doi:10.1136/gut.2008.170530
22. Abdelhamed A, Ezz El-Dawla R, Karadag AS, et al. The impact of isotretinoin on the pituitary-ovarian axis: an interpretative review of the literature. *Reprod Toxicol*. 2021;104:85–95. doi:10.1016/j.reprotox.2021.06.017
23. Schaefer C, Meister R, Weber-Schoendorfer C. Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. *Arch Gynecol Obstet*. 2010;281(2):221–227. doi:10.1007/s00404-009-1112-2
24. Dai WS, LaBraico JM, Stern RS. Epidemiology of isotretinoin exposure during pregnancy. *J Am Acad Dermatol*. 1992;26(4):599–606. doi:10.1016/0190-9622(92)70088-W
25. Tkachenko E, Singer S, Sharma P, et al. US Food and Drug Administration Reports of pregnancy and pregnancy-related adverse events associated with isotretinoin. *JAMA Dermatol*. 2019;155(10):1175–1179. doi:10.1001/jamadermatol.2019.1388
26. The iPledge REMS prescriber guide; 2021. Available from: https://ipledgeprogram.com/#Main/Resources. Accessed July 11, 2023.
27. Henry D, Dormuth C, Winquist B, et al. Occurrence of pregnancy and pregnancy outcomes during isotretinoin therapy. *Cmaj*. 2016;188(10):723–730. doi:10.1503/cmaj.151243

28. Sladden MJ, Harman KE. What is the chance of a normal pregnancy in a woman whose fetus has been exposed to isotretinoin? *Arch Dermatol*. 2007;143(9):1187–1188. doi:10.1001/archderm.143.9.1187
29. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313(14):837–841. doi:10.1056/NEJM198510033131401
30. Villani A, Nastro F, Di Vico F, et al. Oral isotretinoin for acne: a complete overview. *Expert Opin Drug Saf*. 2022;21(8):1027–1037. doi:10.1080/14740338.2022.2102605
31. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945–73.e33. doi:10.1016/j.jaad.2015.12.037
32. Sánchez-Velázquez A, Falkenhain-López D, Arroyo-Andrés J, et al. Apremilast: a novel adjuvant treatment for refractory isotretinoin-induced acne fulminans. *Dermatol Ther*. 2022;35(8):e15637. doi:10.1111/dth.15637
33. Bocquet-Trémoureux S, Corvec S, Khammari A, et al. Acne fulminans and Cutibacterium acnes phylotypes. *J Eur Acad Dermatol Venereol*. 2020;34(4):827–833. doi:10.1111/jdv.16064
34. Lee G, Ferri-Huerta R, Greenberg KB, et al. Acne fulminans in a transgender boy after an increase in testosterone dosage. *JAAD Case Rep*. 2022;21:32–34. doi:10.1016/j.jdcr.2021.11.029
35. Zaba R, Schwartz RA, Jarmuda S, et al. Acne fulminans: explosive systemic form of acne. *J Eur Acad Dermatol Venereol*. 2011;25(5):501–507. doi:10.1111/j.1468-3083.2010.03855.x
36. Fakih A, Goens J, Grozdev I, Dangoisse C, Richert B. Acne fulminans induced by a low dose isotretinoin: case report and review of the literature. *Dermatol Online J*. 2020;26(12). doi:10.5070/D32612051358
37. Dall'oglio F, Puglisi DF, Nasca MR, et al. Acne fulminans. *G Ital Dermatol Venereol*. 2020;155(6):711–718. doi:10.23736/S0392-0488.20.06711-5
38. Fallah H, Rademaker M. Isotretinoin for acne vulgaris - an update on adverse effects and laboratory monitoring. *J Dermatolog Treat*. 2022;33(5):2414–2424. doi:10.1080/09546634.2021.1967269
39. Marasca C, Fabbrocini G, Abategiovanni L, et al. Adalimumab in the management of isotretinoin-induced acne fulminans: report of a case. *Skin Appendage Disord*. 2021;7(2):115–119. doi:10.1159/000512032
40. Liu J, Shi L, Zhang L, et al. Acute acne flare following isotretinoin administration successfully treated by 5-aminolevulinic acid photodynamic therapy. *Photodiagnosis Photodyn Ther*. 2022;39:102893. doi:10.1016/j.pdpdt.2022.102893
41. Borghi A, Mantovani L, Minghetti S, et al. Acute acne flare following isotretinoin administration: potential protective role of low starting dose. *Dermatology*. 2009;218(2):178–180. doi:10.1159/000182270
42. Kaźmierska A, Bolesławska I, Polańska A, et al. Effect of evening primrose oil supplementation on selected parameters of skin condition in a group of patients treated with isotretinoin-a randomized double-blind trial. *Nutrients*. 2022;14(14):2980.
43. Rademaker M. Adverse effects of isotretinoin: a retrospective review of 1743 patients started on isotretinoin. *Australas J Dermatol*. 2010;51(4):248–253. doi:10.1111/j.1440-0960.2010.00657.x
44. Zainab Z, Malik NA, Obaid S, et al. Effectiveness of oral Omega 3 in reducing mucocutaneous side effects of oral isotretinoin in patients with acne vulgaris. *J Ayub Med Coll Abbottabad*. 2021;33(1):60–63.
45. Demircay Z, Kus S, Sur H. Predictive factors for acne flare during isotretinoin treatment. *Eur J Dermatol*. 2008;18(4):452–456. doi:10.1684/ejd.2008.0441
46. Kapała J, Lewandowska J, Placek W, et al. Adverse events in isotretinoin therapy: a single-arm meta-analysis. *Int J Environ Res Public Health*. 2022;19(11):6463. doi:10.3390/ijerph19116463
47. Bettoli V, Guerra-Tapia A, Herane MI, et al. Challenges and solutions in oral isotretinoin in acne: reflections on 35 years of experience. *Clin Cosmet Investig Dermatol*. 2019;12:943–951. doi:10.2147/CCID.S234231
48. Chiriac A, Wollina U. Spontaneous keloids during isotretinoin treatment for acne. *J Cosmet Dermatol*. 2022;21(11):6513–6514. doi:10.1111/jocd.15300
49. Acar Eser N, Kocabeyoğlu S, Atakan N, et al. The effects of the systemic isotretinoin treatment on ocular surface and meibomian glands: a prospective longitudinal study. *Cutan Ocul Toxicol*. 2022;41(2):155–161. doi:10.1080/15569527.2022.2077749
50. Ruiz-Lozano RE, Hernández-Camarena JC, Garza-Garza LA, et al. Isotretinoin and the eye: a review for the dermatologist. *Dermatol Ther*. 2020;33(6):e14029. doi:10.1111/dth.14029
51. Demirok G, Topalak Y, Gündüz Ö, et al. The long-term effect of oral isotretinoin therapy on macula ganglion cell complex thickness. *Cutan Ocul Toxicol*. 2017;36(3):259–262. doi:10.1080/15569527.2016.1265549
52. Citirik M, Tekin K. Excessive serous retinal detachment during the use of isotretinoin. *Int Ophthalmol*. 2018;38(2):763–766. doi:10.1007/s10792-017-0482-x
53. Onder HI, Turan H, Kilic AC, et al. Premacular hemorrhage due to isotretinoin use. *Cutan Ocul Toxicol*. 2013;32(2):170–172. doi:10.3109/15569527.2012.676121
54. Genç Işık İ, Işık MU. Cross-sectional assessment of the ellipsoid zone and the retinal pigment epithelium-Bruch membrane complex after systemic isotretinotin use. *Cutan Ocul Toxicol*. 2022;41(1):67–72. doi:10.1080/15569527.2021.2025386
55. Elshafie M, Srour A, el-Ansarey H, et al. Dermatologists' knowledge and attitude toward isotretinoin ocular side effects in Egypt. *Clin Cosmet Investig Dermatol*. 2021;14:1295–1301. doi:10.2147/CCID.S327870
56. Sánchez-González MC, De-Hita-Cantalejo C, Martínez-Lara C, et al. Oral isotretinoin for acne vulgaris side effects on the ocular surface: hyaluronic acid and galacto-xyloglucan as treatment for dry eye disease signs and symptoms. *Front Med*. 2022;9:959165. doi:10.3389/fmed.2022.959165
57. Moy A, McNamara NA, Lin MC. Effects of isotretinoin on meibomian glands. *Optom Vis Sci*. 2015;92(9):925–930. doi:10.1097/OPX.0000000000000656
58. Gurlevik U, Kemeriz F, Yasar E. The effect of isotretinoin on meibomian glands in eyes: a pilot study. *Int Ophthalmol*. 2022;42(7):2071–2078. doi:10.1007/s10792-021-02205-1
59. de Queiroga IB, Antônio Vieira L, Barros JDN, et al. Conjunctival impression cytology changes induced by oral isotretinoin. *Cornea*. 2009;28(9):1009–1013. doi:10.1097/ICO.0b013e3181a16858

60. Koca S, Oral AY. Assessments of the ocular surface and meibomian gland morphology in patients with treatment-naive acne vulgaris. *Arq Bras Oftalmol*. 2022;86(2). doi:10.5935/0004-2749.20230025
61. Tran PT, Evron E, Goh C. Characteristics of patients with hair loss after isotretinoin treatment: a retrospective review study. *Int J Trichol*. 2022;14(4):125–127. doi:10.4103/ijt.ijt_80_20
62. Lytvyn Y, McDonald K, Mufti A, et al. Comparing the frequency of isotretinoin-induced hair loss at <0.5-mg/kg/d versus <0.5-mg/kg/d versus ≥0.5-mg/kg/d dosing in acne patients: a systematic review. *JAAD Int*. 2022;6:125–142. doi:10.1016/j.jdin.2022.01.002
63. Chelliah P, Glass D. Comprehensive review of reports of menstrual irregularities associated with isotretinoin. *Int J Womens Dermatol*. 2020;6 (5):365–367. doi:10.1016/j.ijwd.2020.07.004
64. Akpolat D. Unexpected effects of oral isotretinoin in adolescents with acne vulgaris. *Cureus*. 2021;13(8):e17115. doi:10.7759/cureus.17115
65. Özçelik S, Kılıç FA. Effects of ısotretinoin on the growth rate and thickness of the nail plate. *Int J Dermatol*. 2021;60(10):1258–1262. doi:10.1111/ijd.15635
66. Busetti BM, Azulay DR, Aguinaga F, et al. Evaluation of CPK levels during acne treatment with oral isotretinoin. *An Bras Dermatol*. 2021;96 (5):626–627. doi:10.1016/j.abd.2020.08.020
67. Mülkoğlu C, Karaosmanoğlu N. Effect of oral isotretinoin on muscle strength in patients with acne vulgaris: a prospective controlled study. *BMC Pharmacol Toxicol*. 2021;22(1):17. doi:10.1186/s40360-021-00483-0
68. 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):77.
69. Acar EM, Şaş S, Koçak FA. Evaluation of musculoskeletal adverse effects in patients on systemic isotretinoin treatment: a cross-sectional study. *Arch Rheumatol*. 2022;37(2):223–229. doi:10.46497/ArchRheumatol.2022.8645
70. Hareedy MS, Tawfik KM. Systemic isotretinoin has an impact on hemoglobin, ferritin, urea, ceruloplasmin, albumin, uric acid levels and neutrophil to lymphocyte ratio in acne patients. *J Cosmet Dermatol*. 2022;21(11):6191–6198. doi:10.1111/jocd.15199
71. National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
72. Zane LT, Leyden WA, Marqueling AL, et al. A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. *Arch Dermatol*. 2006;142(8):1016–1022. doi:10.1001/archderm.142.8.1016
73. Cosansu NC, Yuksekal G, Turan U, et al. Investigation of systemic immune-inflammation index and systemic inflammation response index as an indicator of the anti-inflammatory effect of isotretinoin in patients with acne vulgaris. *Cutan Ocul Toxicol*. 2022;41(2):174–178. doi:10.1080/15569527.2022.2081700
74. Cenk H, Kapicioglu Y, Yologlu S. Does systemic isotretinoin treatment constitute a predisposition to allergic sensitization? *Skinmed*. 2021;19 (1):28–34.
75. Salem Hareedy M, Mahmoud WA, Tawfik KM. Patterns of thyroid dysfunctions in adolescent patients suffering from severe acne during isotretinoin treatment. *Clin Exp Pharmacol Physiol*. 2021;48(10):1317–1326. doi:10.1111/1440-1681.13552
76. Toossi P, Azizian Z, Yavari H, et al. Serum 25-hydroxy vitamin D levels in patients with acne vulgaris and its association with disease severity. *Clin Cases Miner Bone Metab*. 2015;12(3):238–242. doi:10.11138/ccmbm/2015.12.3.238
77. Bremner JD, McCaffery P. The neurobiology of retinoic acid in affective disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32 (2):315–331. doi:10.1016/j.pnpbp.2007.07.001
78. O'Reilly KC, Trent S, Bailey SJ, et al. 13- cis -retinoic acid alters intracellular serotonin, increases 5-HT1A receptor, and serotonin reuptake transporter levels in vitro. *Exp Biol Med*. 2007;232(9):1195–1203. doi:10.3181/0703-RM-83
79. Lane MA, Bailey SJ. Role of retinoid signalling in the adult brain. *Prog Neurobiol*. 2005;75(4):275–293. doi:10.1016/j.pneurobio.2005.03.002
80. Bremner JD, Fani N, Ashraf A, et al. Functional brain imaging alterations in acne patients treated with isotretinoin. *Am J Psychiatry*. 2005;162 (5):983–991. doi:10.1176/appi.ajp.162.5.983
81. 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. doi:10.1016/j.jaad.2016.12.028
82. Li C, Chen J, Wang W, et al. Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis. *BMJ Open*. 2019;9(1):e021549. doi:10.1136/bmjopen-2018-021549
83. Erdoğan Y, Erturan İ, Aktepe E, et al. Comparison of quality of life, depression, anxiety, suicide, social anxiety and obsessive-compulsive symptoms between adolescents with acne receiving isotretinoin and antibiotics: a prospective, non-randomised, open-label study. *Paediatr Drugs*. 2019;21(3):195–202. doi:10.1007/s40272-019-00340-y
84. AlGhofaili FA. Isotretinoin use and risk of depression in acne vulgaris patients in Riyadh. *Saudi Arabia Cureus*. 2021;13(3):e13680.
85. Kridin K, Ludwig RJ. Isotretinoin and the risk of psychiatric disturbances - A global study shedding new light on a debatable story. *J Am Acad Dermatol*. 2022;88(2):388–394.
86. Paljarvi T, McPherson T, Luciano S, et al. Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data. *Br J Dermatol*. 2022;187(1):64–72. doi:10.1111/bjd.21049
87. Hekmatjah J, Chat V, Sierro T, et al. Differences in depression and distress between acne patients on isotretinoin vs oral antibiotics. *J Drugs Dermatol*. 2021;20(2):172–177. doi:10.36849/JDD.5559
88. Sundström A, Alfredsson L, Sjolin-Forsberg G, et al. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. *BMJ*. 2010;341(1):c5812. doi:10.1136/bmj.c5812
89. Lappas AS, Edwards Suarez L, Tzanetakou V, et al. Factors associated with increased suicidality risk following referral for isotretinoin commencement. *Australas Psychiatry*. 2022;30(1):44–48. doi:10.1177/10398562211029955
90. Vona-Giralt G, Vilaplana-Carnerero C, Ouchi D, et al. Risk of psychiatric events in women treated with isotretinoin: a self-controlled study with SIDIAP database. *Expert Opin Drug Saf*. 2022;22(3):1–7.
91. Droitcourt C, Poizeau F, Kerbrat S, et al. Isotretinoin and risk factors for suicide attempt: a population-based comprehensive case series and nested case-control study using 2010–2014 French Health Insurance Data. *J Eur Acad Dermatol Venereol*. 2020;34(6):1293–1301. doi:10.1111/jdv.16005

92. Ugonabo N, Love E, Wong PW, et al. Psychiatric disorders and suicidal behavior in patients with acne prescribed oral antibiotics versus isotretinoin: analysis of a large commercial insurance claims database. *J Am Acad Dermatol*. 2021;85(4):878–884. doi:10.1016/j.jaad.2021.01.107
93. Singer S, Tkachenko E, Sharma P, et al. Psychiatric adverse events in patients taking isotretinoin as reported in a food and drug administration database from 1997 to 2017. *JAMA Dermatol*. 2019;155(10):1162–1166. doi:10.1001/jamadermatol.2019.1416
94. Bray AP, Kravvas G, Skevington SM, et al. The effects of isotretinoin on serotonin: a prospective pilot study on acne patients. *An Bras Dermatol*. 2022;97(4):526–528. doi:10.1016/j.abd.2021.02.011
95. Chen Y-H, Wang W-M, Chung C-H, et al. Risk of psychiatric disorders in patients taking isotretinoin: a nationwide, population-based, cohort study in Taiwan. *J Affect Disord*. 2022;296:277–282. doi:10.1016/j.jad.2021.09.055
96. Layton AM, Cunliffe WJ. Guidelines for optimal use of isotretinoin in acne. *J Am Acad Dermatol*. 1992;27(6 Pt 2):S2–S7. doi:10.1016/S0190-9622(08)80252-6
97. Cunliffe WJ, van de Kerkhof PCM, Caputo R, et al. Roaccutane treatment guidelines: results of an international survey. *Dermatology*. 1997;194(4):351–357. doi:10.1159/000246134
98. Dessinioti C, Zouboulis CC, Bettoli V, et al. Comparison of guidelines and consensus articles on the management of patients with acne with oral isotretinoin. *J Eur Acad Dermatol Venereol*. 2020;34(10):2229–2240. doi:10.1111/jdv.16430
99. Al Muqarrab F, Almohssen A. Low-dose oral isotretinoin for the treatment of adult patients with mild-to-moderate acne vulgaris: systematic review and meta-analysis. *Dermatol Ther*. 2022;35(4):e15311. doi:10.1111/dth.15311
100. Haroun AM, Ibrahim MA, Soliman AS, et al. Systemic isotretinoin for acne treatment: ovarian reserve is safe with the low dose. *Dermatol Ther*. 2022;35(11):e15811. doi:10.1111/dth.15811
101. Thiboutot DM, Dréno B, Abanmi A, 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 Suppl 1):S1–S23.e1. doi:10.1016/j.jaad.2017.09.078
102. Demirci Saadet E. Investigation of relapse rate and factors affecting relapse after oral isotretinoin treatment in patients with acne vulgaris. *Dermatol Ther*. 2021;34(6):e15109. doi:10.1111/dth.15109
103. Rademaker M. Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris. *Int J Dermatol*. 2016;55(5):518–523. doi:10.1111/ijd.12942
104. Lehucher-Ceyrac D, de La Salmonière P, Chastang C, et al. Predictive factors for failure of isotretinoin treatment in acne patients: results from a cohort of 237 patients. *Dermatology*. 1999;198(3):278–283. doi:10.1159/000018130
105. Borghi A, Mantovani L, Minghetti S, et al. Low-cumulative dose isotretinoin treatment in mild-to-moderate acne: efficacy in achieving stable remission. *J Eur Acad Dermatol Venereol*. 2011;25(9):1094–1098. doi:10.1111/j.1468-3083.2010.03933.x
106. Quéreux G, Volteau C, N'Guyen JM, et al. Prospective study of risk factors of relapse after treatment of acne with oral isotretinoin. *Dermatology*. 2006;212(2):168–176. doi:10.1159/000090658
107. Skroza N, Tolino E, Balduzzi V, et al. Advantages of tailored isotretinoin treatment in moderate to severe acne: real-life data. *Front Pharmacol*. 2021;12:733526. doi:10.3389/fphar.2021.733526
108. Chilicka K, Rogowska AM, Szyguła R, et al. Examining quality of life after treatment with azelaic and pyruvic acid peels in women with acne vulgaris. *Clin Cosmet Investig Dermatol*. 2020;13:469–477. doi:10.2147/CCID.S262691
109. Ruilian D, He Y, Wu Q, et al. Quality of life in patients with acne vulgaris: an observational study. *Int J Dermatol Venereol*. 2023;9900. doi:10.1097/JD9.0000000000000315
110. Chilicka K, Rogowska AM, Szyguła R, et al. Association between satisfaction with life and personality types A and D in young women with acne vulgaris. *Int J Environ Res Public Health*. 2020;17(22):8524. doi:10.3390/ijerph17228524
111. Rea S, Tucker S, Frittelli V, et al. A feasibility study for a triple-blind randomized controlled trial investigating the effects of oral isotretinoin on mood and quality of life in patients with acne vulgaris. *Clin Exp Dermatol*. 2018;43(1):54–56. doi:10.1111/ced.13284
112. Yang S, Lu Z, Lin T, et al.; Laser Cosmetology Group, Medical Aesthetics and Cosmetology Branch of Chinese Medical Association, Cosmetic Laser Group, Chinese Society of Dermatology, Laser Group, Cosmetic and Plastic Surgeon Branch of Chinese Medical Doctor Association. Consensus on treatment of acne scars in China (2021). *Int J Dermatol Venereol*. 2022;5(3):121–131. doi:10.1097/JD9.0000000000000229
113. Lee G, Wolf JR, Somers KE. Administrative burden of iPLEDGE deters isotretinoin prescriptions: results from a survey of dermatologists. *Cutis*. 2022;110(1):44–47. doi:10.12788/cutis.0558
114. Yousif J, Adlam T, Grant-Kels JM, et al. The Supreme Court abortion ban impact on dermatology. *J Am Acad Dermatol*. 2022;87(5):1225–1226. doi:10.1016/j.jaad.2022.07.026
115. Zamil DH, Paidisetty PS, Wang LK. Ignoring the elephant in the room-overregulated isotretinoin and unregulated dietary supplements in the United States. *Proc*. 2022;35(6):892–893. doi:10.1080/08998280.2022.2111643
116. Cook M, Perche P, Feldman S. Oral vitamin A for acne management: a possible substitute for isotretinoin. *J Drugs Dermatol*. 2022;21(6):683–686. doi:10.36849/JDD.6781
117. Lim SK, Ha J-M, Lee Y-H, et al. Comparison of vitamin D levels in patients with and without acne: a case-control study combined with a randomized controlled trial. *PLoS One*. 2016;11(8):e0161162. doi:10.1371/journal.pone.0161162
118. Griffin AC, Kern MJ, Kirkwood KL. MKP-1 is essential for canonical vitamin D-induced signaling through nuclear import and regulates RANKL expression and function. *Mol Endocrinol*. 2012;26(10):1682–1693. doi:10.1210/me.2012-1033
119. de Souza Pereira R. Treatment of resistant acne vulgaris in adolescents using dietary supplementation with magnesium, phosphate and fatty acids (Omega 6 and 7): comparison with 13-cis-retinoic acid. *J Diet Suppl*. 2022;1–11. doi:10.1080/19390211.2022.2100550
120. Piszczatoski CR, Powell J. Topical clascoterone: the first novel agent for acne vulgaris in 40 years. *Clin Ther*. 2021;43(10):1638–1644. doi:10.1016/j.clinthera.2021.08.007
121. Valente Duarte de Sousa IC. Guidance for the pharmacological management of acne vulgaris. *Expert Opin Pharmacother*. 2022;23(1):49–62. doi:10.1080/14656566.2021.1990263
122. Ma Z, Kochergin N, Olisova O, et al. Topical antimicrobial peptides in combined treatment of acne patients. *J Cosmet Dermatol*. 2022;21(4):1533–1538. doi:10.1111/jocd.14300

123. Ye D, Xue H, Huang S, et al. A prospective, randomized, split-face study of concomitant administration of low-dose oral isotretinoin with 30% salicylic acid chemical peeling for the treatment of acne vulgaris in Asian population. *Int J Dermatol*. 2022;61(6):698–706. doi:10.1111/ijd.16127
124. Dixit N, Jena A, Panda M, et al. Randomized prospective study of low-dose isotretinoin alone and combination with salicylic acid and mandelic peel against acne tarda. *J Cosmet Dermatol*. 2022;21(10):4398–4404. doi:10.1111/jocd.14973
125. Salah E. Oral Zinc as a novel adjuvant and sparing therapy for systemic isotretinoin in acne vulgaris: a preliminary comparative study. *J Clin Aesthet Dermatol*. 2022;15(10):58–61.
126. Ibrahim SM, Farag A, Hegazy R, et al. Combined low-dose isotretinoin and pulsed dye laser versus standard-dose isotretinoin in the treatment of inflammatory acne. *Lasers Surg Med*. 2021;53(5):603–609. doi:10.1002/lsm.23356
127. Li Y, Zhu J, Zhang Y, et al. Isotretinoin plus 420 nm intense pulsed light versus isotretinoin alone for the treatment of acne vulgaris: a randomized, controlled study of efficacy, safety, and patient satisfaction in Chinese subjects. *Lasers Med Sci*. 2021;36(3):657–665. doi:10.1007/s10103-020-03113-z