



Psychiatric Adverse Events in Patients Taking Isotretinoin - A Review

Ashmi samuel^{1*}, Julie john², Riya alex³, silpa alex⁴, Saflana Thaha⁵, Sherin S⁶, Kavya prathap⁷
 Dr Joseph Mar Thoma Institute of Pharmaceutical Sciences and Research, Kayamkulam, Kerala, India.
 *Corresponding author's E-mail: ashmisamuel303@gmail.com

Received: 05-11-2019; Revised: 19-12-2019; Accepted: 28-12-2019.

ABSTRACT

Isotretinoin is a highly effective medication for severe acne. Although a causal link between isotretinoin and psychiatric adverse effects has been established, widespread media reporting of depression and suicidality with use of isotretinoin have raised concerns in both patients and clinicians and generated numerous cases of costly litigation. The risk of psychiatric adverse events in patients taking isotretinoin must be considered in the context of a known increased risk of suicidal ideation in patients.

Keywords: *Acne vulgaris*, depression, isotretinoin, psychosis, retinoid, suicide.

INTRODUCTION

Isotretinoin is a form of vitamin A. It reduces the amount of oil released by oil glands in your skin, and helps your skin renew itself more quickly. It is used to treat severe nodular acne that has not responded to other treatments, including antibiotics. Isotretinoin is available only from a certified pharmacy under a special program called iPLEDGE. Isotretinoin may also be used for purposes not listed in this medication guide.¹



Figure 1: Isotretinoin tablet

Medicinal uses

Isotretinoin is used primarily for severe cystic acne and acne that has not responded to other treatments. Many dermatologists also support its use for treatment of lesser degrees of acne that prove resistant to other treatments, or that produce physical or psychological scarring. Isotretinoin is not indicated for treatment of prepubertal acne and is not recommended in children less than 12 years of age.

It is also somewhat effective for hidradenitis suppurativa and some cases of severe rosacea. It can also be used to help treat harlequin ichthyosis, lamellar ichthyosis and is used in xeroderma pigmentosum cases to relieve keratoses. Isotretinoin has been used to treat the extremely rare condition fibrodysplasia ossificans progressiva. It is also used for treatment of neuroblastoma, a form of nerve cancer.

Isotretinoin therapy has furthermore proven effective against genital warts in experimental use, but is rarely used for this indication as there are more effective treatments. Isotretinoin may represent an efficacious and safe alternative systemic form of therapy for recalcitrant condylomata acuminata (RCA) of the cervix. In most countries this therapy is currently unapproved and only used if other therapies failed.

Prescribing restrictions

Isotretinoin is a teratogen; there is about a 20–35% risk for congenital defects in infants exposed to the drug *in utero*, and about 30–60% of children exposed to isotretinoin prenatally have been reported to show neurocognitive impairment. Because of this, there are strict controls on prescribing isotretinoin to women who may become pregnant and women who become pregnant while taking isotretinoin are strongly advised to terminate their pregnancies.

In most countries, isotretinoin can only be prescribed by dermatologists or specialist physicians; some countries also allow limited prescription by general practitioners and family doctors. In the United Kingdom and Australia, isotretinoin may be prescribed only by or under the supervision of a consultant dermatologist. Because severe cystic acne has the potential to cause permanent scarring over a short period, restrictions on its more immediate availability have proved contentious. In New Zealand, isotretinoin can be prescribed by any doctor but subsidised only when prescribed by a vocationally-registered general practitioner, dermatologist or nurse practitioner.

In the United States, since March 2006 the dispensing of isotretinoin is run through a website called iPLEDGE. The FDA required the company's marketing the drug in the US, which at the time that iPLEDGE was launched were Roche, Mylan, Barr, and Ranbaxy, to put this website in place as

a risk evaluation and mitigation strategy. These companies formed a group called the Isotretinoin Products Manufacturing Group, and it hired Covance to run the website. Prescribers, pharmacists, and all people to whom the drug is prescribed need to register on the site and log information into it. Women with child-bearing potential must commit to using two forms of effective contraception simultaneously for the duration of isotretinoin therapy and for a month immediately preceding and a month immediately following therapy. Additionally they must have two negative pregnancy tests 30 days apart and have negative pregnancy tests before each prescription is written.

Mechanism of action

Isotretinoin's exact mechanism of action is unknown, but several studies have shown that isotretinoin induces apoptosis (programmatic cell death) in various cells in the body. Cell death may be instigated in the meibomian glands, hypothalamic cells, hippocampus cells and important for treatment of acne—in sebaceous gland cells. Isotretinoin has a low affinity for retinoic acid receptors (RAR) and retinoid X receptors (RXR), but may be converted intracellularly to metabolites that act as agonists of RAR and RXR nuclear receptors.⁵

One study suggests the drug amplifies production of neutrophil gelatinase-associated lipocalin (NGAL) in the skin, which has been shown to reduce sebum production by inducing apoptosis in sebaceous gland cells, while exhibiting an antimicrobial effect on *Cutibacterium acnes*. The drug decreases the size and sebum output of the sebaceous glands. Isotretinoin is the only available acne drug that affects all four major pathogenic processes in acne, which distinguishes it from alternative treatments (such as antibiotics) and accounts for its efficacy in severe, nodulocystic cases. The effect of Isotretinoin on sebum production can be temporary, or remission of the disease can be complete and prolonged.²

Adverse effect

Psychiatric	<ul style="list-style-type: none"> • Depression • Aggravated depression • Aggressive tendencies • Anxiety • Mood alterations 	<ul style="list-style-type: none"> • Abnormal behaviour • Psychotic disorder • Suicidal ideation • Suicide attempt • Suicide
--------------------	---	---

Mechanisms and mode of action

Isotretinoin (13-cis-retinoic acid) is an oral retinoid medication with sebostatic properties, decreasing proliferation of basal sebocytes, reducing sebum production, and inhibiting sebocyte differentiation. Retinoids are a family of compounds derived from vitamin A. 13-cis-retinoic acid is an active form of vitamin A that

binds to retinoic acid receptors (RARs) in the brain and embryonic tissues in the craniofacial region, heart, and thymus. Like glucocorticoid and thyroid hormone receptors, RARs are part of the nuclear receptor superfamily that regulates gene expression in the brain. Notably, RARs regulate expression of homeobox, or *HOX*, genes, which in turn control developmental programs in various species. Accordingly, abnormal retinoid levels can have neurologic effects, and retinoids hold a central place in the history of neurobehavioral teratology.

Beyond its prenatal effects, isotretinoin may influence cognition in adult life. RARs are expressed in the adult hippocampus, thalamus, and pons (RAR α), and the striatum, hypothalamus, and medulla (RAR β), and retinoic acid has been found to modulate synaptic plasticity and neurogenesis in adulthood.⁴

Isotretinoin is hypothesized to induce depression-related behaviors by decreasing adult neurogenesis or altering expression of components of the serotonergic neurotransmitter system, resulting in impaired serotonin signaling. An association of retinoic acid signaling with stress and depression is supported by the overlap between brain areas implicated in both. Furthermore, functional brain imaging has revealed a decrease in brain metabolism in the orbitofrontal cortex—an area established to mediate symptoms of depression—in acne patients treated with isotretinoin.

Forkhead box class O transcription factors may be implicated in both the therapeutic and adverse effects of isotretinoin. Upregulation of Forkhead box protein O1 may inhibit hippocampal neurogenesis.

Teratogenic effects

High levels of vitamin A during pregnancy can be teratogenic. Safe levels are estimated to fall between 25,000 and 37,000 IU/d.

In human beings, isotretinoin is associated with a wide spectrum of birth defects, including craniofacial, heart, and nervous system malformations. Reported effects have included agenesis of the cerebellar vermis; malformation of posterior fossa; multiple leptomeningeal neuroglial heterotopias; hydrocephalus; abnormalities of the corticospinal tracts; mid-hindbrain malformations; craniofacial defects including anotia and microtia; abnormalities of the inner ear; ocular, retinal, or optic nerve abnormalities, including myopia and light sensitivity; psychomotor retardation; mental retardation; learning disabilities; and premature birth.

Isotretinoin is thought to induce cleft palate in human beings by sustaining the expression of epidermal growth factor receptors in medial epithelial cells of the palate at a time when these cells would normally undergo apoptosis, resulting in continued DNA synthesis, proliferation, survival, and shift in cell phenotype.

In nonhuman primate models, isotretinoin has produced defects of the cerebellar vermis by interfering with

processes that subdivide the cerebellum into smaller units; craniofacial skeleton and heart defects due to exposure earlier during gestation; and thymus and cerebellum defects due to exposure later during gestation, with defect severity generally depending on duration of exposure.⁵

Psychiatric effects

Strong evidence, including more than 400 case reports received by the US Food and Drug Administration (FDA) from 1982 to 2000 alone, suggests a link between isotretinoin and depression. During the same time period, 37 suicides were also reported to the FDA. In the United States, questions regarding isotretinoin's psychiatric safety came to broader public attention after a 15-year-old male patient flew a stolen plane into a Florida office tower and his family filed a wrongful death lawsuit against isotretinoin's manufacturer, attributing the pilot's acute psychosis to use of the medication.⁶

Notwithstanding these reports, the association between isotretinoin use and psychiatric illness, including among individuals with no prior psychiatric history, has remained controversial. As recently as 2015, only 37% of 591 board-certified dermatologists participating in a survey study responded that they believed isotretinoin may cause psychiatric disturbances.

Results of 1 study involving Finnish male military conscripts suggested that, on a group level, isotretinoin was not typically associated with depression or suicidal ideation, but individual patients may have idiosyncratic mood reactions. Depression and suicidal ideation were assessed with the Beck Depression Inventory, and Beck Depression Inventory scores were found to decline significantly ($P < 0.001$) among patients taking isotretinoin.

Another study involving the Israeli Defense Forces compared use of mental health services by young adults taking isotretinoin and young adults in a control group, and found a statistically significant intergroup difference ($P = 0.0003$), with the isotretinoin user group showing relatively increased use of mental health resources compared with controls.

Large-scale review and survey studies of isotretinoin side effects have found that 25.16% of adverse effects reported for isotretinoin were psychiatric, and that 1.65% of pediatric patients taking isotretinoin reported psychiatric symptoms. 2017 search of the French National Pharmacovigilance database for systemic acne treatments yielded 71 reports of severe psychiatric disorders involving isotretinoin.⁷

Affective disorders and suicide

Information regarding depression was added to isotretinoin labeling in 1998 in response to numerous reports submitted to the FDA MedWatch system. Meanwhile, suicides during treatment were reported in several countries and brought to public attention.

In a review of drug-induced depression and suicidal behavior reported under the United Kingdom's Yellow Card Scheme from 1998 to 2011, isotretinoin was among the top-5 drugs most frequently associated with reports of depression. In the United States in 2015, isotretinoin ranked in the top 10 of the FDA's database of drugs associated with reports of depression and suicide attempts.

However, numerous authors have suggested either no association with depression, or instead an amelioration of depressive or anxious symptoms with treatment, prompting suggestions that idiosyncratically susceptible patients may exist, or that individuals with a family history or personal history of mental illness may be susceptible.

Psychosis and mania

Isotretinoin is contraindicated in psychosis because it worsens the course of the disease. Similarly, an excess of dietary vitamin A has been reported to induce psychosis.

One literature review incorporating information from case reports, patient charts, and drug registries suggested that many patients identified as depressed while taking isotretinoin in fact showed signs of activation, agitation, elevated mood, and psychosis, and that these symptoms appeared to be more prevalent in patients with a personal or family history of mental illness.⁸

Individual cases of isotretinoin-related psychosis reported in the literature have included a woman without a family history of mental illness experiencing manic psychosis associated with treatment; a young man developing acute psychosis within a few days of starting treatment, and showing rapid improvement after stopping treatment; a 13-year-old male patient experiencing insomnia, delusions, and auditory hallucinations after 2 months of treatment, and experiencing complete remission 2 weeks after stopping treatment and taking olanzapine; and a 25-year-old woman with a family history of bipolar disorder developing psychotic symptoms during treatment, with symptoms remitting after stopping treatment.

Bipolar disorder

Bipolar patients treated with isotretinoin are at risk for exacerbation of mood symptoms, including suicidal ideation.

In Poland, a case analysis comprising 7 female and 2 male patients ages 18 to 27 years admitted to the Department of Psychiatry at the Medical University of Lublin included 1 patient with a bipolar mixed episode and 1 with a rapid cycling bipolar I episode, each temporally associated with isotretinoin treatment.⁹

In another study, a retrospective chart review of 300 outpatients with bipolar disorder identified 10 patients taking isotretinoin. Nine of 10 patients, ages 15 to 39 years, experienced worsening mood symptoms, 3 experienced suicidal ideation, and 8 experienced a reversal of symptoms after isotretinoin discontinuation. Of 9 patients

with worsening mood symptoms, 6 experienced mixed symptoms, 2 experienced depressive symptoms, and 1 experienced hypomanic symptoms.

Other psychiatric case reports

Isotretinoin has been associated with psychiatric disorders and symptoms beyond depression and psychosis in some cases. In 1 instance, a 23-year-old man developed obsessive-compulsive disorder after 7 years of isotretinoin treatment (10–20 mg/d). A combination of fluvoxamine (300 mg/d) and olanzapine (15 mg/d) improved his symptoms. The literature also includes reports of panic attacks in a 20-year-old man and another 17-year-old patient in relation to use of isotretinoin. Instances of erectile dysfunction and increased aggression, respectively, have also been reported in other cases.¹⁰

RESULTS

Between 1997 and 2017, 17 829 psychiatric adverse events with isotretinoin use were reported to the US Food and Drug Administration, with depressive disorders, emotional lability, and anxiety disorders reported most frequently. Of these events, 8936 (50.1%) were reported among men and 8362 (46.9%) among women; the sex of the individual was not reported for 531 events (3.0%). Of the 13 553 reports that included patient age, the mean (SD) age was 22.1 (8.6) years. More than half (52.5%) of all events occurred in 10- to 19-year-old individuals. Whereas depression and anxiety were reported equally between sexes, eating disorders were more common in females (58 of 85 [68.2%]), while attention-deficit/hyperactivity disorder (55 of 83 events [66.3%]) and completed suicides (290 of 368 [78.8%]) were more common in males. The rates of completed suicide were 8.4 and 5.6 suicides per 100 000 patients enrolled in iPLEDGE in 2009 and 2010, respectively.¹¹

CONCLUSIONS

Although depressive disorders and suicidality were frequently reported with isotretinoin use, these reports must be considered in the context of elevated rates of depression and suicide among patients with acne at large. Many psychiatric adverse events unrelated to depression and suicidality were also reported, but it is unclear if they were a result of isotretinoin therapy. Although no causal link between isotretinoin and psychiatric risk has been established, patients taking the drug appear vulnerable to psychiatric concerns.

REFERENCES

1. www.drugs.com Retrieved from <https://www.drugs.com/mtm/isotretinoin.html> Accessed on 15 November 2019
2. wikipedia.org Retrieved from <https://en.wikipedia.org/wiki/Isotretinoin> Accessed on 15 November 2019
3. www.healio.com Retrieved from <https://www.healio.com/dermatology/acne/news/online/%7B548cd0ea-ac3b-4648-a1cd-a8b80e71b2ad%7D/more-data-needed-on-link-between-isotretinoin-psychiatric-events> Accessed on 15 November 2019
4. Segmiller F.M. Psychosis during treatment with isotretinoin. *Ther Adv Psychopharmacol.* 2013;3(4):244–245. [PMC free article] [PubMed] [Google Scholar]
5. Schaffer L.C., Schaffer C.B., Hunter S., Miller A. Psychiatric reactions to isotretinoin in patients with bipolar disorder. *J Affect Disord.* 2010; 122(3):306–308. [PubMed] [Google Scholar]
6. Ludot M., Mouchbac S., Ferreri F. Inter-relationships between isotretinoin treatment and psychiatric disorders: depression, bipolar disorder, anxiety, psychosis and suicide risks. *World J Psychiatry.* 2015;5(2):222–227. [PMC free article] [PubMed] [Google Scholar]
7. Von Broekhoven F., Verkes R.J., Janzing J.G. Psychiatric symptoms during isotretinoin therapy. *Ned Tijdschr Geneeskd.* 2003;147(47):2341–2343. [PubMed] [Google Scholar]
8. Fornaro M. Obsessive-compulsive disorder with bipolar diathesis following Isotretinoin therapy remitting upon treatment with olanzapine and fluvoxamine. *Neuropsychiatr Dis Treat.* 2010;6:719–722. [PMC free article] [PubMed] [Google Scholar]
9. Poblete A., Herskovic M.V., Eva C.P. Panic attacks in a patient treated with isotretinoin for acne. Report of one case. *Rev Med Chil.* 2006;134(12):1565–1567. [PubMed] [Google Scholar]
10. Alcalá Partera J.A. Depression and panic attack in acne treated with isotretinoin. *Semergen.* 2012;38(3):188–191. [PubMed] [Google Scholar]
11. jamanetwork.com Retrieved from <https://jamanetwork.com/journals/jamadermatology/article-abstract/2737332> Accessed on 16 November 2019

Source of Support: Nil, Conflict of Interest: None.

