

ISOTRETINOIN AND PSYCHIATRIC EFFECTS

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ABSTRACT

Isotretinoin is a vitamin A derivative that has been commonly used by dermatologists for the treatment of acne. Isotretinoin has many dose-related side-effects, which have caused many debates lately, especially related to psychiatric and gastrointestinal issues. Since the introduction of isotretinoin into the market, there have been a growing number of reported cases of psychiatric side-effects, including: depression, suicide, aggression, psychosis, mood swings, violent behaviour, hostility, bipolar disorder, and obsessive compulsive disorder. According to some animal studies, isotretinoin can pass the blood-brain barrier and it may cause serious side-effects. On the other hand, it has been shown that isotretinoin can decrease the psychiatric symptoms of many psychiatric patients. Because a definitive causal relationship has not been established, it remains unclear as to whether isotretinoin therapy leads to psychopathology. In this review article, we evaluate the published articles about the psychiatric side-effects of isotretinoin and discuss the psychopathologic effects of isotretinoin.

Keywords: Acne, anxiety, depression, isotretinoin.

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The dermatologists have been using isotretinoin, which is a synthetic retinoid, for >30 years in severe nodulocystic acne treatment. Since isotretinoin has a broad side-effect profile, the FDA has approved isotretinoin only for the treatment of cystic and nodular acne, which is refractory to other forms of treatment.^{1,2} However, dermatologists have frequently prescribed it for less severe acne worldwide because of the great efficacy in acne treatment, which leads to increasing numbers of patients being exposed to the drug.^{3,4}

There have been a growing number of reported cases of psychiatric side-effects after exposure to isotretinoin, including depression, suicide, aggression, psychosis, mood swings, violent behaviour, hostility, bipolar disorder, and obsessive compulsive disorder (OCD).⁵⁻⁸ Since a definitive causal relationship has not been established, it remains unclear whether isotretinoin therapy may

lead to psychopathology. On the other hand, several studies have demonstrated associations between acne and impaired self-esteem, self-confidence, body image, depression, anger, anxiety, social withdrawal, social phobia, somatoform disorders, and suicidal ideation.⁹⁻¹³ It is not clear whether the association between the psychopathology and isotretinoin is a side-effect of the medication, or if the acne causes the psychological effects.^{14,15} In addition, the literature contains credible evidence that isotretinoin treatment may reduce the psychosocial impact of acne.^{15,16} So if the impact of isotretinoin-induced psychiatric side-effects is to be assessed, it is important to consider the unfavourable psychological impact of acne.

In 2002, the American Academy of Dermatology organised a conference and a panel (at the same time) about the safety of isotretinoin and psychiatric side-effects. As a result, they stated that there were faults in the methodology of the available studies and more scientific data were needed to draw conclusions about the

psychological effects of isotretinoin.¹⁷ According to recent European guidelines, it was concluded that depression diagnoses or depressive symptoms did not significantly increase in patients treated with isotretinoin. The data on the risk of suicide are insufficient to establish a significant causative connection.¹⁸ In addition; there are not enough basic scientific data about the effects of retinoids on adult brain function and possible biological mechanisms that may lead to psychopathology. Our review paper aimed to exhibit the potential association between isotretinoin therapy and psychiatric side-effects by reviewing the published works on this topic.

Depression and Suicide

The controversial association between isotretinoin and depression and/or suicide has caused uneasiness among dermatologists since its release. There are several case reports and case series describing depression, suicide, or suicide ideation related to the use of isotretinoin in patients with acne.¹⁹⁻²⁷ For the first time, depressive symptomatology and suicidality due to isotretinoin therapy were reported in 1982 by Meyskens¹⁹ who had been using isotretinoin for patients with advanced cancer at a very high dosage, such as 3 mg/kg/day. 1 year after market release, Hazen et al.²⁰ published one of the first case series reporting depression in 6 of 110 patients related to the use of isotretinoin in patients with acne or a keratinising disorder with a dosage of 1-2 mg/kg/day; the average age was 28.5 years.²⁰ Scheinman et al.²¹ reported that 7 out of 700 patients with cystic acne or cutaneous disorders of keratinisation, psoriasis, or basal cell carcinoma, with a mean age of 32 years, developed clinically significant major depressive disorder, with an average dose of 0.7 mg/kg/day. The onset was not related to dosage or time, and all depressive symptoms markedly improved within 2-7 days after cessation of isotretinoin.²¹ Although there is some evidence from case reports and case series that isotretinoin may be associated with the development of depression or suicidal ideation, we know that it is difficult to make definite conclusions with case report studies.

Studies analysing large population databases have been used to assess the relationship between isotretinoin and depression. An analysis of reports of adverse drug reactions was performed from data from Roche, the World Health Organization, and the United Kingdom Medicines Control Agency from 1982-98. It concluded that the association

between isotretinoin and suicides or psychiatric adverse events (mood swings, depression, amnesia, anxiety, insomnia, and suicide) is much greater than that of antibiotics when used for acne treatment.²⁸ In 2001, a study involving an analysis of the United Healthcare database reported a statistically significant increase in depression in isotretinoin-prescribed patients.²⁹

In two large retrospective database studies funded by the manufacturer of isotretinoin, no increased risk of depression, suicide, or other psychiatric disorders in individuals treated with isotretinoin were found.^{30,31} One of them was a large population-based cohort study by Jick et al.³⁰ in 2000, which included 7,195 isotretinoin users (53% were male, and 79% were aged 10-29 years) and 13,700 oral antibiotic users.³⁰ They could not find any evidence that isotretinoin is associated with an increased risk for newly diagnosed depression, suicide, or other psychiatric disorders. But there was an increased risk of depression/psychosis with increasing age and female sex, and there was also an increased risk of suicide or attempts in patients who reported a previous history of depression or psychosis. The other large retrospective database study by Hersom et al.³¹ in 2003, including 2,821 isotretinoin users aged 12-49 years, revealed no association between the use of isotretinoin and the onset of depression. But neither report has been widely validated because of the limitations of the study methodologies.

Wysowski et al.⁴ reported the largest study assessing cases reported to the FDA Adverse Events Drug Reporting System in the first 18 years from the marketing of isotretinoin. They reported depressive symptoms in 431 exposed patients. 37 US patients committed suicide; 24 while taking isotretinoin and 13 after stopping the drug. 31 (84%) of the 37 persons were male and the median age was 17 years (range, 13-32 years). 22% were reported to have psychiatric history and 62% were reported to have either a psychiatric history or possible contributing factors. The median peak dose was 1 mg/kg per day. The median time from initiation of isotretinoin to suicide was approximately 3 months. 110 patients were reported as having been hospitalised for depression, suicide ideation, and suicide attempt, 85 while using and 25 after stopping isotretinoin. 62 (56%) were female; the median age was 17 years (range, 12-47 years), psychiatric history was reported for 44% of the 110 patients. The median peak dose was 1.1 mg/kg per

day. The authors' conclusion of a causal association was based upon a temporal relationship between taking isotretinoin and the onset of depressive symptomatology, positive de-challenge cases, and positive re-challenge cases. For all that, the authors admitted that their analysis of case reports lacked the scientific proof to determine causality.⁴

A recent Swedish retrospective cohort study included 5,756 patients, of whom 3,613 (63%) were male. The mean age of male patients at first prescription was 22.3 (SD 6.6) years, and that of female patients was 27.1 (8.0) years. They investigated risk for depression and suicide associated with isotretinoin therapy. In total, 128 patients were admitted to the hospital for attempted suicide. The risk of suicide attempts gradually increased the year before isotretinoin treatment, and peaked 6 months following the treatment. In the results the authors signified that suicide risk was already rising prior to treatment, and that the additional risk cannot be attributed to isotretinoin use.¹⁴

Studies concerning depressive disorders or suicide ideation in isotretinoin-treated patients have conflicting results. In a study of 94 US patients who were treated with isotretinoin, 10% reported insomnia and mild depression.³² Hull and Demkiw-Bartel³³ reported a prospective study of 124 patients with acne taking isotretinoin at a dosage of 1 mg/kg. Symptoms of depression were noted in 4% of patients which was sustained throughout treatment.³³ A case control study by Azoulay et al.³⁴ in the Quebec province from 1984 through to 2003, found a statistically significant association between isotretinoin and depression. On the other hand, there have been several controlled studies investigating the possible controversial link between isotretinoin and psychopathology in the setting of neuropsychological testing of various types, but none of these studies demonstrated any increased risk of depression, or suicide attempts.³⁵⁻⁴⁸ In contrast, various testing parameters of anxiety or depression are significantly improved during and after isotretinoin therapy in the majority of studies.³⁵⁻⁴⁷

In 2013, a prospective controlled study was undertaken by Marron et al.,⁴⁹ consisting of 346 patients (58.6% of the participants were women and the mean age was 20.7) with moderate acne, treated with isotretinoin at a total cumulative dose of 120 mg/kg, administered for 30 weeks. They reported that isotretinoin is not a risk factor for

depression; unlike successful treatment of acne, it seems to improve in depressive and anxiety symptoms.⁴⁹ A non-controlled prospective study by Nevoralová and Dvořáková,⁵⁰ in 2013, included 100 patients with acne, of whom 71 (71%) were male and the mean age of the patients was 18.1 years, treated with isotretinoin at a total cumulative dose of 110-150 mg/kg, according to the severity of acne. At baseline, only one male individual had had a previous history of depression. They did not find any depressive symptoms or suicide risk caused by isotretinoin. On the contrary, a statistically significant improvement of depressive symptoms was detected.⁵⁰

Recently, in the study of Psychodermatology Group of the French Dermatology Society, depression and other suicidal tendencies were linked with acne in adolescents rather than isotretinoin therapy.⁵¹ The supporting documents were revised and summarised by the recent review articles.⁵²⁻⁵⁵ In 2012, a systematic review by Bremner et al.⁵⁴ presented evidence to support this relationship in light of the data obtained from individual case reports, case studies, group studies, and database studies.⁵⁴ Once and for all, in 2014, in light of the evidence presented by Bremner and colleagues,⁵⁴ an Australian consensus developed recommendations to emphasise the importance of suitable patient evaluation with a focus on psychological state prior to the onset of isotretinoin and careful monitoring.⁵⁶

With all these data, there is an uncertainty about the association between isotretinoin and psychopathology. Even if there is such a relation, there are no significant data that it is an idiosyncratic effect of the drug or a predictable effect in a subset of patients predisposed to the development of depression. There are also no significant data providing the importance of contributing factors such as age, gender, dosage, previous psychiatric history, personal relationship problems, stressful life events, or alcohol use.

Obsessive Compulsive Disorder

The influence of isotretinoin on serotonin and dopamine levels was displayed in animal studies, but there are insufficient data on human research. Retinoids may lead to a decrease in dopaminergic orbitofrontal functioning.^{9,57} Recent evidence from positron emission tomography studies in human subjects showed isotretinoin to be associated with a decrease in orbitofrontal metabolism, which is known to play a major role in the symptomatology

of both OCD and bipolar disorder.⁵⁸ There is a study by Gupta et al.⁵⁹ addressing improvement in obsessive compulsiveness after topical retinoic acid treatment. Fornaro et al.⁶⁰ reported the first OCD with bipolar diathesis following isotretinoin therapy. It is accentuated that when OCD occurs following isotretinoin treatment, associated psychopathology is generally severe and refractory to conventional treatment.⁶¹ In 2012, Yesilova et al.⁴⁷ examined the effects of isotretinoin treatment on OCD symptoms and found that, besides worsening of obsessive doubting, isotretinoin treatment seems to improve obsessive rumination symptoms in acne patients.⁴⁷ In 2013, a prospective controlled study (patients serving as their own control, pre-treatment, and 6 months follow-up on isotretinoin) by Karadag et al.⁴⁸ showed that there was a significant increase in OCD symptoms in acne patients treated with isotretinoin.

Psychotic Changes

In some of the studies, it was demonstrated that isotretinoin might cause psychotic changes or schizophrenia-like symptoms by affecting the dopaminergic system in animal models.^{9,57,62} Altered dopamine signalling is one of the primary pathogenetic factors in psychosis and schizophrenia. In addition to dopamine, several other neuropeptides implicated in the pathogenesis of schizophrenia are targets of retinoic acid transcription. Goodman⁶³ described evidence linking retinoids to schizophrenia such as retinoid dysregulation or the occurrence of known genetic markers in schizophrenia that happen to be loci of retinoid pathways or metabolic cascades. Villalobos et al.⁶⁴ reported a case in which the patient developed psychosis due to isotretinoin therapy. Pitts,⁶⁵ a former safety evaluator for the FDA, reported 41 (5 were psychotic) cases of positive de-challenge and re-challenge between 1982 and 1998. However, in 2013, in a prospective controlled study including 38 acne patients, psychosis subscale scores did not show any significant difference between pre-treatment and at 6-months of treatment.⁴⁸

Bipolar Disorder

There are conflicting data about the relation between isotretinoin and bipolar disorder in the

literature. Bruno et al.⁶⁶ followed 94 patients receiving different dosages of systemic isotretinoin for moderate-to-severe cystic acne. One of the cases had a diagnosis of manic depression previously that was not adversely affected by isotretinoin.⁶⁶ Cott and Wisner⁶⁷ reported that a patient with a previous history of bipolar disorder had an exacerbation of her psychosis due to isotretinoin. She demonstrated a return to baseline functioning on discontinuation of isotretinoin.⁶⁷ A study involving 500 soldiers treated with isotretinoin for acne reported that 5 of them developed 'manic psychosis.' Three of these patients had a familial bipolar disorder history of a first-degree relative, but none of them had a history of bipolar disorder.⁶² Schaffer et al.⁶¹ suggested that isotretinoin can cause worsening of mood symptoms, including suicidal behaviour, in some patients with bipolar disorder.⁶¹

CONCLUSION

As a result, there is an uncertainty about the association between isotretinoin and psychopathology. Case reports and series strongly suggest a link between the use of isotretinoin and psychopathology, following which the manufacturer created an application of a black box warning of suicide, depression, aggression, and psychosis. However, the results of the available studies and epidemiological data could not provide strong scientific data introducing conclusive evidence. Conversely, there are accumulating data revealing the evidence that rather than cause, isotretinoin may improve psychiatric symptoms in patients with acne. To clarify the uncertain association between isotretinoin and psychiatric side-effects, well designed, double-blind, placebo-controlled studies are necessary. Oral isotretinoin treatment is teratogenic and may cause mucocutaneous side-effects and dryness, possibly also increasing the levels of triglycerides, blood cholesterol, and liver enzymes. Patients with isotretinoin-treated acne should be closely followed-up for side-effects and psychopathology. The patients and their families should be fully informed of the risks and benefits of the medication.

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