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Isotretinoin and psychiatric adverse effects: A literature review

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Abstract
This literature review article discusses the use of isotretinoin and examines its association with psychiatric adverse effects, particularly depression and suicidal ideation. The article presents historical and molecular data on isotretinoin and delves into the literature regarding its psychiatric side effects in the treatment of acne vulgaris. It tries to answer in questions about whether the scientific community has overlooked the significance of the underlying disease and explores the awareness of healthcare professionals regarding these potential adverse effects. Additionally, it investigates the likelihood of these effects based on the available literature to date.

KEYWORDS
isotretinoin, suicide, depression, psychiatry, adverse effects

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1. INTRODUCTION

Isotretinoin, also known as 13-cisretinoicacid (isomerofretinoic acid), is a pharmaceutical substance that was first synthesized in the laboratory in 1955. It received FDA approval for the treatment of moderate to severe acne (acne vulgaris) in 1982 and was first used for the same purpose in Europe in 1983. Retinoic acid (RA) is a metabolite of vitamin A, which humans obtain from red meat and carotenoids [1]. Retinoic acid plays a significant role in both embryonic and adult life. In embryo, it is essential for the proper development of organs and function of the urogenital system, intestinal epithelium, respiratory mucosa, skin, bones, and systems such as central nervous system (CNS), while in adults, it has a role in the structure immune

system cells. In human body, retinoic acid performs all these functions by binding to proteins and receptors such as: 1) Cellular retinoic acid binding protein (CRABP), 2) Retinoic acid receptors (RAR), 3) X receptors (RXR), and 4) Retinoic Acid Response Elements (RARE) [2-4].

Similarly to RA, isotretinoin, as a lipophilic molecule, has the ability to cross the blood-brain barrier. This is the reason why, there is a belief that isotretinoin may affect areas of the limbic system of the brain, which are theoretically associated with depression. It has been proven that isotretinoin reduces neurogenesis in the hippocampus, affects the function of thalamus, hypothalamus, and amygdala, decreases metabolic activity in the prefrontal cortex and induces changes in the function of the serotoninergic and dopaminergic systems of the brain. Another speculated way in which isotretinoin is related to depressive mechanisms is its influence on the metabolic pathway of biotin and homocysteine [3, 4].

As mentioned earlier, isotretinoin is widely used today for the treatment of moderate to severe forms of acne. In fact, the effectiveness of the drug seems to exceed even the most optimistic predictions, as according to a meta-analysis, isotretinoin appears to cure about 85% of patients with severe acne after a treatment of average duration of 4 months [5]. Acne vulgaris is a multifactorial, chronic disease with complex pathophysiological mechanisms, mainly characterized by inflamed nodules and swelling on face, neck, chest, and back. It ranks as the eighth most common disease worldwide and the most common dermatological condition. It affects 80-90% of teenagers globally, but even more than 5% of adults over the age of 40 may carry scars from their adolescent acne. In the U.S. alone, more than $100 million is spent annually on acne products, whereas the total cost for its treatment in the U.S. amounts to $1 billion per year [5, 6]. Like all drugs, isotretinoin has side effects, affecting various systems of the body. The most significant of these side effects include changes in the metabolic profile of patients (increase in TGs, Glucose, Cholesterol, decrease in HDL etc.) and teratogenicity [6].

Specifically for teratogenicity, many efforts have been made to inform patients receiving isotretinoin treatment since 1988 and manufacturer Roche. Patients were encouraged to use two different forms of contraception in order to avoid unwanted pregnancies. In 2002, SMART program (System to Manage Accutane-Related Teratogenicity) was implemented to further enhance patient education. After its failure, (pregnancy incidents decreased from 127 to 120 per year), iPledge program was tested in 2006. Unfortunately, to date, it has been proven that iPledge does not surpass its predecessor in effectiveness [7].

2. WHY HAVE WE COME TO BLAME THE MIRACULOUS ISOTRETINOIN?

It all started in 1982 through the work of Meyskens. While working with patients in advanced stages of cancer, and by administering massive doses of isotretinoin, he reported that 25% of his patients exhibited depressive symptoms and suicidal ideation [8].

In 1983, Hazen et al. followed up with a case series of patients who developed depression after taking isotretinoin [9].

Between 1982 and 2000, FDA received reports of 394 cases of depression and 37 suicides in the United States. Between 1983 and 2003, 56 cases of psychiatric adverse events related to isotretinoin were reported in Canada.

Between 1982 and 1998, 42 cases of psychiatric adverse events, including a small number of suicide attempts were reported in United Kingdom. Between 1995 and 1998, 12 cases of depression and 3 suicide attempts in patients taking isotretinoin were reported in Australia [10].

To make matters worse, the Adverse Drug Event Reporting System (ADERS) labelled isotretinoin as the only non-psychotropic drug in the top 10 drugs causing suicidal ideation and in the top 5 drugs causing depression [11].

3. "ISOTRETINOIN SHOULD BE USED WITH CAUTION IF NECESSARY"

One of the staunchest opponents of isotretinoin use in the international literature is the physician and researcher Dr. Douglas Bremner. In his articles in 2008, 2012, and 2021, he addresses various reasons why we should be cautious about isotretinoin and its potential relationship with depression and suicide. Bremner believes that the promotion of isotretinoin use is because this drug is considered to be the "silver bullet" of dermatology against acne vulgaris [4].

Additionally, in his articles, Bremner discusses the difficulty of designing appropriate studies to answer questions raised, citing the high cost, the need for massive patient sample, the inability to plan blind trials due to obvious side effects of isotretinoin (e.g. dry skin), and ethical dilemmas in study design such as the adverse effect of suicidal ideation [3].

Through his work Bremner makes some valid points about the plausible ways in which isotretinoin could lead to psychiatric adverse effects. He

refers to the temporal association between isotretinoin and depression, as well as in the existence of De-challenge/Re-challenge cases. In addition he underlines the dose-response adverse effects and he presents studies in mice showing cognitive impairment and depressive symptoms after isotretinoin administration. He also presents possible mechanisms in which isotretinoin could affect the mood. Finally, he refers to the existence of drugs in the same class with isotretinoin which seem to cause psychiatric adverse effects (for example vitamin A overdose).

Before Bremner, Wysowski et al. in 2001 attempted to incriminate isotretinoin use through reporting cases of depression with or without suicidal ideation [12].

The same was attempted in 2006 by Strahan & Reimer, focusing on recording potential mechanisms of action [13].

In 2009, Kontaxakis et al. established a clear association between isotretinoin and depression, which, as they note, can occur from 1 day to 4 months after drug administration. They also highlighted the possible occurrence of psychosis or mania [8].

In 2010, Schaffer et al., despite using a small sample of 300 patients with a history of bipolar affective disorder, of whom 10 received isotretinoin, concluded that isotretinoin worsened the mood of bipolar patients (9 described mood disorders) [14].

Table I

Articles which support the safe use of isotretinoin and find no relation to its administration and depression or suicidal thoughts

Author & Date	Type of Article	Sample	Conclusion
Jacobs et al. (2001)[15]	Review- Suicide, depression, and isotretinoin: Is there a causal link?	19 articles from MEDLINE	There is no evidence that isotretinoin is a necessary or sufficient factor for depression or suicide.
Hersom et al. (2003)[16]	Isotretinoin and antidepressant pharmacotherapy: A prescription sequence symmetry analysis	7360+2821 Antidepressant and minocycline or isotretinoin	The results do not support an association between the use of isotretinoin and the onset of depression.
Marqueling and Zane (2005)[17]	Depression and Suicidal Behaviour in Acne Patients Treated with Isotretinoin: A Systematic Review	9 articles included from potential 214 studies	A potential association between isotretinoin use and depression or suicidal behavior in acne vulgaris patients is not identified.
Chia et al. (2005)[18]	Isotretinoin Therapy and Mood Changes In Adolescents with Moderate to Severe Acne: A Cohort Study	131 subjects (101 finally)	The use of isotretinoin in the treatment of moderate-severe acne in adolescents did not increase symptoms of depression. On the contrary, treatment of acne either with conservative therapy or with isotretinoin was associated with a decrease in depressive symptoms.
Kaymak et al. (2009)[19]	Report: Comparison of depression, anxiety and life quality in acne vulgaris patients who were treated with either isotretinoin or topical agents	78 acne patients: isotretinoin treatment (n=37) or topical treatment (n=41)	Results of the present study indicate that there is no increase in depressive and anxiety symptoms in the isotretinoin treatment group compared to that in the topical group. Instead, successful treatment of acne seems to improve both depressive and anxiety symptoms and improve quality of life.
Gnanaraj et al. (2015)[20]	Decrease in “Hamilton Rating Scale for Depression” Following Isotretinoin Therapy in Acne: An Open-Label Prospective Study	150 patients (143 finally)	Our study proves that oral isotretinoin causes significant clearance of acne lesions. It causes significant reduction in depression scores and is not associated with an increased incidence of depression or suicidal tendencies.

Metekoglu et al. (2018)[21]	Original Paper: Does isotretinoin cause depression and anxiety in acne patients?	112 acne patients (93 finally)	The results of this study indicate that there was no increase in HAD-D and HAD-A scores in acne patients who treated with isotretinoin. There was a significant decrease in HAD-D scores at the end of therapy. In addition, our study reveals that successful treatment of acne with isotretinoin improves HAD-D, HAD-A, GAGS, and CADI scores at the end of therapy.
Erdogan et al. (2019)[22]	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	102 adolescents using isotretinoin (n=60) and antibiotics(n=42)	We found that neither isotretinoin nor antibiotic treatment affected the levels of depression, anxiety, and suicide in acne patients. Moreover, both isotretinoin and antibiotic treatment were shown to improve the quality of life, social anxiety, and obsessive–compulsive symptoms in acne patients.
Algamdi et al. (2020)[23]	Original Article: Evaluating Depression Among Acne Vulgaris Patients Treated with Isotretinoin	29 patients (18 finally) – 12 with isotretinoin and 6 with doxycycline (control group)	This study showed that, after 8 weeks of starting treatment, isotretinoin at 0.5 mg/kg has no risk of developing depression. The results of this study did not reveal a direct relationship between the use of isotretinoin and the development of depression. Furthermore, optimum control and treatment of acne vulgaris have shown to improve depression scores.
Al Ghofaili et al. (2021)[24]	Original Article: Isotretinoin Use and Risk of Depression in Acne Vulgaris Patients in Riyadh, Saudi Arabia	179 patients - 119 patients were in the isotretinoin group	Isotretinoin treatment for acne does not appear to be associated with a statistically significant increased risk of depression in our population.
Ugonabo et al. (2021)[25]	Psychiatric disorders and suicidal behaviour in patients with acne prescribed oral antibiotics versus isotretinoin: Analysis of a large commercial insurance claims database	72,555 patients - 42,848 group of antibiotics and 30,012 group of isotretinoin	Compared to the general population, acne patients prescribed isotretinoin were less likely to engage in suicidal behavior. Further exploration into the slight increase in suicidal behavior seen in isotretinoin patients 1 year after therapy is warranted.
Yu-Chen Huang et al. (2017)[26]	Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis	31 studies included from potential 762 articles	Isotretinoin treatment for acne does not appear to be associated with an increased risk for depression. Moreover, the treatment of acne appears to ameliorate depressive symptoms.
Changqiang Li et al. (2019)[5]	Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis	20 studies included from potential 632 articles	This study suggested an association of the use of isotretinoin in patients with acne with significantly improved depression symptoms.
Bagatin et al. (2020)[1]	Expert Review of Clinical Pharmacology: The use of isotretinoin for acne – an update on optimal dosing, surveillance, and adverse effects	comprehensive literature search on PubMed database, up to March 2020, regarding oral isotretinoin	There is not currently established evidence based causal relationship between depression and oral isotretinoin therapy for acne. Therefore, isotretinoin should not be contraindicated for patients with known history of psychiatric disorder.

Kridin and Ludwig (2023)[27]	Isotretinoin and the risk of psychiatric disturbances: A global population-based retrospective cohort study shedding new light on a debatable story	2 groups of patients with acne managed by isotretinoin (n=75,708) and oral antibiotics (n=75,708). Comparison for 9 psychiatric outcomes	Isotretinoin confers lower risk of 6 psychiatric comorbidities and comparable risk of suicidal attempts.
Wen Tan et al. (2023)[28]	Risk of Suicide and Psychiatric Disorders Among Isotretinoin Users: Systematic Review and Meta-analysis	25 studies including 1,625,891 participants were included in the review and 24 in the meta-analysis	Isotretinoin users do not have increased risk of suicide or psychiatric conditions but may instead have a lower risk of suicide attempts at 2 to 4 years following treatment.

4. ISOTRETINOIN IS A SAFE DRUG WITH NO ASSOCIATION TO DEPRESSION OR SUICIDALITY

In contrast, there are many articles that support that the use of isotretinoin is completely safe, as they do not recognize any correlation with depression and suicidality. These articles include both systematic reviews and meta-analyses, as well as original studies. Table I summarizes these studies and their results.

As shown in the table above, many authors not only reject the correlation between isotretinoin and depression or suicidality but, on the contrary, argue that the quickest possible administration of isotretinoin in severe acne may lead to an improvement in patients' mood.

5. IS THE SIGNIFICANCE OF THE ORIGINAL DISEASE BEING OVERLOOKED?

Many authors have sought the explanation for the increased depression and risk of suicidality in patients with severe acne, not so much in the treatment they receive, but in the initial disease itself. Articles by Halvorsen et al. and Misery et al. in 2011 discuss adolescent girls and boys with severe acne, who respectively show double or triple the risk of suicidal ideation compared to their peers with little or no acne. These results remained the same in multifactorial models with adjustments for variables such as income or social inclusion. This fact led authors to conclude that the high rates of suicidality in adolescents receiving isotretinoin included, to some extent, adolescents who expressed this symptom due to acne and not due to treatment [29, 30].

Moving in this direction comes the study by Samuels et al. in 2020, in which the author proposes the quickest possible administration of isotretinoin as a key treatment for acne, considering that the disease itself generates anxiety and depressive symptoms [31].

On the contrary, in Gupta's research in 2023, there is a conclusion for a relationship between acne and suicidality, which has not been precisely studied, and therefore, the administration of isotretinoin should be in caution [32].

6. THE MORE NEUTRAL STANCE

There is a category of researchers avoiding to stand for or against the use of isotretinoin. In this category many articles emphasize that suicidality is quite rare and usually concerns vulnerable patient groups, such as those with pre-existing psychiatric history.

In the studies by Droicourt et al. and Magin et al. in 2005, suicide cases are discussed as very rare instances, possibly due to idiosyncratic mechanisms [10, 33, 34].

In the study by Oliveira et al. in 2017, the authors conclude that there is a relationship between depression, suicidal behaviour, and isotretinoin use, but it is not clear. So there must be a further investigation [35].

Finally, the studies by Sundstrom et al. in 2010 and by Wolverton et al. in 2013, discuss the hypothesis of "lost hope", according to which the patient may come to treatment with unrealistic hopes about its outcome. When these hopes are not realized, the patient is burdened with an additional distress that may worsen, or even contribute to the onset of depressive symptoms and suicidal ideation [7, 36].

7. WHAT ABOUT THE ROLE OF HEALTH PROFESSIONALS

In a letter to the editor in 2020, Taylor and Barbieri highlighted the inadequate depression screening

conducted by dermatologists in the U.S. to their outpatient patients with cystic acne [37].

This view was supported by the study of Nagler et al., which asserted that until 2015, only 37% of 591 certified dermatologists in the U.S. were aware of the possible psychiatric side effects of isotretinoin [38, 39].

In the same direction, McDonald et al. in 2017 modified the PHQ-9 to PHQ-2, creating an algorithm for easy and qualitative screening for depression in dermatological patients [40].

8. CONCLUSION

As evident from the literature to date, the administration of isotretinoin can lead to psychiatric side effects (mainly depression and suicidal ideation) with idiosyncratic mechanisms and in extremely rare cases. There is rich potential in exploring the precise relationship between isotretinoin and psychiatric disorders, but for this to happen, the design of RCTs with placebo drug is necessary. We must not forget the influence of severe acne on the mental health of patients, especially considering that the age group primarily affected by the disease (adolescents) is very vulnerable. Bibliographically, emerges a need for particular care in individuals belonging to vulnerable groups, such as those with a previous psychiatric history. However, to date there are no utter contraindications for isotretinoin administration in these patients. So it is worth emphasizing that all patients are entitled to access a better quality of life, something that isotretinoin therapy has been proven to offer.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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