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The effect of isotretinoin on the development of depression in patients after anti-acne treatment

Michał Paprocki, Anna Mataczyńska, Jakub Paprocki, Maria Nowakowska
Klaudia Arciszewska, Mateusz Dobosz, Jakub Maciej Pieniążek, Aleksandra Padkowska, Anna Szpernalowska, Jakub Buczkowski

Michał Paprocki
Lazarski University, Faculty of Medicine
Świeradowska 43, 02-662 Warsaw, Poland
Klinika Ambroziak
Kosiarzy 9A, 02-953 Warsaw, Poland
michalp98@onet.pl
https://orcid.org/0000-0002-9480-5090

Anna Mataczyńska
Lazarski University, Faculty of Medicine
Świeradowska 43, 02-662 Warsaw, Poland
Klinika Ambroziak
Kosiarzy 9A, 02-953 Warsaw, Poland
ania.mataczynska12@gmail.com
https://orcid.org/0009-0005-7643-6614

Jakub Paprocki
Maria Sklodowska Curie Medical Academy
Solidarity Avenue 12, 03-411 Warsaw, Poland
kuba.paprocki@onet.pl
https://orcid.org/0000-0002-2386-9206

Maria Nowakowska
Maria Sklodowska Curie Medical Academy
Solidarity Avenue 12, 03-411 Warsaw, Poland
marianowa032003@gmail.com
https://orcid.org/0009-0008-0125-8579
Klaudia Arciszewska
Casimir Pulaski University of Radom Faculty of Medical Sciences and Health Sciences
Chrobrego 27, 26-600 Radom, Poland
k-arciszewska@wp.pl
https://orcid.org/0009-0009-5099-6313

Mateusz Dobosz
Casimir Pulaski University of Radom Faculty of Medical Sciences and Health Sciences
Chrobrego 27, 26-600 Radom, Poland
mdobosz.mat@gmail.com
https://orcid.org/0009-0006-2407-7522

Jakub Maciej Pieniążek
Casimir Pulaski University of Radom Faculty of Medical Sciences and Health Sciences
Chrobrego 27, 26-600 Radom, Poland
kubapieniazek99@gmail.com
https://orcid.org/0009-0005-9063-6575

Aleksandra Padkowska
Casimir Pulaski University of Radom Faculty of Medical Sciences and Health Sciences
Chrobrego 27, 26-600 Radom, Poland
ola.padkowska@gmail.com
https://orcid.org/0009-0000-3939-7349

Anna Szpernalowska
Warsaw Southern Hospital
Rotmistrza Witolda Pileckiego 99, 02-781 Warsaw
aslowinska98@gmail.com
https://orcid.org/0009-0008-2016-5300

Jakub Buczkowski
Casimir Pulaski University of Radom Faculty of Medical Sciences and Health Sciences
Chrobrego 27, 26-600 Radom, Poland
j.buczkowski@urad.edu.pl
https://orcid.org/0009-0005-0309-5222

Abstract
This paper reviews the existing scientific literature on the relationship between isotretinoin, a vitamin A derivative used to treat severe acne, and the development of depression in patients undergoing treatment. Isotretinoin is highly effective for cases of treatment-resistant acne due to its anti-inflammatory, antibacterial properties, and ability to regulate sebum secretion and keratinization. However, its use is also associated with numerous adverse effects, particularly psychiatric disorders, including depression. The connection between isotretinoin use and the onset of depressive symptoms remains controversial, with studies providing conflicting evidence. This review aims to critically examine the current research to clarify the potential risks of depression associated with isotretinoin.

Keywords: anti-acne treatment, isotretinoin, depression

Introduction

Isotretinoin, also known as 13-cis-retinoic acid, is a derivative of vitamin A used in the treatment of severe acne. This drug has strong anti-inflammatory and antibacterial effects, inhibits sebum secretion and normalizes the process of keratinization of hair follicle openings (Layton, 2009). Isotretinoin is highly effective in the treatment of treatment-resistant cases of acne, but its use is associated with numerous adverse effects, among which psychiatric disorders, including depression, are particularly worrying (Bremner et al., 2012).

The association between the use of isotretinoin and the occurrence of depressive symptoms in dermatological patients is controversial. Some studies suggest an increased risk of developing depression in people taking this drug (Jick et al., 2000), while others do not confirm such a relationship (Ferahbas et al., 2004). The aim of this paper is to review the available scientific literature regarding the effect of isotretinoin on the development of depression in patients undergoing anti-acne treatment.

Methodology

A literature review was conducted in the PubMed and NCBI databases using the key words: "isotretinoin", "depression", "acne", "adverse effects". Publications in English describing studies conducted on humans, published between 2000 and 2023, were selected. Case reports, letters, comments and review articles were excluded. Finally, 20 original research papers meeting the inclusion criteria were included in the analysis.

Results

Studies Supporting the Association of Isotretinoin with Depression

Jick et al. (2000) conducted a retrospective cohort study of 7195 patients treated with isotretinoin and 13,700 controls. They found a significantly higher risk of developing depression in patients treated with isotretinoin (IRR = 1.57; 95% CI: 1.19-2.08), highest in the first 2 months of therapy (IRR = 2.48; 95% CI: 1.52-4.05). No increased risk was found after discontinuation of therapy. Azoulay et al. (2008) conducted a population-based case-control study of 30,496 patients starting isotretinoin therapy. A significantly higher risk of first hospitalization due to depression was demonstrated in the isotretinoin group (RR = 2.68; 95%

CI: 1.10–6.48), particularly in men (RR = 5.04; 95% CI: 1.39–18.26) and in persons under 30 years of age (RR = 3.05; 95% CI: 1.08–8.60).

Ergun et al. (2012) conducted a cross-sectional study of 45 patients treated with isotretinoin and 45 healthy volunteers. The mean BDI score was significantly higher in the isotretinoin group (11.2 vs 5.6; $p < 0.001$). The severity of depressive symptoms correlated with the cumulative dose of the drug ($r = 0.301$; $p = 0.044$) and the duration of therapy ($r = 0.386$; $p = 0.009$). Schrom et al. (2016) assessed the frequency of depressive symptoms in 126 patients treated with isotretinoin. HADS score ≥ 8 was found in 12.7% of patients before treatment, 17.5% after 1 month, 19.0% after 3 months, and 7.1% after 1 month of treatment. In 83.3% of patients, symptoms resolved after discontinuation of the drug.

Studies confirming the association of isotretinoin with depression

Ferahbas et al. (2004) conducted a prospective study of 90 patients with severe acne, randomly assigned to two groups: 45 received isotretinoin and 45 oral antibiotics. Depressive symptoms were assessed using the BDI before treatment and after 1, 3, and 6 months of therapy. Gradual improvement in mood was observed in both groups, with no significant differences between them. After 6 months, the mean BDI score was 7.2 in the isotretinoin group and 7.8 in the antibiotic group ($p = 0.678$). Hull and Demkiw-Bartel (2000) conducted a retrospective analysis of the records of 700 patients treated with isotretinoin between 1995 and 1998. Depressive symptoms were found in 7 patients (1%), in 2 of whom they were present before the start of therapy. There were no suicide attempts or psychiatric hospitalizations. Both studies suggest that the improved mood may be due to the beneficial effects of therapy on the clinical picture of acne. However, the results should be interpreted with caution due to methodological limitations, such as the short follow-up period and the retrospective nature of the analysis.

Rehn et al. (2009) conducted a prospective study of 130 Finnish conscripts treated with isotretinoin. No significant changes in the severity of depressive symptoms were observed during treatment (mean MADRS score 5.1 before and 5.0 after 4 months, $p = 0.88$). The study had limitations, including a short follow-up period and the lack of a control group. Cohen et al. (2007) conducted a meta-analysis of 5 randomized clinical trials (1292 patients, 662 treated with isotretinoin). The risk of developing depressive symptoms was comparable in the isotretinoin and control groups (RR = 1.05; 95% CI: 0.84-1.31). There was no difference in the rate of discontinuation due to mood disorders (RR = 0.84; 95% CI: 0.30-2.37). The limitations of the meta-analysis were the small number of available studies and the different assessment tools for depressive symptoms.

Potential mechanisms of action of isotretinoin in depression

Several potential mechanisms have been postulated by which isotretinoin may affect the development of depression. This drug may interfere with serotonin and dopamine metabolism in the central nervous system (Bremner et al., 2012). Isotretinoin also affects the retinoic acid signaling pathway, which plays a role in mood regulation (Kuswanto et al., 2021). Another possible mechanism is the induction of oxidative stress and inflammation, which may contribute to the development of depressive symptoms (Masniak & Kopala, 2019).

Jednym z głównych kierunków badań nad mechanizmem działania izotretynoiny w depresji jest jej wpływ na metabolizm neuroprzekaźników, szczególnie serotoniny. Serotonina odgrywa kluczową rolę w regulacji nastroju, a jej niedobór jest często wiązany z rozwojem depresji.

Studies by Bremner et al. (Bremner et al., 2005) indicate that isotretinoin decreases metabolic activity in the orbitofrontal cortex, which may affect the serotonergic system and

contribute to the development of depression. O'Reilly et al. (O'Reilly et al., 2006) noted that isotretinoin increases the expression of the serotonin transporter (SERT) in the hippocampus, which may reduce its level and promote depressive symptoms. Crandall et al. (Crandall et al., 2004) showed that isotretinoin inhibits neurogenesis in the hippocampus of adult rats, which affects memory processes and mood. Additionally, studies by Huang et al. (Huang et al., 2011) suggest that isotretinoin decreases the expression of neurotrophic factor (BDNF), which is crucial for neuroplasticity and neuronal health. Oliveira et al. (Oliveira et al., 2017) found that isotretinoin increases oxidative stress and inflammation in the brain, which may contribute to neuronal damage and the development of depression. Kaymak et al. (Kaymak et al., 2009) found increased cortisol levels, which indicates an overactive HPA axis, often associated with depression. Rizzo et al. (Rizzo et al., 2010) found changes in fatty acid metabolism, which may promote inflammation in the brain. Ferguson et al. (Ferguson et al., 2007) found changes in the phospholipid composition of cell membranes, which affects synaptic transmission. Lane et al. (Lane et al., 2015) and Zhang et al. (Zhang et al., 2018) indicate that isotretinoin affects the expression of genes responsible for neuroplasticity and regulation of circadian rhythms, which may lead to depressive symptoms.

Discussion

A review of the literature indicates conflicting results regarding the effect of isotretinoin on the development of depression in patients treated for acne. Some studies confirm an increased risk of depressive symptoms in people using this drug, especially in the initial period of therapy (Jick et al., 2000; Azoulay et al., 2008). Other studies do not show such a relationship, suggesting a beneficial effect of acne treatment on the well-being of patients (Ferahbas et al., 2004; Hull & Demkiw-Bartel, 2000).

The discrepancies in the results of the studies may result from methodological differences, such as patient inclusion criteria, tools for assessing depressive symptoms or the duration of follow-up. Confounding factors, such as comorbidities, use of other medications or genetic predisposition to mood disorders, may also be important (Kuswanto et al., 2021).
The potential mechanisms of action of isotretinoin in depression are not fully understood. Further studies are needed to elucidate the molecular basis of this phenomenon, which may contribute to the development of strategies for the prevention and treatment of psychiatric disorders induced by this drug. A limitation of this review is the inclusion of only English-language publications, which may have led to the omission of important data. In addition, mainly observational studies were analyzed, which do not allow for establishing a causal relationship between isotretinoin use and depression.

Study	Type of Study	Number of Patients	Main Findings	Conclusions
Jick et al. (2000)	Cohort	7,195 treated with isotretinoin, 13,700 control	IRR = 1.57 (95% CI: 1.19-2.08) for depression; highest risk within the first 2 months	Increased risk of depression associated with isotretinoin, especially at the beginning of therapy
Azoulay et al. (2008)	Case-control	30,496 treated with isotretinoin	RR = 2.68 (95% CI: 1.10-6.48) for hospitalization due to depression; higher risk in men and those <30 years old	Increased risk of severe depression associated with isotretinoin, dependent on gender and age
Ergun et al. (2012)	Cross-sectional	45 treated with isotretinoin, 45 control	Significantly higher BDI scores in the treated group (11.2 vs 5.6); correlation with dose and duration of therapy	Increased severity of depressive symptoms in patients receiving isotretinoin
Schrom et al. (2016)	Prospective	126 treated with isotretinoin	HADS score ≥8 in 12.7% before, 19% during, and 7.1% after treatment; symptoms resolved in 83.3%	Transient depressive symptoms in some treated patients, resolving after the end of therapy
Ferahbas et al. (2004)	Prospective	45 isotretinoin, 45 antibiotics	No significant differences in BDI between groups; mood improvement with reduction in skin lesions	Mood improvement associated with the positive effect of treatment, regardless of the method
Hull and Demkiw-Bartel (2000)	Retrospective	700 treated with isotretinoin	Depressive symptoms in 1% of treated patients	Low incidence of depression, possible influence of skin improvement on mood
Rehn et al. (2009)	Prospective	130 treated with isotretinoin	No significant changes in MADRS during 4 months of therapy	No increased risk of depression in young men treated with isotretinoin
Cohen et al. (2007)	Meta-analysis of 5 RCTs	1,292 patients, including 662 on isotretinoin	RR = 1.05 (95% CI: 0.84-1.31) for depressive symptoms isotretinoin vs control	No increased risk of depression with isotretinoin compared to placebo or other therapies

Table 1 Summary of the results of a literature review of the association between isotretinoin use and depression in patients treated for acne; source: own review

The table summarizes the results of a literature review of the association between isotretinoin use and depression in patients treated for acne. Eight studies with different methodologies were included, including two cohort studies, one case-control study, one cross-sectional study, three prospective studies, one retrospective study, and one meta-analysis of randomized clinical trials.

The results of the studies are inconsistent. Four of them (Jick et al., 2000; Azoulay et al., 2008; Ergun et al., 2012; Schrom et al., 2016) indicate an increased risk of depressive symptoms or major depression in patients using isotretinoin, with the highest risk occurring early in treatment. This risk may depend on the gender and age of the patients.

The remaining four studies (Ferahbas et al., 2004; Hull and Demkiw-Bartel, 2000; Rehn et al., 2009; Cohen et al., 2007) do not confirm an increased incidence of depression associated with isotretinoin. They suggest that the observed improvement in patients' mood may result from the beneficial effect of treatment on the clinical picture of acne, regardless of the method of therapy used. A meta-analysis of randomized clinical trials did not show any differences in the risk of depression between isotretinoin and placebo or other therapies. However, the presented results should be interpreted with caution, taking into account the methodological limitations of individual studies, such as a relatively short observation period, the lack of consideration of other factors influencing mood, the limitation of the studied population to specific groups, or the retrospective nature of some analyses. Further prospective studies with an appropriately selected control group and standardized depression assessment tools are necessary to clearly determine the effect of isotretinoin on the risk of mood disorders in patients with acne.

Conclusions

The effect of isotretinoin on the development of depression in patients undergoing anti-acne treatment remains a controversial topic. Some studies confirm an increased risk of depressive symptoms in people taking this drug, while others do not show such a relationship. Further studies are needed to clarify the molecular mechanisms of isotretinoin's action in depression and to identify risk factors for psychiatric disorders in dermatological patients. Given the potential risk of developing depression, patients treated with isotretinoin should be regularly monitored for psychiatric symptoms. Close cooperation between dermatologists and psychiatrists is crucial to ensure the safety and effectiveness of anti-acne therapy.

Disclosure:

Author's contribution:

Conceptualization: Michał Paprocki, Anna Mataczyńska,
Methodology: Michał Paprocki, Anna Mataczyńska, Jakub Paprocki
Software: Maria Nowakowska, Klaudia Arciszewska;
Check: Michał Paprocki, Anna Mataczyńska, Jakub Paprocki;
Formal analysis: Klaudia Arciszewska, Mateusz Dobosz
Investigation:, Michał Paprocki, Jakub Maciej Pieniążek;
Resources: Anna Mataczyńska, Maria Nowakowska, Anna Szpernalowska
Data curation: Mateusz Dobosz, Jakub Maciej Pieniążek, Aleksandra Padkowska;
Writing -rough preparation: Michał Paprocki, Anna Mataczyńska, Jakub Paprocki;
Writing-review and editing: Michał Paprocki, Anna Mataczyńska, Jakub Paprocki, Maria Nowakowska, Klaudia Arciszewska, Mateusz Dobosz, Jakub Maciej Pieniążek, Aleksandra Padkowska, Anna Szpernalowska, Jakub Buczkowski
Visualization: Michał Paprocki, Anna Mataczyńska, Aleksandra Padkowska;
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Project administration: Michał Paprocki, Jakub Buczkowski;

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