

Causal nexus between isotretinoin and neuropsychological symptoms: a study of depression and suicidal ideation events

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit. It is estimated that over 80% of adolescents and young adults in Portugal have acne vulgaris. Isotretinoin is indicated for the more severe cases and can cause various adverse effects including psychiatric reactions such as depression and suicidal ideation.

The Infarmed Information Circular nr. 052/CD/550.20.001 from 27th March 2018 highlights the inclusion in the information of isotretinoin-containing products of the risk of psychiatric disorders. The circular notes the fact that evidence for this association is limited and even contradictory, since psychiatric problems are often potentiated by the appearance or worsening of acne. The need for further updated evidence was the drive for the present study.

The first case of possible induction of depressive symptoms by isotretinoin was reported in 1983. The US Food and Drug Administration (FDA) published a warning on a possible association in 1998. According to the FDA, isotretinoin comes in fourth place in the list of drugs that are most frequently associated with the appearance of depressive symptoms; this association requires further investigation.

In March 2018, the European Medicines Agency (EMA) decided that prescribing guidelines for oral retinoids needed to include an alert on the possible occurrence of neuropsychiatric conditions, namely depression, anxiety and mood disorders.

Systematic Literature Review

A systematic literature review was conducted to answer the following research question: what is the relation between isotretinoin therapy in patients with a diagnosis of acne vulgaris and the appearance of pathological disorders such as depression and/or suicidal ideation?

A search in the PubMed database yielded 206 results, of which 35 were included in the review after filtering by predefined selection criteria. An analysis of the selected articles/studies concluded that in no case was there a definitive conclusion regarding an association between isotretinoin and depression and/or suicidal ideation. Given that most studies looked at this association by using questionnaires applied to patients undergoing treatment, their results can be fraught with a high degree of subjectivity and risk of bias. Moreover, few studies look at the biological viewpoint for this potential association, which makes it difficult to anticipate any mechanisms that may be at the origin of symptoms.

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For a more in-depth discussion of the results obtained in our review, data from adverse drug reaction (ADR) reports in the WHO (World Health Organization) Uppsala Monitoring Centre (UMC) database was consulted. A search for drug-ADR pair reports in Portugal and worldwide was undertaken on the Vigilyze database using the International Nonproprietary Names of the active ingredients and the Medical Dictionary for Regulatory Activities (MedDRA) terms. In order to analyze the relation between isotretinoin, suicidal ideation and depression, **the HLT Suicidal and selfinjurious behaviour and the HLGT Depressed Mood Disorders and Disturbance** were selected. Drug-reaction disproportionality measures are presented on the table below.

Disproportionality Measures	N_{observed}	N_{expected}	N_{drug}	N_{reaction}	CI₀₂₅	CI
HLT Suicidal and Self-Injurious Behaviour (national)	3	0	69	248	0,3	2,4
HLT Suicidal and Self-Injurious Behavior (global)	3974	465	72 848	194 759	3,0	3,1
HLGT Depressed Mood Disorders and Disturbance (national)	10	0	69	547	2,6	3,6
HLGT Depressed Mood Disorders and Disturbance (global)	9228	760	72 848	318 442	3,6	3,6

Disproportionality measures for HLT Suicidal and Self-Injurious Behaviour and for HLGT Depressed Mood Disorders and Disturbance, at national and global levels.

In conclusion, the results from our systematic review of the literature do not match the quantitative data obtained, the latter seeming to support a causal relation as listed in the Summary of the Product's Characteristics (SPC).

Safety studies are needed that should be specifically designed to look at the various possible dimensions of a causal nexus between isotretinoin and depression/suicidal ideation, namely the biological/biochemical (especially mechanistic and pharmacogenomic) dimension, the psychological dimension and the social dimension. Awareness of patients on risks associated with isotretinoin is paramount, as well as monitoring by healthcare professionals of their mental health status throughout the course of treatment.

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Compiled by Patrícia Catalão



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