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Guest Editorial

Isotretinoin use, mood changes and suicidality. What is the link?

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For over four decades, isotretinoin has shown unparalleled efficacy in the management of severe recalcitrant acne. However, controversies exist about its psychiatric safety profile. This editorial discusses the alleged causal role of isotretinoin in the development of psychiatric adverse events in light of the best available evidence.

Keywords
Acne vulgaris; isotretinoin; mood; psychiatric disorders; suicidality.

Isotretinoin is an oral retinoid first approved by the US Food and Drug Administration (FDA) in 1982 for the management of recalcitrant nodulocystic acne. This drug has proven highly effective (i.e. long-term skin benefits are evident in almost all treated patients) when standard treatments such as oral antibiotics and topical therapies fail, leading to substantial improvements in the quality of life of people affected by the most severe and persistent forms of acne vulgaris. Soon after release to the market, however, important safety concerns were raised about this agent, especially regarding its powerful teratogenicity, which was described in humans during the first year of marketing. In addition, isotretinoin rapidly began to be associated with serious psychiatric adverse events such as mood lability, depression and suicidal behaviour, prompting drug regulatory agencies in different countries to issue specific warnings in the early 2000s. Such an association is supported by numerous spontaneous reports of adverse drug reactions and preliminary findings of early cohort studies of people treated with this retinoid. Despite the observational nature of these data and the fact that no mechanisms of action of this drug have been established for psychiatric events, a causal link has been hypothesised and, in the field of psychiatry, isotretinoin has largely been demonised over the last four decades, which is probably unfair in light of the best available evidence.

Evidence from population-based cohort studies

The most robust epidemiological data supporting the alleged role of isotretinoin in the development of psychiatric disturbances derives from a cohort study conducted in Sweden[1] with people prescribed this drug during the 1980s, being therefore some of the first patients to be treated with isotretinoin. Subsequent larger cohort studies, however, do not support the association between exposure to this retinoid and the development of adverse psychiatric reactions.[2–4]

In their early retrospective study of 5756 patients, Sundström et al[1] reported a slightly increased incidence of suicidal behaviour among isotretinoin users compared with the general population within 6 months of completing treatment (standardised incidence ratio: 1.78, 95% CI: 1.04–2.85). However, it is of note that the risk of attempted suicide was already rising before the start of treatment: from 0.99 (95% CI: 0.65–1.44) 3 years before treatment initiation to 1.57 (95% CI: 0.86–2.63) during the year preceding exposure to isotretinoin. Interestingly, the risk decreased within 1 year after treatment completion and rapidly became close to that observed for the general population, remaining so throughout a 15-year follow-up period. These findings suggest that severe acne itself might contribute to the emergence of psychiatric events, while pharmacological treatments often prescribed to severe acne patients before (i.e. some classes of oral antibiotics) and during the first months (i.e. oral corticosteroids) of isotretinoin treatment could also be involved in the observed outcomes. Some support for this hypothesis is provided by a recent global population-based study[2] showing no differences as regards the risk of attempted suicide or major depressive disorder at 20-year follow-up between isotretinoin users ($n = 75\,708$) and a propensity-matched sample of acne patients receiving oral antibiotics without prior exposure to oral retinoids ($n = 75\,708$). What is more, for most of the psychiatric outcomes analysed (depressive symptoms, bipolar disorder, post-traumatic stress disorder, anxiety and adjustment disorder) and all-cause mortality, the risk was lower among isotretinoin users, and similar overall results were found in a time-stratified analysis restricted to the initial 3 months of treatment.[2] Consistent findings are available from another recent study,[3] which analysed the psychiatric outcomes of 29 943 Taiwanese individuals newly diagnosed with acne between 2000 and 2015 and no previous suicide attempts or psychiatric diagnosis, out of which 9981 received isotretinoin. In a multivariable analysis including medical comorbidities and demographic characteristics as covariates, no association was observed between isotretinoin treatment and risk of psychiatric events (suicidal behaviour, anxiety, obsessive–compulsive disorder, mood disorders or schizophrenia) during the first year of follow-up, and similar nonsignificant results were observed throughout the remaining 15-year period.[3] In keeping, the largest cohort study conducted to date,[4] which was based on retrospective data of more than 400 000 patients that represented virtually all the French population receiving a course of isotretinoin between 2009 and 2016, showed no evidence of an increased risk of suicide attempts compared with the general population. In addition, this study reported that psychiatric history at treatment initiation (severe mental illness or suicide attempt) was a significant predictor of suicidal behaviour during exposure to isotretinoin (odds ratio: 18.21, 95% CI: 9.96–33.30).[4]

Finally, a recent meta-analysis[5] of 24 reports (mostly cohort studies, both prospective and retrospective) involving 1 625 891 participants showed that the rates of different psychiatric outcomes among isotretinoin-treated patients were not higher than those in the general population: the 1-year pooled absolute risk of suicide attempts was 0.14% (95% CI, 0.04–0.49; seven studies), while pooled absolute risks of 3.83% (95% CI, 2.45–5.93; 11 studies), 0.57% (95% CI, 0.31–1.07; two studies) and 0.13% (95% CI, 0.08–0.23; three studies) were estimated for 'depression', bipolar disorder and psychotic disorders, respectively. Furthermore, a small secondary analysis

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revealed that isotretinoin treatment was not associated with an increased risk of suicidal behaviour or psychiatric disorders considering follow-up periods of up to 4 years.[5]

Despite evidence from cohort studies being quite consistent, some limitations should be acknowledged. First, all large studies used retrospective designs.[1–4] However, smaller prospective studies have yielded similar findings.[5] In addition, in reports comparing isotretinoin-exposed against unexposed acne patients,[2,3] groups were not matched on acne severity. Further, the similar and even better outcomes observed in some studies among isotretinoin-treated individuals are possibly caused by indication bias (i.e. patients with severe psychiatric conditions could have been less prone to receiving oral retinoids). However, the fact remains that there is no evidence that isotretinoin confers an increased psychiatric risk to acne patients. It is also interesting to note that similar insights are drawn from the findings of studies conducted in very different sociocultural contexts.[2–4]

Evidence from case reports and case series

Since its introduction in 1982, isotretinoin has repeatedly been associated with severe psychiatric events and, by the early 2000s, it was the only non-psychiatric drug ranked within the top ten medications linked with depression and suicide attempts in terms of absolute number of spontaneous reports submitted to the FDA Adverse Event Reporting System (FAERS).[6] Of note, however, this should not be surprising as acne is most prevalent in the age group with the highest risk of new-onset severe psychiatric disorders. In addition, individuals prescribed isotretinoin are often exposed to stressful experiences and emotional pain as a result of severe persistent acne. That is, the target population of isotretinoin is at an increased risk of developing both spontaneous and drug-related psychiatric events. Further, the relative frequency of these early reports could not be obtained as no register of the total number of prescriptions was available by that time. In more recent years, with the implementation of teratogenic risk managing plans in several countries, valuable data for research have become available from programmes that restrict the dispensing of isotretinoin to enrolled patients. For example, in a study based on the reports of side-effects with this retinoid as the primary suspect drug submitted to the FAERS, the incidence of completed suicide among isotretinoin-treated individuals was calculated using data from patients enrolled in the FDA iPLEDGE programme between 2009 and 2010.[7] This study showed that the rates of completed suicide among isotretinoin users were not higher – these were indeed lower – than those in the general US population.[7]

The strongest evidence for a causal relationship between isotretinoin use and psychiatric outcomes derives from case reports and case series that document, in addition to a temporal association between drug exposure and emergence of psychiatric events, positive dechallenges (psychiatric disturbances disappear or improve when removing the drug), often with psychotropic treatment, and positive rechallenges (psychiatric events reappear after restarting the drug).[6,8] Despite positive dechallenge–rechallenge being strongly suggestive of a causal effect, most reports[6] do not meet crucial quality criteria (i.e. dosage information and objective measures for psychiatric outcomes are not available, for example). Further, while it is indeed possible that isotretinoin is responsible for the psychiatric reactions described in some case reports, the available evidence is insufficient to refute that these represent difficult-to-predict idiosyncratic reactions.

At present, there is paucity of data from patients with severe psychiatric disorders. The largest study is based on only ten cases identified through a retrospective chart review of 300 out-patients with a bipolar disorder diagnosis.[8] Nine of these patients were found to exhibit illness exacerbation (mainly mood instability or mixed features) when exposed to isotretinoin. However, outcomes were appraised using dichotomous measures, and no information was available regarding patients' mood state at treatment initiation, psychiatric care (two patients were not medicated), exposure to other drugs often administered together with isotretinoin (i.e. corticosteroids) or other information needed to better ascertain a potentially destabilising effect of oral retinoids in this clinical population.

Clinical and research implications

Recalcitrant nodular acne tends to appear during adolescence and often lasts for years or even decades, causing, in many cases, permanent scarring or disfigurement. Thus, the skin condition for which isotretinoin has been approved is associated with early persistent pain – both physical and emotional – and can put very young individuals at an increased risk of living adverse experiences, which may, in turn, lead to an increased psychiatric vulnerability. Indeed, depressive symptoms and severe acne often co-occur and, in the field of dermatology, it is widely accepted that successfully treating acne has a beneficial effect on mood, self-esteem and quality of life.[2,5] By contrast, concerns about isotretinoin-induced psychiatric events are quite frequent among psychiatrists, sometimes accompanied with an underestimation of the psychological consequences of skin disorders and limited knowledge of the unparallelled efficacy of isotretinoin in the most severe cases of acne. Further, approaches to severe psychiatric disorders tend to focus quite exclusively on 'biological variables' while overlooking the possible impact of early experiences, which, however, not only have been shown to predict illness course but also psychosocial outcomes such as coping abilities and symptom burden.[9]

At present, there is no robust evidence to discourage isotretinoin treatment beforehand based on psychiatric concerns in severe acne patients unresponsive to first- and second-line treatments or with a risk of permanent scarring. However, patients should always be informed about the risk of psychiatric side-effects – which have currently been described for many other non-psychiatric drugs though – in addition to being fully monitored during and after exposure to isotretinoin. Individuals with a personal or family psychiatric history should be approached more cautiously, weighing risks and benefits on a case-by-case basis; while there is no robust evidence to support that isotretinoin destabilises the mood of patients with severe psychiatric conditions, this population may be more susceptible to the possible destabilising effects of different drugs.[4] Indeed, although this is merely speculative, the differences observed between the first cohort study showing an increased risk of suicidal behaviour[1] and more recent research showing nonsignificant outcomes[2–5] could be partially explained by the fact that, since the third decade of isotretinoin marketing, dermatologists have been less willing to offer isotretinoin to patients with a pre-existing severe psychiatric condition as a result of the warnings and restrictions released. For patients with an increased susceptibility, low-dose isotretinoin treatment could be an adequate option, as suggested by reports of rechallenge describing its efficacy in treating acne in the absence of re-emergence of psychiatric reactions.[6] Also of note, the fact that some medications typically used for the treatment of psychiatric conditions can cause or exacerbate acne should not be overlooked. These considerations warrant an approach to severe acne that acknowledges the complex relationship that exists among this dermatologic condition, psychiatric disorders

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and their treatments, thus involving synergistic dialogue between dermatologists and psychiatrists.

Finally, further research should include prospective designs with a thorough dosage register, documentation of concomitant medications, more complete baseline and follow-up standardised assessment of psychiatric status that considers different nuances of suicidality and specific mood variables such as depression, mixed features and lability and, not least, assessment of the clinical course of severe acne.

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