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Isotretinoin Induced Psychotic Mania: A Case Report

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SUMMARY

Biological, genetic and psychosocial factors may play a role in the aetiology of bipolar mood disorder (BPD). BPD episodes might be triggered by isotretinoin, a retinoid derivative of vitamin A with a role in cellular proliferation and differentiation. Due to its association with depression, suicidal ideation and suicide attempts, American Food and Drug Administration (FDA) issued a placement of a label warning for isotretionin. Personal or family history of psychiatric disorders was emphasized in the literature for the risk of mood episodes following isotretionin treatment. Here we aim to present the case of an 18-year old young male adult, without personal or family history of a psychiatric disorder, who developed psychotic mania within the first week of isoretinoin which was prescribed for acne vulgaris. Psychotic mania symptoms receded within one week after starting olanzapine (10mg/day). We believe this case is significant in demonstrating the occurence of a manic episode after isoretinoin in individuals lacking a personal or family history of psychiatric diagnoses.

Keywords: Isotretinoin, mania, psychosis, drug side effects

INTRODUCTION

Isotretinoin, a synthetic oral retinoid and vitamin A derivative, is an isomer of retinoicacid that plays a role in cell proliferation and differentiation by regulating gene transcription (Kontaxakis et al. 2009). Used in the treatment of resistant advanced cystic acne and nodular acne since 1982 (Wysowski and Pitss 2001, Hull and D'Arcy 2003), it has a wide range of side effects including depression and suicidal atttempts (Wysowski and Pitss 2001, Hull and D'Arcy 2003, Kontaxakis et al. 2009, Singer et al. 2019). It is included among the top ten drugs associated with suicide that have been reported to the FDA which in 1998 made it cumpolsory to include the warning that its use caused psychiatric problems such as depression, psychosis and suicidal ideation on the packaging of all generic brands (Wysowski and Pitss 2001, Hull and D'Arcy 2003).

Given the conflicting results in the various case reports in the literature on the relationship between retinoic acid derivatives and psychiatric disorders, the subject has been debated for nearly 20 years. Acne can cause various psychological problems in adolescents with adverse effects on the perception of body image leading to depressive symptoms, decreased self-esteem and anxiety. Successful treatment of acne in individuals without serious psychiatric comorbidites has led to regression of moderate depressive and anxiety symptoms correlating with acne per se (Rubinow et al. 1987, Kellett and Gawkrodger 1999, Ludot et al. 2015).

Methodological inadequacies were pointed out (Marqueling and Zane 2007, Kontaxake et al. 2009) in prescription analyses, retrospective follow up studeis, some prospective follow up studies and a review claiming the lack of any significant relationship between isotretinoin use and psychiatric disorders, depression and suicidal events (Jick et al. 2000, Hersom et al. 2003, Hull and Demkiw-Bartel 2005, Chia et al. 2005, Cohen et al. 2007, Marqueling and Zane 2007). It was argued that isotretinoin use was associated with psychiatric disorders on the basis of the side effects reported to both the World Health Organization (WHO) and the FDA, in case reports and the challenge de-challenge, re-challenge studies demonstrating the relationship between psychiatric disorders and the biological action mechanism of isotretinoin (Kontaxakis et al. 2009).

BPD and related mood disorders are among the psychiatric disorders claimed to be caused by isotretinoin use. A recent

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review of the psychiatric side effects of isotretinoin use reported to the FDA between 1997 and 2017 has ranked these adverse outcomes as depression, suicidal ideation and attempts, emotional lability, anxiety disorders, insomnia, psychotic disorder, BP affective disorder, self harming behaviour, attention deficit and hyperactivity disorder and eating disorders. In the same review the incidence of completed suicidal attempts among patients treated with isotretinoin was found to be lower than that in the general population of the USA, but references were not made to the cases of BPD and affective disorders (Singer et al. 2019).

One case of psychotic mania was reported to the the Canadian Side Effcct Reporting System (Bremner et al. 2012). The diagnostic data on the 9 patients consulting a psychiatry clinic between 2011 and 2014 for affective disorder development while on isotretinoin therapy showed that 4 were in major depressive episode, 3 had repetitive major depressive episode, one had mixed episode and one had rapid-cycling BPD-1. Analyses have shown that the predictors for affective disorder development were family history of affective disorder and personal history of an episode of psychiatric disorder (Karakula-Juchnowicz et al. 2016). A retrospective evaluation of 300 BPD patients identified 10 patients in the 15-39 year age range using isotretinoin, 6 of whom had mixed symptoms, 2 had depressive symptoms and 1 had developed hypomania symptoms (Schaffer et al. 2010). Investigations on 500 military personnel identified 5 with ''manic psychosis" and 3 with a history of suicidal attempt. Also, obsessive-compulsive disorder, history of neurological trauma or family history of major psychiatric disorders were demonstrated in all the personnel (Barak et al. 2005). In a review on 53 cases of psychiatric disorder development when using retinoic acid derivatives, one case of BPD flare up was observed (Le Moigne et al. 2018).

The above cited evidence points to a relationship between isotretinoin use and development of BPD symptoms. Investigations made on the cases indicate that individuals with personal or family history of psychiatric disorders may develop mainly depression, followed by mixed episodes and rarely hypomania or psychotic mania after isotretinoin use. In this report, however, we are presenting a case of manic psychosis in an 18-years old male patient without a personal or family history of pscyhiatric diagnoses.

CASE

The 18-years-old male, a senior high school student, was brought to the psychiatry clinic by his parents with complaints that had developed on the second day of starting treatment with isotretinoin (20mg/day) prescribed after consulting the dermatology clinic one week previously for complaints of acne. His need for sleep was reduced on the second day of the therapy with development of attention deficit symptoms, increased mobility and psychomotor energy on the following days and addition of symptoms of increased speech, flight of ideas and grandiose delusions of finding hiself superior and more talented in comparison to others on the day before arriving at the psychiatry outpatient clinic. This was his first psychiatric consultation and he did not have a personal or family history of any psychiatric disorder. In his psychiatric examination his appearance was disorganised although compatible with his socioeconomic status. He was conscious, his place, person and time orientations were normal; his mood was euphoric and affect euphoric and irritable. It was determined that the amount and speed of his talking had increased; his associations were accelerated, he had flight of ideas and attention deficit and his concentration was easily distracted; his thought contents had grandiose delusions; his psychomotor activity was distinctly increased and he lacked insight. Consultative report from the dermatology clinic indicated the presence of erythematous papulopustules with open and closed comedones. The requested neurological examination report and the results of cranial MRI and EEG, the biochemical and toxicological tests were all within normal limits. Oral isotretinoin treatment was discontinued under the control of a dermatologist, and topical erythromycin + benzoylperoxide cream was started instead. Olanzapine (10 mg/day) treatment was started after diagnosis of psychotic mania. His behavioural control and close follow up was ensured on an outpatient basis by the assistance of his relations. On the 7th day of the treatment, his YMRS score had decreased to 5. Olanzapine dose was reduced to 5 mg/day and further reduced to 2.5mg/day after 6 months of monthly follow up without any observed mood disorder.

DISCUSSION

The manic psychosis symptoms presenting within the first week of starting isotretinoin treatment of the 18-years old patient for acne vulgaris subsided within one week after discontinuing the treatment. These observations together with the absence of a personal or family history of pscyhiatric disorders and not determining during his psychiatric examination any cause to precipitate mania suggested that isotretinoin treatment underlied the observed disorder. The temporal relationship between the use of isotretinoin and the emergence of psychotic mania which regressed after discontinuing the drug and also not finding any other cause to trigger the attack were evaluated as a "probable relationship" according to the World Health Organization UMC Causality Assessment System (WHO 2019). Although starting olanzapine treatment concurrently with the discontinuation of isotretinoin treatment reduces the reliability of this conclusion and prevents an ideal evaluation, not having

given antipsychotic treatment would have been medically inappropriate.

Psychotic mania is one of the mood episodes of BPD which involves a complex genetic transition under the shared effects of both genetic and environmental factors (Rybakowski 2017). It is known that psychotic mania episodes can occur in susceptible individuals exposed to psychosocial stressors, using cannabis and antidepressants (Goldbergand Truman 2003, Uher 2014). Hereinabove the likelihood of the emergence of depressive, mixed or manic episodes after isotretinoin use by individuals with psychiatric diagnoses including BPD or a family history of psychiatric disorder has already been discussed. Since only two other similar cases have been reported in the literature (Erensoy et al. 2014, Lucca et al. 2016), the case discussed in this report is believed to make a significant contribution to the relevant literatıre in showing that an individual can present with a manic episode after isotretinoin use despite not having a personal or family history of psychiatric disorders.

The cause-effect relationship of isotretinoin and mania can be discussed from different standpoints of whether isotretinoin is a trigger for BPD episodes, whether the episodes are started in susceptible individuals or whether the manic episode is secondary to isotretinoin use. Previously reported data demonstrate that isotretinoin can trigger all BPD episodes including mania (Cott and Wisner 1999, Schaffer et al. 2010, Karakula-Juchnowicz et al. 2016). There may be two alternative possibilities for the episodes to present in individuals without previous BPD diagnosis. Hence, the symptoms may be secondary to isotretinoin use as for example seen after substance and steroid use and can be classified as 'Drug / Substance Related Bipolar Disorder and Related Disorders' according to the DSM-5 (American Psychiatric Association 2013), when discontinuing isotretinoin as the cause and starting supportive therapy after a short while should be adequate. The second possibility is to evaluate isotretinoin as an environmental risk factor similar to the use of cannabis in adolescence and exposure to stressful life events in adulthood for the development of BPD in susceptible individuals (Uher 2014) such that the individual then continues to live as a BPD patient. Kontaxakis et al. (2010) have argued in reference to 4 cases of susceptibility with family history of psychiatric disorders that genetic factors may predispose some individuals to the psychiatric side effects of isotretinoin and that the observed psychiatric symptoms may be the products of gene-environment interaction where isotretinoin functions as an environmental stressor. The longitudinal follow up of these cited 3 cases and perhaps similar cases to be reported later also gains significance for understanding the possible action of isotretinoin as an environmental stressor as discussed here above.

Several possible alternatives draw attention in relation to pscyhotic mania induction by isotretinoin which is an isomer of retinoic acid (RA) with influences on cell proliferation and differentiation by regulating gene transcription required not only in the embryo for the control of the development of many organs including the central nervous system but also for the proliferation and differentiation of adult organ systems. (Kontaxakis et al. 2009). RA receptors (RA-R) are found in the adult brain in the hippocampus, thalamus and the pons as the RA-Rα and in the striatum, hypothalamus and the medulla as the RA-Rβ (Suuberg 2019). In the limbic system, RA signals are detected in the hippocampus, medial prefrontal cortex, cingulate cortex, thalamus, and the hypothalamus where RA modulates synaptic plasticity and neurogenesis (Suuberg 2019) and regulates the transcription of dopamine-2 and glutamate receptor genes (Kontaxakis et al. 2009). Isotretinoin impairs serotonin signaling by reducing adult neurogenesis and changing the components of the serotonergic neurotransmitter system. Functional brain imaging has demonstrated a decrease in the orbitofrontal cortex metabolism in patients treated with isotretinoin (Suuberg 2019). The demonstrated effects of isotretinoin on the orbitofrontal cortex associated with affective and psychotic disorders and on the limbic system areas and cortical zones associated with BPD (Lim et al. 2013, Maletic and Raison 2014) may play a role in the development of isotretinoin related psychotic mania.

The hypothalamus, where RA is an endogenous regulator, is part of the hypothalamic-pituitary-adrenal (HPA) axis and a central component in the response to stress and may be another area that can be degraded by isotretinoin. Hyperactivity of this system has been demonstrated in BPD (MaleticandRaison 2014). The density of cells expressing RA-Rα increase in the corticotropin releasing hormone (CRH) neurons in the paraventricular nuclei of the hypothalamus in BPD where the RA-R mediate CRH gene expression (Chen et al. 2009).

Studies on animal models have shown hyperactivity of the HPA, and loss of plasticity and reduced hypothalamic neurogenesis similar to the reports of mood disorders observed after retinoid use in humans. (Kontaxakis et al. 2009, Le Moigne et al. 2018). The enhanced RA signal resulting from the increase in RA-Rα after isotretinoin use in humans can mimic the activation in this pathway and, hence, provide another mechanism for induction of mood disorders.

Moreover, decrease in 5-methyltetrahydrofolate and increase in homocysteine were reported after isotretinoin use (Bremner et al. 2012, Suuberg 2019) where 5-methyltetrahydrofolate is an intermediate of the synthesis of S-adenosylmethionine (SAM), which enters the synthesis of dopamine, noradrenaline and acts as a methyl donor in DNA methylation reactions (Bremner et al. 2012). Elevation of homocysteine by

isotretinoin use leading to DNA hypomethylation and reduced neurotransmitter synthesis may provide an additional mechanism that can contribute to the development of BPD and other psychiatric disorders. These observations evince that isotretinoin can contribute to the development of BPD through alternative mechanisms. Still, the questions remain on whether the psychotic mania due to isotretinoin use should be classified as "Drug / Substance-Related BPD and Related Disorder" or as "BPD-I" in which isotretinoin plays a role as an environmental factor. In this respect, longitudinal follow up on the three cases, including ours, with isotretinoin triggered psychotic mania in the absence of a personal or family history of psychiatric disorder gains importance with expectation of further light to be shed on the issue by identification of similar cases.

Past reports without appropriate psychiatric examination on cases of "Depression" attributed to isotretinoin use are likely to involve manic symptoms, agitation, nervousness and sleep disorders indicative of mania or mixed mood attacks which are more prevalent among those with personal or family history of pscyhiatric disorders (Truitt et al. 2018). In this respect, psychiatric consultation is important in evaluating the psychiatric side effects of isotretinoin in individuals with or without a previously known psychiatric illness both for better understanding the relationship of the drug with psychiatric symptoms and the timely access of the patient to treatment. In the case we present here and the 2 cases reported by Erensoy et al. (2014) and Lucca et al. (2016), starting mood stabilizer and antipsychotic treatment after discontinuing isotretinoin use resulted in rapid regression of manic symptoms. On the other hand, antipsychotic agent had to be added to mood stabiliser therapy to manage the isotretinoin triggered pscyhomania attack in a BPD patient who preferred to continue to use isotretinoin (Cott and Wisner 1999). The same approach has been generally applied in other BPD cases opting to maintain isotretinoin use after presenting with psychotic attack (Barak et al. 2005; Schaffer et al. 2010; Karakula-Juhowitz et al. 2016; Le Moigne et al. 2018). On this basis, we recommend terminating isotretinion use and starting with symptomatic therapy in patients going through manic attack, and when isotretinoin cannot be discontinued, to adjust, on a case basis, the dosage of mono or combined antimanic and mood stabiliser therapy.

CONCLUSION

Isotretinoin, the effective agent for treating acne over the last 40 years, continues to be used despite the FDA warning on the risk of psychiatric outcomes including depression, psychosis and suicidal attempts (Singer et al. 2019). It needs must be remembered that while isotretinoin cures acne and thereby boosts mental health by improving perception of body image and self-esteem (Rubinow et al. 1987), it can also cause psychiatric disorders including depression and mania through biological mechanisms (Kontaxakis et al. 2009).

Patients on isotretinoin therapy must be followed up against the development of psychiatric disorders including psychotic mania attacks, with special attention on those who have a personal or family history of psychiatric disorders. In the event of a manic attack, as in the case we present here, discontinuing isotretinoin use and initiating psychiatric treatment with follow up at short intervals should ensure rapid regression of manic episode symptoms and regain of normal mental health. When isotretinoin use cannot be discontinued, it would be appropriate to start with mood stabilizer treatment, or to escelate the dose of any ongoing treatment with such agents.

It is imperative that the acne treatment in individuals with a personal or family history of psychiatric disorder should be carried out conjointly with dermatology and psychiatry specialists to enable the rapid control of mood attacks in risk groups. Cases similar to ours without known risk factors should also be montiored for symptoms of mania and other psychiatric disorders and be referred without delay to the psychiatry clinic when necessary for ascertaining the diagnosis and rapid initiation of treatment.

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