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Inter-relationships between isotretinoin treatment and psychiatric disorders: Depression, bipolar disorder, anxiety, psychosis and suicide risks

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Abstract

Isotretinoin (Accutane) is a treatment for severe acne that is resistant to other forms of treatment, including antibiotics and topical treatments. The prescription of this drug has been controversial ever since its initial marketing in 1982. It is the only non-psychotropic drug in the Food and Drug Administration top 10 drugs found to be associated with depression. Recently, Bremner *et al* published an extensive review (until 2010) of the evidence for the association of retinoic acid (RA) with depression and suicide. Some patients who are admitted in psychiatric hospitals report a history of present or past treatment with isotretinoin. Then, the imputability of the molecule in the occurrence of disorders represents necessarily an important question for both professionals and their patients. This paper aims to specify the links between the drug and specific psychiatric disorders. A review of the literature related to isotretinoin, RA, vitamin A, depression, suicide, anxiety, bipolar disorder, psychosis, schizophrenia was performed. Many studies demonstrated an increased risk of depression, attempted suicide and suicide following isotretinoin treatment. However, isotretinoin may have an antidepressant impact, according to some dermatological papers. They consider treating acne with this efficient treatment could improve self-image and make the patient feel better. Several studies showed that patients with bipolar disorder had an increased risk for a clinical exacerbation of symptoms undergoing treatment with isotretinoin. A few studies also seem to suggest a possible link between isotretinoin and psychosis. Nonetheless, studies point out a link between retinoid dysregulation and schizophrenia through modulation of dopamine receptors. From this review, we propose guidelines for isotretinoin prescription to healthcare professionals.

Key words: Isotretinoin; Retinoic acid; Vitamin A; Suicide; Anxiety; Bipolar disorder; Psychosis; Schizophrenia

Core tip: Isotretinoin is a treatment for severe acne. The prescription of this drug has been controversial ever since its initial marketing in 1982. This paper aims

to specify the links between the drug and psychiatric disorders such as depression, suicide, anxiety, bipolar disorder and psychosis. Many studies demonstrated an increased risk of depression, attempted suicide and suicide following isotretinoin treatment. Several studies showed that patients with bipolar disorder had an increased risk for a clinical exacerbation of symptoms undergoing treatment with isotretinoin. A few studies also seem to suggest a possible link between isotretinoin and psychosis. From this review, we propose guidelines for isotretinoin prescription to healthcare professionals.

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INTRODUCTION

Since 1982 the United States Food and Drug Administration (FDA) has approved isotretinoin for the treatment of cystic and nodular acne that is not responsive to other forms of treatment (including antibiotics). Isotretinoin [13-cis retinoic acid (RA)] belongs to retinoids, a group of compounds derived from the essential nutrient vitamin A, which performs a large number of functions in many systems among them the central nervous system (CNS). The majority of these functions are performed by RA, the most active form of vitamin A, which binds to retinoic receptors to control gene expression in the brain. Thirty years later, the prescription remains controversial[1]. Drug regulatory agencies worldwide are now warning isotretinoin-treated patients about the risk of potential psychiatric side effects, particularly of depression and suicide[2].

Since its first use, many studies alert about a possible correlation between the use of isotretinoin and psychiatric disorders. In 2005, the FDA established a black box warning for suicide, depression, aggression and psychosis. The first aim of this article is to list the literature (from pubMed) in order to specify links between isotretinoin and depression, anxiety, bipolar disorder, and psychosis. A lot of papers respond to the only two keys words isotretinoin and depression. Among all these papers, we chose to select those that enable to show the differences between both psychiatric and dermatological points of view. Thus, forty-one papers were included.

Finally, we propose guidelines for isotretinoin prescription to healthcare professionals.

Isotretinoin and CNS

It is now established that isotretinoin is highly teratogenic, especially regarding the CNS. Fetal malformations as exencephaly, prosencephaly and hydrocephalus have occurred[1]. More recent works suggested that RA may influence the adult brain.

Bremner *et al*[2] highlights RA function in the striatum, hippocampus, frontal cortex and hypothalamus, brain areas all involved in depression.

13-cis RA may cause a dysregulation of neurotransmitters in striatum and hippocampus (in particular the dopaminergic system) and an inhibition of hippocampal neurogenesis[2,3].

In 2005, Bremner *et al*[2,4] studied the influence of isotretinoin on brain metabolism measured by Positron Emission Tomography Fluorodeoxyglucose. They showed a significant reduction in orbitofrontal cortex (a brain region associated with depression) metabolism after a 4-mo of isotretinoin treatment.

The study exposed a correlation between decreased orbitofrontal metabolism and headache during the treatment. Subjects sensitive to isotretinoin-induced effects on the CNS such as headache may also be susceptible to other neuropsychiatric side effects, such as depression[2,4,5].

Retinoids may lead to a decrease in orbitofrontal functioning *via* their effects on the hippocampus, a brain area that modulates dopaminergic function in the orbitofrontal cortex. The hypothesis of a dysregulation in hippocampal-orbito-frontal function caused by isotretinoin could explain how it contributes to promote depression[4].

The RA has also an action in the hypothalamus[2,6]. Shearer *et al*[6] have identified the synthesis of RA in tanycytes (by the retinaldehyde deshydrogenase) and the presence of RA receptors in hypothalamus neurons. RA can be released into the hypothalamus and regulate a number of genes among them those implicated in corticotropin-releasing hormone (CRH) synthesis.

Chen *et al*[7] highlights an increased density of receptor acid retinoic α-expressing cells in the hypothalamic paraventricular nucleus of patients with affective disorders. Increased RA signaling promoted by isotretinoin may mimic the augmentation of the pathway resulting from the elevation in RA receptor α[4,7]. RA receptor α might contribute to regulating the activity of CRH neurons *in vivo* and by this mechanism may contribute for depression as this hormone is known for playing a key role in its pathogenesis.

Hypervitaminosis A and psychiatric disorders

Bremner *et al*[2] reported a number of cases of mental symptoms associated with vitamin A toxicity. For example, the rare < pibloktoq syndrome > in people living within the Arctic Circle (that may be secondary to consuming polar bear or seal liver, which contain very high vitamin A levels). This syndrome includes symptoms ranging from depression to violence outbursts.

To investigate the link between hypervitaminosis A and psychiatric disturbances, studies on mefloquine (an antimalarial drug) are of value. Mefloquine is

known for a long time to have neuropsychiatric side effects. It has been linked to severe anxiety and depression, cognitive disturbances, psychosis and violence. Mawson[8] presented the hypothesis that mefloquine toxicity is an endogenous form of hypervitaminosis A. It is the only drug that targets the liver-stage Plasmodium falciparum parasites. Mefloquine acts as a dehydrogenase inhibitor that causes accumulation of retinyl esters in the liver, resulting in hepatocellular damage and the destruction of malaria parasites *in situ*. This is followed by the discharge of stored retinoids into the circulation in toxic concentrations before their transportation to the brain. Neuropsychiatric adverse effects result thus, as manifestations of an endogenous form of hypervitaminosis A. Acute vitamin A toxicity includes nausea, vomiting, headache, vertigo, blurred vision, increased intracranial pressure, irritability and muscular incoordination[8].

LITERATURE REVIEW

Isotretinoin, anxiety and depression

The effect of isotretinoin on mood and suicide risk is a matter of concern.

Preliminary evidence of links between RA and depression has come from behavioral studies on animals. Researchers suggested administration of 13-cis-RA in mice during 6 wk increases depression-related behaviors [decreased swimming in a (forced swim) test and poorer performance in (tail suspension) tests][9].

In adults, Bremner, an American psychiatrist[2], published in 2012 an extensive review (until 2010) on RA and affective disorders. Bremner *et al*[2] have outlined a relationship between isotretinoin and depression. The evidence included case reports, temporal association between onset of depression and exposure to the drug, challenge-rechallenge studies (depression resolved after discontinuation of the drug and in some cases returned with its reintroduction), dose response, biologic plausibility and class effect (review of neuropsychiatric effects of hypervitaminosis A). Moreover, they reported that the incidence of depression in large studies of isotretinoin-treated patients ranges from 1% to 11%. For some researchers[10,11] it corresponds to the annual incidence of major depressive disorders in adolescents.

Between 1990 and 2001, pharmacologists, dermatologists and a psychiatrist (Sundström *et al*[12]) led an important retrospective cohort study with 5756 patients aged 15 to 49 years who were prescribed isotretinoin for severe acne. This Swedish cohort demonstrated an increased risk of attempted suicide up to 6 mo after the end of treatment. The authors specified that severe acne is an independent risk factor for attempted suicide. Furthermore, they reported that an additional risk may be present, but can't be established with certainty, during and up to one year after treatment, and for this reason recommend a close monitoring for suicidal behavior. They add that there is no reason to refuse this treatment for patients who have attempted suicide. Indeed, they observe fewer recurrences with the patients having such a history in comparison to those having started such behaviors in connection with the treatment.

The major part of the dermatology community[13-23] states that there is no causal link between isotretinoin and depression with this postulate: acne causes anxiety and depression; treating acne with isotretinoin is a way to manage depression (improved self-image and positive behavioral effects). For example, Halvorsen *et al*[15] support a link between acne and suicidal ideation, mental health problems, and social impairment based on a large cross-sectional study of Norwegian adolescents. On the contrary, Magin *et al*[24] found no relationship between presence of acne or acne severity and measures of depression and anxiety. Hahm *et al*[14] found no correlation between beck depression inventory (BDI) scores and acne grade, but they suggested that improvement in depression symptoms are caused directly by quality of life in connection with acne improvement (APSEA score: Assessment of Psychological and Social Effects of Acne) rather than by improvement in acne grade.

A recent prospective observational longitudinal study[20] with a sample of 346 subjects treated for moderate acne highlights a significant reduction of Hospital Anxiety and Depression Scale (HADS) scores for anxiety and depression after isotretinoin treatment. A prospective and uncontrolled study[22] conducted between 2006 and 2008 included 100 patients suffering from moderate to severe acne. Before the treatment, six percent of the patients had suffered from depressive symptoms. The isotretinoin treatment did not seem to make these symptoms worse. By contrast, the study demonstrated that isotretinoin treatment of acne significantly improved depressive symptoms. Comparisons of the BDI-Ⅱ scores indicate that improvement in mood was statistically significant between months 0 and 1, 4 and 7, and 0 and 9 during the isotretinoin course. No suicide risk was reported during follow-up. McGrath *et al*[21] shows that successful treatment of acne significantly improves quality of life, particularly in those with more depressive symptoms at the outset. Yesilova *et al*[25] showed that performance avoidance score in Liebowitz Social Anxiety Scale (LSAS), pain and social functioning scores in SF-36 (Short-Form) were significantly better at the end of isotretinoin treatment. In their conclusion, the authors state that isotretinoin treatment improves the quality of life and social anxiety symptoms in acne patients.

Thirty-three patients with acne vulgaris completed a study[10] led between 2010 and 2011; rumination (MOCQ), depression and anxiety symptoms (HADS) improved significantly after 6 mo of oral isotretinoin treatment. On the other hand, doubting, a dimension of obsessive-compulsive symptoms was significantly

worse after treatment.

Two recent comparative studies from dermatological papers should be mentioned: A prospective and comparative study[26] included 85 patients: 46 with moderate acne (20 treated with isotretinoin and 26 patients were a control group treated with vitamin C) and 39 with severe acne (21 with isotretinoin, and 18 with vitamin C). In moderate and severe acne patients, there was no significant difference between the patients taking isotretinoin and the control group in any of the psychological tests [Measure of Psychological Stress (MPS), BDI, State Trait Anxiety Inventory (STAI) and APSEA tests]. The use of isotretinoin in the treatment of moderate to severe acne did not increase the symptoms of depression and anxiety. Another study[18] compared during 4 mo quality of life, anxiety and depressive symptoms between two groups of patients suffering from acne: the first group received the isotretinoin treatment (n = 37) and the control group received a topical treatment (n = 41). The two groups were the same in terms of Dematology Life Quality Index (DLQI), BDI, Hospital Anxiety and Depression (HAD) scores at baseline. However, at the end of the second month, quality of life was significantly more impaired in the topical treatment group compared to the isotretinoin group. At the end of the fourth month, quality of life and all psychological test scores had a significantly greater improvement in the isotretinoin group. Depressive and anxiety symptoms did not increase in the isotretinoin treatment group in comparison to the topical group[18].

Nonetheless, Goodfield *et al*[27] published in 2010 guidelines concerning the isotretinoin prescription in the British Journal of Dermatology. They recommend: first, the inventory of psychiatric histories for all patients candidate for isotretinoin prescription. Then, patients and their families should be sensitive of the possible potential for mood change. Finally, a direct enquiry about psychological symptoms should be made at each clinic visit.

Isotretinoin and bipolar disorder

The first episode of bipolar disorders is frequent during late adolescence. Lithium is recommended as the first-line medication for this pathology. Acne is not an unusual side effect of lithium. As lithium-related acne is often resistant to usual treatments, isotretinoin is frequently prescribed for this particular resistant acne. Several studies showed that BD patients treated with isotretinoin are at risk for clinically significant exacerbation of mood symptoms, including suicidal ideation. This exacerbation could arise in spite of a concurrent use of maintenance psychiatric medicines.

Isotretinoin prescription in BD patients

In 1988, Bigby *et al*[28] described a BD patient taking lithium who became suicidal after six and a half weeks of isotretinoin treatment. In 1999, Cott *et al*[29] described a case report of a BD woman taking lithium who developed after 4 wk of isotretinoin treatment, signs of previous psychotic manic symptoms decompensations. The addition of an antipsychotic allowed the complete resolution of the episode.

In 2010, a retrospective chart review[30] of 300 BD patients identified 10 patients treated with isotretinoin. Nine of the ten patients experienced an exacerbation of mood symptoms: six mixed symptoms, two depressive symptoms and one hypomanic symptom. Three of them developed suicidal ideation. Symptoms began from 4 to 20 wk after initiation of therapy and resolved with discontinuation in all but 1 patient. Besides, seven of the nine patients were taking maintenance psychiatric medications for BD at the time of the apparent reaction.

Isotretinoin prescription in non BD patients

Barak *et al*[31] of 500 soldiers with no prior history of psychiatric diagnosis treated with isotretinoin for severe acne reported that five of these patients developed manic psychosis within 8 mo of exposure. This was accompanied by a suicide attempt for three of them. In three cases, they found a family history of BD in a first degree relative. A personal history of obsessive-compulsive disorder (OCD) was also found for three patients.

In 2010, Fornaro[32] described a 25-year-old patient who developed OCD following isotretinoin treatment. An unexpected mood switch was observed 1 mo after the introduction of an antidepressant (fluvoxamine). This points out to the possible link between an iatrogenic induced OCD and an increasing risk for bipolar disorder.

Isotretinoin and psychosis

Bremner *et al*[2] reported cases of hypervitaminosis A associated with psychotic symptoms. A few studies in the literature state a possible link between isotretinoin and psychosis[16,33].

The neurobiological hypothesis for schizophrenia and psychotic symptoms is an increase in dopaminergic stimulation or sensitivity in the limbic system[34].

In fact, Goodman[35-37] points out a link between retinoid dysregulation and schizophrenia. He suggested that dysregulation by retinoids may be an important factor in the etiology of this pathology.

The evidence of this association is based on three points, according to these studies. First, retinoid dysfunction produces congenital anomalies, the same found in schizophrenic patients. Additionally, schizophrenia and the retinoid cascade have been linked to the same gene loci. Finally, RA regulates the transcriptional activation of the Dopamine D2 receptor and other schizophrenia candidates (as serotonin and glutamate receptors)[35-37].

A microarray study of schizophrenia in human brains published by Goodman[38] reported that two proteins (aldehyde dehydrogenase 1A1 and albumin), both important for the transport and function of the

vitamin A are altered in these patients. Thus, RA, the final metabolic product of the retinoid cascade, would be insufficient in schizophrenia. Unavailability of RA impairs transcriptional regulation of retinoid target genes like the Dopamine D2 Receptor, which is a candidate gene in schizophrenia. The expression of dopamine receptors has indeed shown to be regulated by RA[38,39]. So, Citver *et al*[40] proposed retinoid analogs as candidates for the treatment of schizophrenia, by altering the downstream expression of dopamine D2 receptors. Furthermore, mutations for the acid retinoic receptors demonstrated in mice could reduce expression of D1 and D2 receptors and do impair dopamine signaling[38,41].

DISCUSSION

This paper aims to discuss the relationship of treatment with isotretinoin to depression, bipolar disorder and psychosis.

Literature studies have demonstrated two opposing views as to the role of isotretinoin from two differing clinical specialties. The psychiatric literature (cf Bremner) suggests a causal link between isotretinoin and depression. The dermatological literature suggests that acne is an independent risk factor for depression and isotretinoin could be used to improve depression by treating acne and improving self-image. These differing views could be explained by a recruitment bias. Dermatologists may not have been aware of the occurrence of psychiatric disorders.

There is strong evidence from the psychiatric literature that demonstrates an association of isotretinoin to depression, probable clinical exacerbation of bipolar mood disorder and possible links to psychosis.

It is important that isotretinoin be prescribed only for severe acne, resistant to several course of antibiotics. The patients that may be susceptible to these side effects may not be able to be predicted. However, an assessment of previous psychiatric histories (by means of questionnaires preliminary to the isotretinoin's prescription) and current psychiatric state may be helpful in identifying them.

Close monitoring of these patients for neuropsychiatric side effects seems to be very important during isotretinoin therapy. For example, headache symptoms could constitute an alert symptom. In patients undergoing lithium therapy who develop acne, a careful risk/benefit analysis on withdrawal of treatment should be undertaken. The responsibility of lithium in the occurrence of acne may be established with the highest certainty possible. Then, the mental state of the patient has to be evaluated: is its pathology balanced under lithium? In this case, it may be risky to stop lithium treatment, although there are many other pharmacological choices today such as anticonvulsants and atypical antipsychotics (please find adequate references). The optimal treatment may be discussed with both professionals and patient in order to choose the best option available.

There is also a debate between nephrologists and psychiatrists regarding lithium and renal insufficiency. Nephrologists recommend to stopping the treatment if the patient develops a renal insufficiency. Psychiatrists will tend to maintain the treatment, especially if they consider it's the only molecule able to stabilize the patient.

CONCLUSION

Opposing views as to the role of isotretinoin in the occurrence of depression are discussed. Even if the risks of suicide appear weak, a general principle of patient therapy monitoring should be introduced. Further studies to establish links to bipolar disorder and psychosis during isotretinoin therapy are required. Careful risk/benefit analysis of patients developing acne on lithium treatment should be undertaken.

A multidisciplinary approach of the patient (during the liaison psychiatry for example) is here particularly relevant in order to permit discussion between specialists about this treatment.

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