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Psychiatric and Developmental Effects of Isotretinoin (Retinoid) Treatment for Acne Vulgaris

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ABSTRACT

Background: An association between isotretinoin (13-cis-retinoic acid, sold under trade names including Accutane [Hoffmann-La Roche Inc, Basel, Switzerland]) and birth defects, depression, and suicide is well documented but controversial. A link to psychosis and exacerbation of bipolar symptoms is less extensively addressed in the literature.

Objective: Given recent conceptualization of psychotic disorders as neurodevelopmental, and current interest in possible shared etiology of different neurodevelopmental disorders such as psychosis, autism, and intellectual disability, this review concurrently examines the literature on developmental (primarily teratogenic) and psychiatric side effects of isotretinoin exposure. The goal of concurrent review is to identify shared mechanisms in the literature that may inform future efforts to clarify the neurocognitive and psychiatric effects of isotretinoin exposure at different developmental stages or given different genetic backgrounds.

Methods: Literature was obtained by PubMed search for the term *isotretinoin* in combination with each of the terms *psychosis*, *psychiatric*, and *teratogenic*. Resulting articles met inclusion criteria for review if they addressed psychiatric side effects of isotretinoin treatment or the neurobehavioral teratology of isotretinoin.

Results: The association of isotretinoin exposure with prenatal developmental toxicity is well established. Although numerous reports also link isotretinoin treatment with psychiatric side effects, this association remains controversial.

Conclusions: The extent to which isotretinoin influences pediatric and adult development and cognition, and whether and why certain individuals may be susceptible to psychiatric side effects, remains to be clarified. *Curr Ther Res Clin Exp*. 2019; 80:XXX–XXX)

Background

Isotretinoin is a prescription retinoid medication used to clear severe and otherwise treatment-resistant acne.[1] Although isotretinoin has been an efficacious drug with high rates of permanent remission for many patients, adverse effects including but not limited to inflammatory bowel disease, psychosis, and excessive bone growth have frequently been reported.[2–10] This review specifically addresses developmental (primarily teratogenic) and psychiatric side effects of isotretinoin exposure or use.

The teratogenicity of retinoid compounds is well established, and alongside thalidomide, isotretinoin may be considered 1 of the 2 best-known examples of drugs causing serious birth defects, including brain and craniofacial malformations.[11–13] Association of isotretinoin use with depression and anxiety has been more controversial, although numerous reports have documented these and other psychiatric adverse effects.[3–5,7–10]

Given recent conceptualization of psychotic disorders as neurodevelopmental, and current interest in the shared etiology of different neurodevelopmental disorders such as psychosis, autism, and intellectual disability, concurrent review of the developmental and psychiatric consequences of isotretinoin exposure or use may yield insights that inform future investigation of perturbed retinoid signaling at different developmental stages or given different genetic backgrounds.

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Methods

Literature was obtained by English-language PubMed search for the term *isotretinoin* in combination with each of the terms *psychosis*, *psychiatric*, and *teratogenic*. Results met inclusion criteria for review if they addressed psychiatric side effects of isotretinoin treatment or the neurobehavioral teratology of isotretinoin.

Mechanisms and mode of action

Isotretinoin (13-cis-retinoic acid) is an oral retinoid medication with sebostatic properties, decreasing proliferation of basal sebocytes, reducing sebum production, and inhibiting sebocyte differentiation.[14]

Retinoids are a family of compounds derived from vitamin A. 13-cis-retinoic acid is an active form of vitamin A that binds to retinoic acid receptors (RARs) in the brain and embryonic tissues in the craniofacial region, heart, and thymus. Like glucocorticoid and thyroid hormone receptors, RARs are part of the nuclear receptor superfamily that regulates gene expression in the brain. Notably, RARs regulate expression of homeobox, or *HOX*, genes, which in turn control developmental programs in various species. Accordingly, abnormal retinoid levels can have neurologic effects, and retinoids hold a central place in the history of neurobehavioral teratology.[15–21]

Beyond its prenatal effects, isotretinoin may influence cognition in adult life. RARs are expressed in the adult hippocampus, thalamus, and pons (RARα), and the striatum, hypothalamus, and medulla (RARβ), and retinoic acid has been found to modulate synaptic plasticity and neurogenesis in adulthood.[19]

Isotretinoin is hypothesized to induce depression-related behaviors by decreasing adult neurogenesis or altering expression of components of the serotonergic neurotransmitter system, resulting in impaired serotonin signaling.[22] An association of retinoic acid signaling with stress and depression is supported by the overlap between brain areas implicated in both.[15] Furthermore, functional brain imaging has revealed a decrease in brain metabolism in the orbitofrontal cortex—an area established to mediate symptoms of depression—in acne patients treated with isotretinoin.[23]

Forkhead box class O transcription factors may be implicated in both the therapeutic and adverse effects of isotretinoin. Upregulation of Forkhead box protein O1 may inhibit hippocampal neurogenesis.[24]

Teratogenic effects

High levels of vitamin A during pregnancy can be teratogenic. Safe levels are estimated to fall between 25,000 and 37,000 IU/d.[18]

In human beings, isotretinoin is associated with a wide spectrum of birth defects, including craniofacial, heart, and nervous system malformations. Reported effects have included agenesis of the cerebellar vermis; malformation of posterior fossa; multiple leptomeningeal neuroglial heterotopias; hydrocephalus; abnormalities of the corticospinal tracts; mid-hindbrain malformations; craniofacial defects including anotia and microtia; abnormalities of the inner ear; ocular, retinal, or optic nerve abnormalities, including myopia and light sensitivity; psychomotor retardation; mental retardation; learning disabilities; and premature birth.[25–35]

Isotretinoin is thought to induce cleft palate in human beings by sustaining the expression of epidermal growth factor receptors in medial epithelial cells of the palate at a time when these cells would normally undergo apoptosis, resulting in continued DNA synthesis, proliferation, survival, and shift in cell phenotype.[36]

In nonhuman primate models, isotretinoin has produced defects of the cerebellar vermis by interfering with processes that subdivide the cerebellum into smaller units; craniofacial skeleton and heart defects due to exposure earlier during gestation; and thymus and cerebellum defects due to exposure later during gestation, with defect severity generally depending on duration of exposure.[37,38]

Psychiatric effects

Strong evidence, including more than 400 case reports received by the US Food and Drug Administration (FDA) from 1982 to 2000 alone, suggests a link between isotretinoin and depression. During the same time period, 37 suicides were also reported to the FDA.[39–42] In the United States, questions regarding isotretinoin's psychiatric safety came to broader public attention after a 15-year-old male patient flew a stolen plane into a Florida office tower and his family filed a wrongful death lawsuit against isotretinoin's manufacturer, attributing the pilot's acute psychosis to use of the medication.[43]

Notwithstanding these reports, the association between isotretinoin use and psychiatric illness, including among individuals with no prior psychiatric history, has remained controversial.[44–52] As recently as 2015, only 37% of 591 board-certified dermatologists participating in a survey study responded that they believed isotretinoin may cause psychiatric disturbances.[53]

Results of 1 study involving Finnish male military conscripts suggested that, on a group level, isotretinoin was not typically associated with depression or suicidal ideation, but individual patients may have idiosyncratic mood reactions. Depression and suicidal ideation were assessed with the Beck Depression Inventory, and Beck Depression Inventory scores were found to decline significantly ($P < 0.001$) among patients taking isotretinoin.[54]

Another study involving the Israeli Defense Forces compared use of mental health services by young adults taking isotretinoin and young adults in a control group, and found a statistically significant intergroup difference ($P = 0.0003$), with the isotretinoin user group showing relatively increased use of mental health resources compared with controls.[55]

Large-scale review and survey studies of isotretinoin side effects have found that 25.16% of adverse effects reported for isotretinoin were psychiatric, and that 1.65% of pediatric patients taking isotretinoin reported psychiatric symptoms.[7,56] A 2017 search of the French National PharmacoVigilance database for systemic acne treatments yielded 71 reports of severe psychiatric disorders involving isotretinoin.[5]

Affective disorders and suicide

Information regarding depression was added to isotretinoin labeling in 1998 in response to numerous reports submitted to the FDA MedWatch system.[43] Meanwhile, suicides during treatment were reported in several countries and brought to public attention.[57,58]

In a review of drug-induced depression and suicidal behavior reported under the United Kingdom's Yellow Card Scheme from 1998 to 2011, isotretinoin was among the top-5 drugs most frequently associated with reports of depression.[59] In the United States in 2015, isotretinoin ranked in the top 10 of the FDA's database of drugs associated with reports of depression and suicide attempts.[60]

However, numerous authors have suggested either no association with depression, or instead an amelioration of depressive or anxious symptoms with treatment, prompting suggestions that idiosyncratically susceptible patients may exist, or that individuals with a family history or personal history of mental illness may be susceptible.[61–76]

Psychosis and mania

Isotretinoin is contraindicated in psychosis because it worsens the course of the disease.[77] Similarly, an excess of dietary vitamin A has been reported to induce psychosis.[22]

One literature review incorporating information from case reports, patient charts, and drug registries suggested that many patients identified as depressed while taking isotretinoin in fact showed signs of activation, agitation, elevated mood, and psychosis, and that these symptoms appeared to be more prevalent in patients with a personal or family history of mental illness.[3]

Individual cases of isotretinoin-related psychosis reported in the literature have included a woman without a family history of mental illness experiencing manic psychosis associated with treatment; a young man developing acute psychosis within a few days of starting treatment, and showing rapid improvement after stopping treatment; a 13-year-old male patient experiencing insomnia, delusions, and auditory hallucinations after 2 months of treatment, and experiencing complete remission 2 weeks after stopping treatment and taking olanzapine; and a 25-year-old woman with a family history of bipolar disorder developing psychotic symptoms during treatment, with symptoms remitting after stopping treatment.[78–81]

Bipolar disorder

Bipolar patients treated with isotretinoin are at risk for exacerbation of mood symptoms, including suicidal ideation.[82–84]

In Poland, a case analysis comprising 7 female and 2 male patients ages 18 to 27 years admitted to the Department of Psychiatry at the Medical University of Lublin included 1 patient with a bipolar mixed episode and 1 with a rapid cycling bipolar I episode, each temporally associated with isotretinoin treatment.[71]

In another study, a retrospective chart review of 300 outpatients with bipolar disorder identified 10 patients taking isotretinoin. Nine of 10 patients, ages 15 to 39 years, experienced worsening mood symptoms, 3 experienced suicidal ideation, and 8 experienced a reversal of symptoms after isotretinoin discontinuation. Of 9 patients with worsening mood symptoms, 6 experienced mixed symptoms, 2 experienced depressive symptoms, and 1 experienced hypomanic symptoms.[82]

Other psychiatric case reports

Isotretinoin has been associated with psychiatric disorders and symptoms beyond depression and psychosis in some cases. In 1 instance, a 23-year-old man developed obsessive-compulsive disorder after 7 years of isotretinoin treatment (10–20 mg/d). A combination of fluvoxamine (300 mg/d) and olanzapine (15 mg/d) improved his symptoms.[85] The literature also includes reports of panic attacks in a 20-year-old man and another 17-year-old patient in relation to use of isotretinoin.[86,87] Instances of erectile dysfunction and increased aggression, respectively, have also been reported in other cases.[88,89]

Animal studies

Animal model responses to isotretinoin administration support an association with psychiatric adverse effects. In 1 study, mice treated with isotretinoin gel (0.05%) or tacrolimus ointment (0.1%, in each case, 5 × the clinical dose) showed lower activity in an open-field test, depressive-like behavior in a tail suspension test, damaged cytoarchitecture, changes in the serotonergic system, and increased expression of apoptosis-related proteins in the hippocampus.[90]

In other cases, studies have shown impairments in spatial learning and memory, and reduced cell proliferation in the hippocampus and subventricular zone, following 13-cis-retinoic acid treatment in a mouse model (using a clinical dose of 1 mg/kg/d); or few effects on spatial learning and memory in rats (with a dose of 7.5 mg/kg).

In contrast with the results in animal studies, in a human study, memory significantly improved with isotretinoin treatment (dose correlated with improvement in total trial score [$P = 0.025$]), with the authors mentioning but discounting the possibility of a practice effect given repetition of the memory test.[91–93]

Mechanisms revisited: Psychiatric effects

Given the possible association between isotretinoin and psychosis, it is notable that retinoid dysregulation has previously been linked to schizophrenia. Relatives of individuals with schizophrenia also show various congenital anomalies similar to, but less severe than, those caused by retinoid dysfunction.[83,94,95]

Additionally, isotretinoin treatment, schizophrenia, and depression have each been associated with elevated homocysteine levels, prompting the suggestion that isotretinoin-induced homocysteine elevation may contribute to psychiatric side effects.[96]

At least 1 author has suggested similarities between genetic intellectual disability syndromes (including forms of autism) and neuroteratogenic syndromes caused by isotretinoin; for example, observing that individuals with Fragile X syndrome and Williams syndrome show neuropsychological profiles similar to those of children exposed to isotretinoin during early embryogenesis.[97]

Other effects: Sleep

The search for literature related to psychiatric effects of isotretinoin yielded a single description of Kleine-Levin syndrome, characterized by periodic hypersomnia and cognitive and behavioral symptoms, in close temporal relation to the start of isotretinoin treament.[98]

A study on isotretinoin treatment and sleep showed that sleep efficiency increased ($P = 0.036$), sleep latency decreased ($P = 0.023$), and nighttime sleep generally improved in patients.[99]

Genetics

Kontaxakis et al[100] speculated that genetic factors may predispose certain individuals to psychiatric adverse effects when taking isotretinoin, based on 4 cases observed in 2008 where psychiatric symptoms were deemed likely attributable to isotretinoin use. Two cases involved patients with a family history of psychosis and affective disorder, and for these patients isotretinoin induced mixed clinical syndromes with both psychotic and depressive features. The other 2 cases involved patients with a family history of affective disorder or psychosis, and for these patients isotretinoin induced nonpsychotic major depression and schizophrenia, respectively. The authors speculated that isotretinoin-induced psychiatric symptoms may be the product of a gene–environment interaction, where isotretinoin treatment functions as an environmental stressor.[100]

Conclusions

The extent to which isotretinoin influences postnatal development and cognition, and whether certain individuals are particularly susceptible to psychiatric side effects, remains to be clarified. Questions or topics warranting further investigation may include:

- Clarification of the effect of isotretinoin on memory in humans, given previously conflicting results in human and animal studies;

- Clarification regarding the reasons for variation in the timing and duration of psychiatric symptoms reported by individuals during and after isotretinoin treatment; and
- Whether certain genotypes are more susceptible to psychiatric or other side effects, such as effects on sleep, when taking isotretinoin.

Further study could help to tailor the information provided to individuals considering undergoing or prescribing treatment with isotretinoin, and increase attention to, and improve management of, possible side effects. Particular vigilance may be warranted in the case of patients with a personal or family history of bipolar disorder or other psychiatric illness.

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Conflicts of Interest

The author has indicated that she has no conflicts of interest regarding the content of this article.

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