



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

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## ARTICLE INFO

### Article history:

Received 10 November 2018

Accepted 29 January 2019

### Key words:

acne vulgaris  
depression  
isotretinoin  
psychosis  
retinoid  
suicide

## 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

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## Background

Isotretinoin is a prescription retinoid medication used to clear severe and otherwise treatment-resistant acne.<sup>1</sup> 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.<sup>2–10</sup> 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.<sup>11–13</sup> Association of isotretinoin use with depression and anxiety has been more controversial, although numerous reports have documented these and other psychiatric adverse effects.<sup>3–5,7–10</sup>

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.<sup>14</sup>

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.<sup>15–21</sup>

Beyond its prenatal effects, isotretinoin may influence cognition in adult life. RARs are expressed in the adult hippocampus, thalamus, and pons (RAR $\alpha$ ), and the striatum, hypothalamus, and medulla (RAR $\beta$ ), and retinoic acid has been found to modulate synaptic plasticity and neurogenesis in adulthood.<sup>19</sup>

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.<sup>22</sup> An association of retinoic acid signaling with stress and depression is supported by the overlap between brain areas implicated in both.<sup>15</sup> 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.<sup>23</sup>

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.<sup>24</sup>

### *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.<sup>18</sup>

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.<sup>25–35</sup>

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.<sup>36</sup>

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.<sup>37,38</sup>

### *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.<sup>39–42</sup> 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.<sup>43</sup>

Notwithstanding these reports, the association between isotretinoin use and psychiatric illness, including among individuals with no prior psychiatric history, has remained controversial.<sup>44–52</sup> 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.<sup>53</sup>

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.<sup>54</sup>

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.<sup>55</sup>

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.<sup>7,56</sup> A 2017 search of the French National Pharmacovigilance database for systemic acne treatments yielded 71 reports of severe psychiatric disorders involving isotretinoin.<sup>5</sup>

### *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.<sup>43</sup> Meanwhile, suicides during treatment were reported in several countries and brought to public attention.<sup>57,58</sup>

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.<sup>59</sup> 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.<sup>60</sup>

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.<sup>61–76</sup>

### Psychosis and mania

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

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.<sup>3</sup>

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.<sup>78–81</sup>

### Bipolar disorder

Bipolar patients treated with isotretinoin are at risk for exacerbation of mood symptoms, including suicidal ideation.<sup>82–84</sup>

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.<sup>71</sup>

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.<sup>82</sup>

### 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.<sup>85</sup> 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.<sup>86,87</sup> Instances of erectile dysfunction and increased aggression, respectively, have also been reported in other cases.<sup>88,89</sup>

### 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.<sup>90</sup>

In other cases, studies have shown impairments in spatial learning and memory, and reduced cell proliferation in the hip-

pocampus 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.<sup>91–93</sup>

### 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.<sup>83,94,95</sup>

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.<sup>96</sup>

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.<sup>97</sup>

### 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 treatment.<sup>98</sup>

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.<sup>99</sup>

### Genetics

Kontaxakis et al<sup>100</sup> 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.<sup>100</sup>

### 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.

## Acknowledgments

No assistance or monetary support was received at any time.

## Conflicts of Interest

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

## References

- Ward A, et al. Isotretinoin. A review of its pharmacological properties and therapeutic efficacy in acne and other skin disorders. *Drugs*. 1984;28(1):6–37.
- Cyrułnik AA, et al. High-dose isotretinoin in acne vulgaris: improved treatment outcomes and quality of life. *Int J Dermatol*. 2012;51(9):1123–1130.
- Truitt JM, et al. Isotretinoin: the ups are just as troubling as the downs. *G Ital Dermatol Venereol.* 2018. doi:10.23736/S0392-0488.18.05979-5.
- Oliveira JM, et al. Association of isotretinoin with depression and suicide: a review of current literature. *J Cutan Med Surg*. 2018;22(1):58–64.
- Le Moigne M, et al. Psychiatric disorders, acne and systemic retinoids: comparison of risks. *Expert Opin Drug Saf*. 2017;16(9):989–995.
- Vallerand IA, et al. Efficacy and adverse effects of oral isotretinoin for acne: a systematic review. *Br J Dermatol*. 2018;178(1):76–85.
- Brzezinski, P., et al. 2017. Adverse effects of isotretinoin: a large, retrospective review. 30(4).
- Karadag AS, et al. Effects of isotretinoin treatment on general psychiatric symptoms, quality of life and social phobia in acne vulgaris patients. *J Eur Acad Dermatol Venereol*. 2013;27(2):260–261.
- Casagrande Tango R. Psychiatric side effects of medications prescribed in internal medicine. *Dialogues Clin Neurosci*. 2003;5(2):155–165.
- Wooltorton E. Accutane (isotretinoin) and psychiatric adverse effects. *CMAJ*. 2013;186(1):66.
- Balon R, Riba M. Should women of childbearing potential be prescribed valproate? A call to action. *J Clin Psychiatry*. 2016;77(4):525–526.
- Pinheiro SP, et al. Concomitant use of isotretinoin and contraceptives before and after iPledge in the United States. *Pharmacoepidemiol Drug Saf*. 2013;22(12):1251–1257.
- Schonfeld TL, Amoura NJ, Kratochvil CJ. iPLEDGE allegiance to the pill: evaluation of year 1 of a birth defect prevention and monitoring system. *J Law Med Ethics*. 2009;37(1):104–117.
- Orfanos CE, Zouboulis CC. Oral retinoids in the treatment of seborrhea and acne. *Dermatology*. 1998;196(1):140–147.
- Bremner JD, McCaffrey P. The neurobiology of retinoic acid in affective disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(2):315–331.
- Bremner JD, Shearer KD, McCaffrey PJ. Retinoic acid and affective disorders: the evidence for an association. *J Clin Psychiatry*. 2012;73(1):37–50.
- Hull PR, D'Arcy C. Isotretinoin use and subsequent depression and suicide: presenting the evidence. *Am J Clin Dermatol*. 2003;4(7):493–505.
- Hendrickx AG, Peterson P, Hartmann D, Hummler H. Vitamin A teratogenicity and risk assessment in the macaque retinoid model. *Reprod Toxicol*. 2000;14(4):311–323.
- Adams J. The neurobehavioral teratology of retinoids: a 50-year history. *Birth Defects Res A Clin Mol Teratol*. 2010;88(10):895–905.
- Pilorget H, et al. Isotretinoin (RoAccutane) embryopathy. A case report. *J Gynecol Obstet Biol Reprod (Paris)*. 1995;24(5):511–515.
- Guillonneau M, Jacqz-Aigrain E. Teratogenic effects of vitamin A and its derivatives. *Arch Pediatr*. 1997;4(9):867–874.
- O'Reilly K, Bailey SJ, Lane MA. Retinoid-mediated regulation of mood: possible cellular mechanisms. *Exp Biol Med (Maywood)*. 2008;233(3):251–258.
- Bremner JD, et al. Functional brain imaging alterations in acne patients treated with isotretinoin. *Am J Psychiatry*. 2005;162(5):983–991.
- Melnik BC. Isotretinoin and FoxO1: A scientific hypothesis. *Dermatoendocrinol*. 2011;3(3):141–165.
- Hansen LA, Pearl GS. Isotretinoin teratogenicity. Case report with neuropathologic findings. *Acta Neuropathol*. 1985;65(3–4):335–337.
- Merlini, L., et al. Mid-hindbrain malformations due to drugs taken during pregnancy. *J Child Neurol*. 29(4):538–544.
- Mondal D, Shenoy R, Mishra S. Retinoic acid embryopathy. *Int J Appl Basic Med Res*. 2017;7(4):264–265.
- Moerike S, et al. Temporal bone pathology in fetuses exposed to isotretinoin. *Pediatr Dev Pathol*. 2002;5(4):405–409.
- Fraunfelder FT, Fraunfelder FW, Edwards R. Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol*. 2001;132(3):299–305.
- Troncoso SM, Rojas HC, Bravo CE. Isotretinoin embryopathy. Report of one case. *Rev Med Chil*. 2008;136(6):763–766.
- Willhite CC, Lovey A, Eckhoff C. Distribution, teratogenicity, and embryonic delivered dose of retinoid Ro 23-9223. *J Craniofac Genet Dev Biol Suppl*. 2000;2:193–209.
- Lammer EJ, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313(14):837–841.
- Conner CS. Isotretinoin: a reappraisal. *Drug Intell Clin Pharm*. 1984;18(4):308–309.
- Shirazi M, et al. Congenital microtia in a neonate due to maternal isotretinoin exposure 1 month before pregnancy: case report. *J Obstet Gynaecol Res*. 2015;41(6):975–978.
- Meadows M. The power of Accutane. The benefits and risks of a breakthrough acne drug. *FDA Consum.* 2001;35(2):18–23.
- Abbott BD, Pratt RM. Retinoic acid alters epithelial differentiation during palatogenesis. *J Craniofac Genet Dev Biol*. 1991;11(4):315–325.
- Makori N, Peterson PE, Hendrickx AG. 13-cis-retinoic acid causes patterning defects in the early embryonic rostral hindbrain and abnormal development of the cerebellum in the macaque. *Teratology*. 2001;63(2):65–76.
- Korte R, Hummler H, Hendrickx AG. Importance of early exposure to 13- cis retinoic acid to induce teratogenicity in the cynomolgus monkey. *Teratology*. 1993;47(1):37–45.
- Rogers D, Pies R. General medical drugs associated with depression. *Psychiatry (Edmont)*. 2008;5(12):28–41.
- Fakour Y, et al. The effect of isotretinoin (RoAccutane) therapy on depression and quality of life of patients with severe acne. *Iran J Psychiatry*. 2014;9(4):237–240.
- Azoulay, L., et al. Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 69(4):526–532.
- Byrne A, Hnathko G. Depression associated with isotretinoin therapy. *Can J Psychiatry*. 1995;40(9):567.
- Enders SJ, Enders JM. Isotretinoin and psychiatric illness in adolescents and young adults. *Ann Pharmacother*. 2003;37(7–8):1124–1127.
- O'Donnell J. Overview of existing research and information linking isotretinoin (Accutane), depression, psychosis, and suicide. *Am J Ther*. 2003;10(2):148–159.
- Smith EV, et al. What's new in acne? An analysis of systematic reviews published in 2009–2010. *Clin Exp Dermatol*. 2011;36(2):119–122 quiz 123.
- Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol*. 2001;45(4):515–519.
- Thakrar BT, Robinson NJ. Isotretinoin and the risk of depression. *J Clin Psychiatry*. 2009;70(10):1475.
- Kontaxakis VP, et al. Isotretinoin and psychopathology: a review. *Ann Gen Psychiatry*. 2009;8:2.
- Miller MC. Questions & answers. Does the acne drug, isotretinoin (Accutane), cause depression and suicide, or are the psychiatric risk exaggerated? *Harv Ment Health Lett*. 2005;22(4):8.
- van Broekhoven F, Verkes RJ, Janzing JG. Psychiatric symptoms during isotretinoin therapy. *Ned Tijdschr Geneesk*. 2003;147(47):2341–2343.
- O'Connell KA, Wilkin JK, Pitts M. Isotretinoin (Accutane) and serious psychiatric adverse events. *J Am Acad Dermatol*. 2003;48(2):306–308 author reply 308.
- Jacobs, D. G., N. L. Deutsch, and M. Brewer. Suicide, depression, and isotretinoin: is there a causal link? *J Am Acad Dermatol*. 45(5):S168–75.
- Nagler AR, Orlow SJ. Dermatologists' attitudes, prescription, and counseling patterns for isotretinoin: a questionnaire-based study. *J Drugs Dermatol*. 2015;14(2):184–189.
- Rehn LM, et al. Depressive symptoms and suicidal ideation during isotretinoin treatment: a 12-week follow-up study of male Finnish military conscripts. *J Eur Acad Dermatol Venereol*. 2009;23(11):1294–1297.
- Friedman T, et al. Increased use of mental health services related to isotretinoin treatment: a 5-year analysis. *Eur Neuropsychopharmacol*. 2005;16(6):413–416.
- Hodgkiss-Harlow CJ, Eichenfield LF, Dohil MA. Effective monitoring of isotretinoin safety in a pediatric dermatology population: a novel "patient symptom survey" approach. *J Am Acad Dermatol*. 2011;65(3):517–524.
- Wolkstein P. Isotretinoin, depression and medias. *Ann Dermatol Venereol.* 2010;137(Suppl 2):S69–S71.
- . Isotretinoin: psychiatric disorders. *Prescrire Int*. 2008;17(98):242.
- Thomas KH, et al. Reporting of drug induced depression and fatal and non-fatal suicidal behaviour in the UK from 1998 to 2011. *BMC Pharmacol Toxicol*. 2014;15:54.
- Barak Y, et al. Affective psychosis following Accutane (isotretinoin) treatment. *Int Clin Psychopharmacol*. 2005;20(1):39–41.
- Huang YC, Cheng YC. Isotretinoin for acne and risk of depression: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;76(6):1068–1076 2017a.



62. Huang YC, Cheng YC. No evidence for increased anxiety in acne patients treated with isotretinoin. *J Eur Acad Dermatol Venereol*. 2017;31(7):e344–e345 2017b.
63. Rubio-Garcia L, Pulido-Diaz N, Jimenez-Lopez JL. Isotretinoin and depressive symptoms in patients with severe and recurrent acne. *Rev Med Inst Mex Seguro Soc*. 2015;53(Suppl 1):S54–S59.
64. Chia CY, et al. Isotretinoin therapy and mood changes in adolescents with moderate to severe acne: a cohort study. *Arch Dermatol*. 2005;141(5):557–560.
65. Marron SE, Tomas-Aragones L, Boira S. Anxiety, depression, quality of life and patient satisfaction in acne patients treated with oral isotretinoin. *Acta Derm Venereol*. 2013;93(6):701–706.
66. Kaymak Y, Taner E, Taner Y. Comparison of depression, anxiety and life quality in acne vulgaris patients who were treated with either isotretinoin or topical agents. *Int J Dermatol*. 2009;48(1):41–46.
67. Ferahbas A, et al. A pilot study evaluating anxiety and depressive scores in acne patients treated with isotretinoin. *J Dermatolog Treat*. 2004;15(3):153–157.
68. Rubinow DR, Peck GL, Squillace KM, Gnatt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. *J Am Acad Dermatol*. 1987;17(1):25–32.
69. Suarez B, et al. Isotretinoin was not associated with depression or anxiety: A twelve-week study. *World J Psychiatry*. 2016;6(1):136–142.
70. Cohen J, Adams S, Patten S. No association found between patients receiving isotretinoin for acne and the development of depression in a Canadian prospective cohort. *Can J Clin Pharmacol*. 2007;14(2):e227–e233.
71. Hanna KJ, et al. Affective disorders as potential complication of anti-acne treatment with isotretinoin: a case series. *J Affect Disord*. 2016;204:154–158.
72. Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol*. 2000;136(10):1231–1236.
73. McGrath EJ, et al. A prospective trial of the effects of isotretinoin on quality of life and depressive symptoms. *Br J Dermatol*. 2010;163(6):1323–1329.
74. Hahm BJ, et al. Changes of psychiatric parameters and their relationships by oral isotretinoin in acne patients. *J Dermatol*. 2009;36(5):255–261.
75. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg*. 2007;26(4):210–220.
76. Chia CY, et al. Isotretinoin therapy and mood changes in adolescents with moderate to severe acne: a cohort study. *Arch Dermatol*. 2005;141(5):557–560.
77. Kepska A, et al. Dermatitis artefacta as a symptom of schizophrenia? *Postepy Dermatol Alergol*. 2014;31(4):277–279.
78. Lucca JM, et al. A case report of isotretinoin-induced manic psychosis. *Indian J Dermatol*. 2016;61(1):120.
79. Rajagopal S. Acute psychosis induced by isotretinoin. *Indian J Psychiatry*. 2014;56(3):295–297.
80. Valderrama F, Gomez A, Restrepo D. Isotretinoin therapy for acne vulgaris and first episode psychosis in an adolescent patient. *Rev Colomb Psiquiat*. 2017;46(1):50–54.
81. Segmiller FM, et al. Psychosis during treatment with isotretinoin. *Ther Adv Psychopharmacol*. 2013;3(4):244–245.
82. Schaffer LC, Schaffer CB, Hunter S, Miller A. Psychiatric reactions to isotretinoin in patients with bipolar disorder. *J Affect Disord*. 2010;122(3):306–308.
83. Ludot M, Mouchbac S, Ferreri F. Inter-relationships between isotretinoin treatment and psychiatric disorders: depression, bipolar disorder, anxiety, psychosis and suicide risks. *World J Psychiatry*. 2015;5(2):222–227.
84. Von Broekhoven F, Verkes RJ, Janzing JG. Psychiatric symptoms during isotretinoin therapy. *Ned Tijdschr Geneesk*. 2003;147(47):2341–2343.
85. Fornaro M. Obsessive-compulsive disorder with bipolar diathesis following isotretinoin therapy remitting upon treatment with olanzapine and fluvoxamine. *Neuropsychiatr Dis Treat*. 2010;6:719–722.
86. Poblete A, Herskovic MV, Eva CP. Panic attacks in a patient treated with isotretinoin for acne. Report of one case. *Rev Med Chil*. 2006;134(12):1565–1567.
87. Alcalá Partera JA. Depression and panic attack in acne treated with isotretinoin. *Semergen*. 2012;38(3):188–191.
88. Tirado Sanchez A, Leon Dorantes G. Erectile dysfunction during isotretinoin therapy. *Actas Urol Esp*. 2005;29(10):974–976.
89. Rouve N, et al. Prescribed drugs and violence: a case/noncase study in the French Pharmacovigilance Database. *Eur J Clin Pharmacol*. 2011;67(11):1189–1198.
90. Wu, H., et al. 2016. Developmental neurotoxic effects of percutaneous drug delivery: behavior and neurochemical studies in C57BL/6 mice. 11(9): e0162570.
91. Ormerod AD, et al. Influence of isotretinoin on hippocampal-based learning in human subjects. *Psychopharmacology (Berlin)*. 2012;221(4):667–674.
92. Crandall J, et al. 13-Cis-retinoic acid suppresses hippocampal cell division and hippocampal-dependent learning in mice. *Proc Natl Acad Sci*. 2004;101(14):5111–5116.
93. Ferguson SA, Berry KJ. Oral Accutane (13-cis-retinoic acid) has no effects on spatial learning and memory in male and female Sprague-Dawley rats. *Neurotoxicol Teratol*. 2007;29(2):219–227.
94. Goodman A. Congenital anomalies in relatives of schizophrenic probands may indicate a retinoid pathology. *Schizophr Res*. 1996;19(2-3):163–170.
95. Strahan JE, Raimor S. Isotretinoin and the controversy of psychiatric adverse effects. *Int J Dermatol*. 2006;45(7):789–799.
96. Ghanizadeh A, Namazi MR. A novel explanation for isotretinoin-induced psychiatric problems and its practical implication. *Clin Exp Dermatol*. 2011;36(2):205–206.
97. Adams J. Similarities in genetic mental retardation and neuroteratogenic syndromes. *Pharmacol Biochem Behav*. 1996;55(4):683–690.
98. Smedje H, et al. Onset of Kleine-Levin Syndrome in association with isotretinoin treatment. *Acta Paediatr*. 2010;99(6):946–948.
99. Ismailogullari S, et al. Effects of isotretinoin treatment on sleep in patients with severe acne: a pilot study. *J Eur Acad Dermatol Venereol*. 2012;26(6):778–781.
100. Kontaxakis VP, et al. Genetic vulnerability and isotretinoin-induced psychiatric adverse events. *World J Biol Psychiatry*. 2010;11(2):158–159.