A Review of Isotretinoin and Its Association in Affective Disorder

By

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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
BRAC University
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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at BRAC University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

The ethical principles of scientific research include honesty, integrity, transparency, and respect for human subjects. This review article adheres to these principles by thoroughly reviewing the available literature and presenting the findings in an objective and unbiased manner. The study has been conducted in accordance with relevant ethical guidelines, including obtaining informed consent from human subjects where applicable. The authors declare that there are no conflicts of interest in this study and all results reported are accurate and reliable. The study upholds the principle of confidentiality by ensuring that personal information of subjects and sources of funding are not disclosed. The authors acknowledge the contributions of all relevant sources of information, and any discrepancies or limitations in the data are reported in a transparent and honest manner. We are committed to promoting scientific progress and contributing to the development of new and innovative therapeutic strategies for human health.

Abstract

Isotretinoin is a medication used in the treatment of severe to moderate acne. However, several studies have reported a potential association between Isotretinoin use and affective disorders (depression, anxiety, suicidal ideation). In the review, an attempt is made to understand how the use of Isotretinoin is associated with affective disorder. Several published materials reporting psychiatric side effects following Isotretinoin treatment including case reports were being studied for this review. Some studies have proposed a possible connection between Isotretinoin usage and affective disorders where retinoic acid plays a crucial role. Retinoic acid may cross the blood-brain barrier so it can have an effect on CNS which may lead to affective disorder. However, no causal relationship has not been established and the link between Isotretinoin use and psychiatric events remains controversial. Because of the lack of evidence, broad research is needed to understand the relationship between Isotretinoin and mental health outcomes.

Keywords: Isotretinoin, vitamin A, retinoic acid, depression and suicide

Dedication

To my friends and family.

Acknowledgement

I extend my heartfelt appreciation to all those who have contributed to the completion of this research. I am deeply grateful to God for providing me the opportunity to work with such wonderful people from the School of Pharmacy, BRAC University. I am honored to have been guided by my esteemed supervisor, Farzana Islam, Lecturer at the School of Pharmacy, whose support, guidance, dedication, and expertise have driven me to excel in this field. I would like to extend my gratitude to Professor Dr. Hasina Yasmin, Program Director and Assistant Dean at the School of Pharmacy, for imparting valuable knowledge, and to Professor Dr. Eva Rahman Kabir, Dean at the School of Pharmacy, for her unwavering support and motivation. I also want to acknowledge the efforts of all the faculty members at the School of Pharmacy, BRAC University, and express my gratitude to my friends and seniors for their guidance and my family members for their unwavering support.

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List of Acronyms

Retinoic Acid	RA
Retinoic Acid Receptors	RARs
Retinoid X Receptors	RXRs
Food and Drug Administration	FDA
Canadian Saskatchewan Health Database	CSHD
United Kingdom General Practice Research Database	UKGPRD
Hypothalamic-pituitary-adrenal	HPA

Chapter 1

Introduction

1.1 Acne formation

Acne is an inflammatory condition of the pilosebaceous units of the skin that usually affects adolescents and manifests clinically as comedones (the pathognomonic lesion), papules, pustules, nodules, cysts, and sometimes scarring on the face, upper arms, neck, trunk and buttocks, either attenuated (icepick, boxcar, or rolling) or exaggerated (hypertrophic papular, or bridging (Zaenglein, 2018). Generally, inflammation (swelling and redness) in the pores is what causes acne, which is produced by overactive oil glands in the skin as well as by an accumulation of oil, dead skin cells, and bacteria, which leads to clogged pores (Dawson & Dellavalle, 2013). To be more specific, inflammation of the pilosebaceous duct leads to acne, which is caused by four different pathophysiological mechanisms:

• Abnormal growth and shedding of keratinocytes, which leads to ductal blockage (Dawson & Dellavalle, 2013).

• Increased sebum production because of androgens (Dawson & Dellavalle, 2013).

• Propionibacterium acnes grew in number (Dawson & Dellavalle, 2013).

• Inflammation (Dawson & Dellavalle, 2013).

Micro-comedones are the most common early sign of acne. They are caused by an increase in androgen production, which leads to abnormal epithelial damage to the skin and follicular blockage. Sebum production also keeps increasing when the number of androgens in the bloodstream rises. This causes the follicles that are blocked to fill with lipid-rich material and produce noticeable comedones, both open and closed. The production of P. acnes is facilitated

by the fact that sebum acts as a substrate for the growth of bacteria. Lastly, P. acnes puts out chemicals that make inflammation worse, which spreads when comedones break open and let bacteria into the skin (Dawson & Dellavalle, 2013). This inflammation shows up as inflammation-causing papules, pustules, nodules, and cysts (Dawson & Dellavalle, 2013).

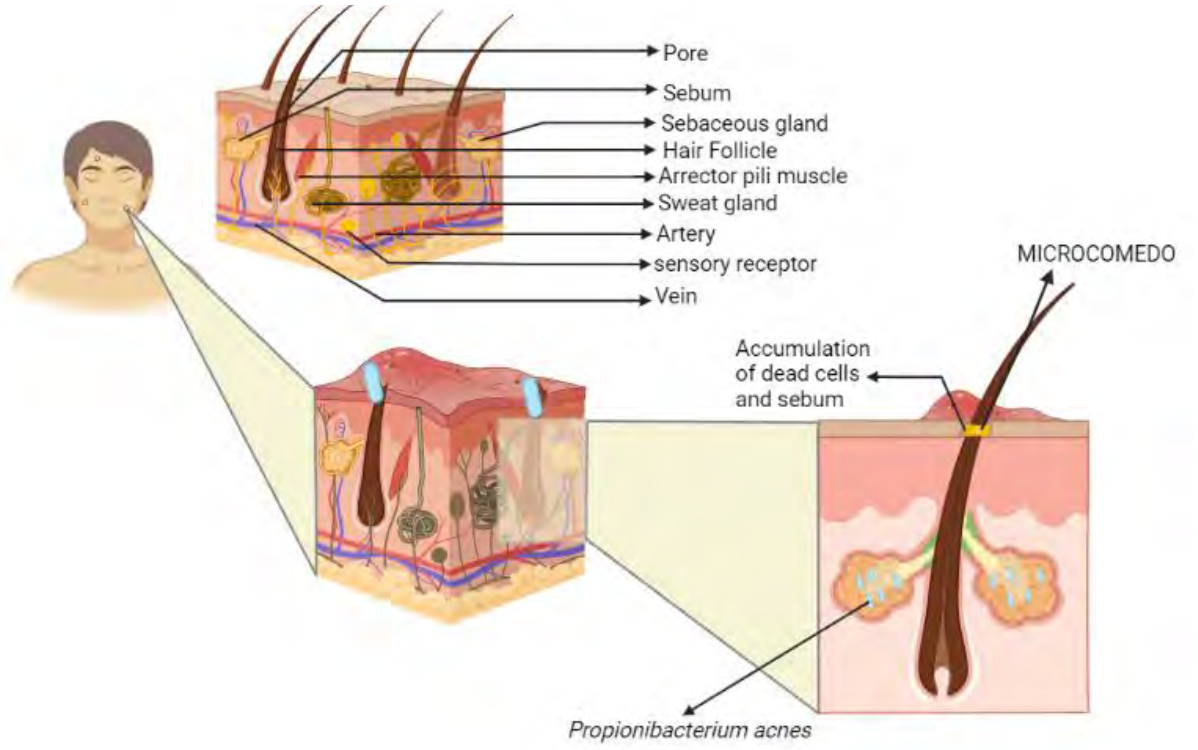


Figure 1: Healthy skin cell & formation of acne due to microcomedo accumulation by dead cells and sebum, and also for P. acnes

It should be noted that, teenagers (adolescence) are mostly susceptible to acne. According to The UN and WHO Adolescence are defined as to be between an age span of 10-19. During puberty, hormones become more active, which in turn stimulates the oil glands of the skin (Sizonenko, 1978). Because of this, acne is most common in people when they are in their teen years.

1.2 Common medications for acne

The key to curing a disease is receiving early, efficient, and safe treatment. In recent years, there has been a proliferation of therapy options for acne. Some of those are: topical agent

retinoids, topical antibiotics, benzoyl peroxide, combination products (antibiotic-benzoyl peroxide combinations and antibiotic-retinoid), other topical treatments (salicylic acid, azelaic acid), hormonal therapies, systemic agents, Isotretinoin and oral antibiotics (Dawson & Dellavalle, 2013).

1.3 Isotretinoin

One of the effective treatments for moderate to severe acne is oral Isotretinoin (Jick et al., 2000). Because of its potentially adverse consequences, Isotretinoin is regarded as a very controversial medication (Wolverton & Harper, 2013). According to chemical structure, oral Isotretinoin (13-cis retinoic acid) falls under retinoid family and can be divided into first, second, and third generations. The US Food and Drug Administration (FDA) permitted oral Isotretinoin (13-cis-retinoic acid) as a therapy for moderate to severe in 1982 (Layton, 2009). The effectiveness of Isotretinoin has not been surpassed by any other medicine to date and is still the most efficacious acne treatment available, and it has helped many patients achieve both long-term recovery and significant improvement (Layton, 2009). That is why Isotretinoin is considered as gold standard for acne treatment. The capsule form of Isotretinoin is mostly available in the market. Normally, an oral dosage of 0.5-1 mg/kg/day divided twice a day is prescribed to be taken for a period of 15-20 weeks in case of adults. The dosage can be increased up to 2 mg/kg/day (as tolerated) if the condition is quite severe and causes scarring, or if it is predominantly expressed on the trunk of the body (John P. Cunha, 2021). Physicians in Bangladesh also prescribes Isotretinoin to the patients, which increases the demand of this drug. That is why, a number of reputed companies in Bangladesh are manufacturing Isotretinoin in different brand names. A list of those companies is mentioned below in table 1.

Table 1: List of different Isotretinoin brands available in Bangladesh.

Isotretinoin Brand Name	Dosage form	Strength	Company
Rematip	Capsule	10 mg	Drug International Ltd
Reticap	Capsule	10 mg	UniMed UniHealth
Reticap	Capsule	20 mg	UniMed UniHealth
Roaccutane	Capsule	10 mg	Roche Bangladesh Ltd
Roaccutane	Capsule	20 mg	Roche Bangladesh Ltd

1.4 Retinoids

Isotretinoin is also known as 13-cis-retinoic acid. Retinoic acid is a biologically active form of vitamin A that plays a vital role in several physiological processes (Carazo et al., 2021). Retinol, retinal, and retinoic acid are all biologically active forms of vitamin A and provitamin A that are metabolized by the body and interact with many molecular targets, such as nuclear receptors (Carazo et al., 2021). Vitamin A is an important nutrient. The liver is the primary storage organ for vitamin A because of its fat-soluble nature (Albahrani & Greaves, 2016). Vitamin A-like activities may be found in a wide variety of retinoids, in both naturally occurring and manufactured variations of retinol. There are two primary forms of vitamin A found in the food of humans: active form of vitamin A (retinol, retinoic acid, retinal) and provitamin A carotenoids such as beta-carotene (Rafeeq et al., 2020). Both of these forms are referred to as preformed vitamin A. Retinol, tretinoin (also known as all-trans-retinoic acid), alitretinoin and Isotretinoin (13-cis-retinoic acid) are all examples of first-generation retinoids (9-cisretinoic acid) (Goodman & Gilman, 2006). Acitretin is an example of a member of the second generation of retinoids, which are sometimes referred to as aromatic retinoids and these retinoids were produced by shifting the cyclic end group. Arotinoids is the name given to the third generation of retinoids, which contain additional changes (Goodman & Gilman, 2006).

Tazarotene and bexarotene are also examples of compounds that belong to this generation. Adapalene, a retinoid-like compound that is derived from naphthoic acid and has characteristics similar to those of retinoids, does not precisely fall into any of the three generations (Goodman & Gilman, 2006). Retinoic Acid (RA) is a substance that can affect how genes are expressed in the body. It exerts this function by the activation of two groups of receptors called Retinoic Acid Receptors (RARs) and Retinoid X Receptors (RXRs). These receptors are part of the superfamily of thyroid/steroid hormone receptors (Winterfield et al., 2003). Retinoids are molecules that can bind to nuclear receptors, which are proteins involved in regulating gene expression. When a retinoid molecule binds to a nuclear receptor, the resulting complex can then bind to specific regions on DNA called promoters, which are responsible for turning genes on or off. This binding of the retinoid-nuclear receptor complex to the promoter regions can ultimately regulate the expression of target genes (Saurat, 1999). The proteins produced by genes play a role in both the beneficial effects and the adverse effects of these drugs (Shroot, 1998). The different types of receptors, namely α, β, and γ, have the ability to combine in both homo and heterodimers. These receptors respond to retinoids and are present in various tissues, which express different combinations of RAR and RXR subtypes. The activity of these receptors is determined locally based on the specific combination of subtypes expressed in the tissue (Petkovich, 2001). Most of what is present in human skin is RAR and RAR. The alternating single and double bonds in first and second-generation retinoids allow them to have flexibility in binding, which enables them to bind with multiple retinoid receptors. This relatively low level of receptor selectivity may result in increased adverse consequences. Third-generation retinoids have a more inflexible structure than earlier-generation retinoids, resulting in their ability to interact with a smaller number of retinoid receptors (Chandraratna, 1998). Retinoids are involved in a various range of biological events. Acne, photoaging, and hyperpigmentation are just some of the skin issues that can be improved by their application.

That is why, they are so popular in the field of dermatology. The formation and behavior of skin cells can be changed by retinoids, which is how they act. They stimulate the turnover of cells and decrease the production of comedones (tiny, flesh-colored, white, or dark lumps, roughen skin), which are the clogged hair follicles that lead to acne. In addition to this, they aid in the formation of collagen, a protein that is responsible for the mobility of skin, and in the prevention of the breakdown of elastin, another protein that is responsible for the flexibility of skin. It has been discovered that retinoids have a substantial influence on the development and function of the brain (Lippmann et al., 2014). Research has shown that retinoids are involved in regulating several aspects of brain development, including the generation of neurons, the formation of synapses, and the myelination of nerve fibers (O'Reilly et al., 2008). Retinoids are important for the establishment of the neural crest and the differentiation of neural stem cells into the many types of neurons and glia that occur during embryonic development. Retinoids play an essential role in both of these processes. The fact that retinoids are lipid-soluble and can easily cross the blood-brain barrier has led to the accumulation of evidence in recent years, indicating that they may impact the functioning of the adult brain, particularly in areas such as learning and memory, locomotor activity, and depression (O'Reilly et al., 2008). The development of the brain, spinal cord, and retina in the eye is extremely important, and it is crucially relevant. Synaptic formation, which is the process by which neurons communicate with one another, is another area in which retinoids are involved and play a function. The creation of synapses and the growth of dendrites, which are the branches of neurons that receive messages from other neurons, are regulated by retinoids in the developing brain. Furthermore, retinoids also have a function in the maturation of nerve cells. In addition, retinoids have a role in the production of myelin, a fatty material that insulates nerve fibers and makes the transmission of nerve impulses easier. Myelin is formed when retinoids are combined with vitamin A. Due to their ability to dissolve in fats, retinoids can penetrate the protective barrier

that separates the bloodstream from the brain, and they can impact different cellular functions, which may or may not involve the activation of genes through ATRA and RAR signaling pathways (O'Reilly et al., 2008). Retinoids applied topically can reduce inflammation and restore order to disorganized keratinization in sebaceous follicles. Additionally, they have the potential to improve the absorption of other topical drugs.

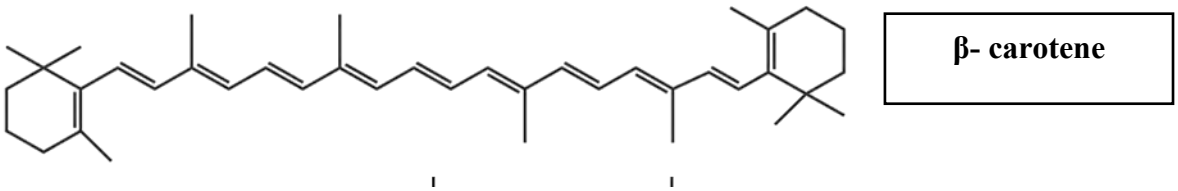


Figure 2: Structure of β- carotene

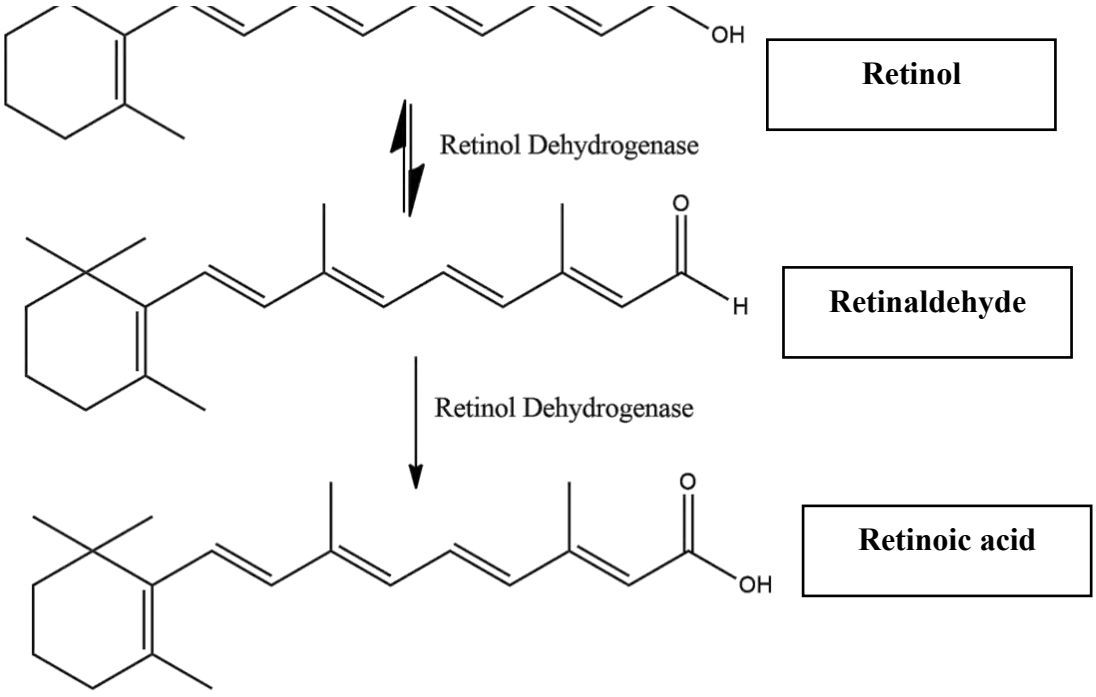


Figure 3: Differents forms of retinols

1.5 Oral Isotretinoin

Oral Isotretinoin has outstanding effectiveness in treating severe acne and has the potential to generate lasting remissions even after only one round of treatment (Bagatin & Costa, 2020;

Layton, 2009). Isotretinoin is available in oral capsule form. The typical dosage for Isotretinoin ranges from 0.5 mg to 2 mg per kilogram of body weight taken every day for a period of 16 to 20 weeks (del Rosso, 2012). The exact dose and duration of treatment will rely on the severity of acne and how the patient reacts to the medicine. Isotretinoin is one of the first-generation retinoids (13-cis-retinoic acid). Retinoids are a group of substances that come from vitamin A and have numerous roles in the body, some of which are carried out by retinoic acid, a derivative of vitamin A (Bremner & McCaffery, 2008).

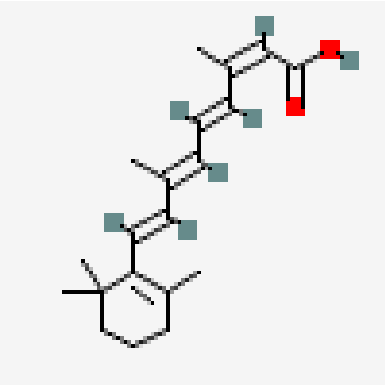


Figure 4: Structure of Isotretinoin

Table 2: Isotretinoin IUPAC name and Molecular formula

Name	Isotretinoin
IUPAC name	(2*Z*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)-nona-2,4,6,8-tetraenoic acid
Molecular Formula	C20H28O2

When Isotretinoin was first used to treat acne, it was noted for its ability to clean up nodules and cysts and bring about a sustained remission of those lesions. Isotretinoin works to treat acne by three main mechanisms: first, it helps the skin to shed its outer layer more naturally; second, it reduces the number of cells that produce oil in the skin and decreases the amount of

oil that is produced; and third, it reduces the amount of a type of bacteria that can cause inflammation in acne (Layton and Cunliffe, 1992; Harper and Thiboutot, 2003). Isotretinoin can act as a pro-drug that is converted inside cells into substances that stimulate retinoic acid nuclear receptors (RARs and RXRs), but it does not have significant binding capability with cellular retinol-binding proteins or retinoic acid nuclear receptors (RARs and RXRs) (Layton, 2009). The following five metabolites of Isotretinoin are considered to be of significant biological importance: 13-cis-4-oxo-retinoic acid (4-oxo-Isotretinoin), all-trans-4-oxo-retinoic acid (4-oxo-tretinoin), all-trans-RA (tretinoin), 9-cis-4-oxo-retinoic acid and 9-cisretinoic acid are the forms of retinoic acid that have been synthesized (Layton, 2009). Individuals with severe acne have high levels of sebum secretion. Administering 30-60 mg/day of 4-oxo-Isotretinoin orally for 4 weeks results in a mean reduction of 70% in sebum excretion levels, compared to the same dosage of oral Isotretinoin over the same period. This is in comparison to the reduction that can be achieved with oral Isotretinoin over the course of 4 weeks (Layton, 2009). In terms of its ability to decrease sebum production, Isotretinoin is superior to both all-trans-retinoic acid and 9-cis-retinoic acid. It is also superior to all-trans-retinoic acid. Only tretinoin and 4-oxo-tretinoin are capable of binding to RAR, the receptor that is believed to play an essential role in the retinoid therapy of acne. Isotretinoin causes much larger intracellular amounts of tretinoin than does the incubation of SZ 95 human sebocytes with isotretinoin (Layton, 2009). Due to the incubation with tretinoin, extremely high quantities of tretinoin were formed within the cells, meanwhile the concentration of Isotretinoin was almost nil. Changes in plasma concentration of these metabolites could potentially explain variations

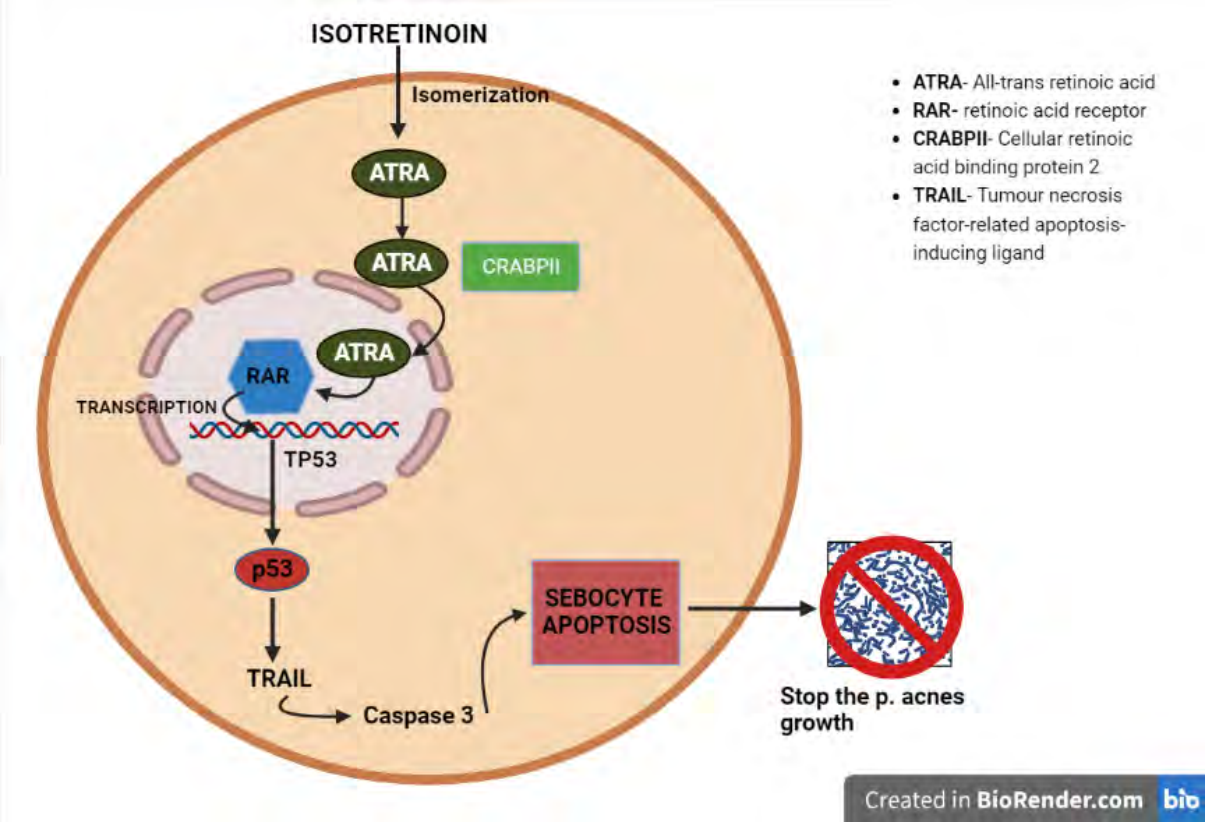


Figure 5: Possible mechanism of action of Isotretinoin ((John P. Cunha, 2021; Layton, 2009; Melnik, 2017)

in the degree of therapeutic response, as well as the severity of side effects and their incidence in particular individuals. New studies indicate that oral Isotretinoin induces the death of sebaceous gland cells, known as sebocytes, without requiring activation of the RAR receptors. This suggests that the reduction in sebum production is due to the shrinkage of the sebaceous glands (Layton, 2009). By limiting hyper-keratinization, Isotretinoin is responsible for the remarkable reduction in comedogenesis. Isotretinoin taken orally does not have an antibacterial effect on its own, but it does change the microenvironment of the pilosebaceous duct so that it is significantly less hospitable to the colonization of P. acnes. This is achieved by significantly reducing the size of the pilosebaceous duct as well as the SER. The end result is a suppression of P. acnes that is way higher than the suppression seen with a combination of oral and topical antibiotic treatment. It has also been proposed that, similar to all-trans-retinoic acid, Isotretinoin might boost host defensive systems and modify monocyte chemotaxis. This would help explain, at least in part, why the medicine has an anti-inflammatory impact (Layton, 2009).

Large decline in the population of P. acnes is another factor that contributes to the overall improvement in acne inflammation. A divisive medication, Isotretinoin has drawn a lot of attention lately. There may be an increased risk of pseudotumor cerebri when Isotretinoin is used with tetracycline antibiotics. Retinoids taken orally are powerful teratogens that can result in profound birth defects. This means that women of reproductive age should exercise extreme caution while using systemic retinoids.

1.6 Probable Affective Disorder of Isotretinoin

In the recent past, a number of cases has been reported relating affective disorder caused by Isotretinoin. Affective disorders are mental diseases that have an impact on the feelings and thoughts of a person. It is possible that the symptoms will be pretty severe. They will not leave entirely on their own in the vast majority of situations. Individuals who had an excess of vitamin A in their system, known as hypervitaminosis A, displayed symptoms such as depression, increased anxiety, and irritability (O'Reilly et al., 2008). Reports shows that, neuropsychiatric adverse effects such as depression, suicidal ideation, suicide, anxiety, mania, impulsivity, emotional lability, aggressiveness, aggression, and psychosis began to appear (Bremner, 2021). Depression and bipolar illness are by far the most prevalent types of affective disorders.

Substantial evidence, such as the fact that the Food and Drug Administration (FDA) in the United States received more than 400 case reports on Isotretinoin and depression between the years 1982 and 2000 alone, implies a connection between the two. During the same period of time, the FDA received another report of 37 people who had committed suicide (Suuberg, 2019). The safety of isotretinoin regarding psychiatric effects gained more attention in the US, when a 15-year-old male patient taking Isotretinoin crashed a stolen plane into a Florida office tower. The family member of the patient filed a lawsuit against the manufacturer of Isotretinoin

for wrongful death, claiming that the medication had caused the pilot's acute psychosis. Although, the lawsuit was settled out of court by the manufacturer of Isotretinoin but still its effect remains doubtful (Suuberg, 2019). The adult brain expresses the necessary molecular components for retinoic acid signaling, and research indicates that retinoids may be involved in affective disorders due to the overlap between brain regions involved in retinoic acid function, stress, and depression (Bremner & McCaffery, 2008). Recent research in mice showed that animals displayed depressive-like behaviors, such as decreased swimming in a forced swim test and lower performance in tail suspension tests, after being treated with 1 mg/kg/day with Isotretinoin for 6 weeks (O'Reilly et al., 2006). 1.65% of pediatric patients who took Isotretinoin reported having psychiatric symptoms, which was found to be consistent with the findings of large-scale reviews and surveys of the effects of Isotretinoin, which found that 25.16% of the adverse effects identified for Isotretinoin were psychiatric in nature (Suuberg, 2019). Retinoids, due to their affinity for fat, have the ability to penetrate the protective barrier of the brain that separates the bloodstream from the brain tissue. This enables them to impact a variety of cellular functions, both those that involve ATRA and RAR-mediated gene transcription and those that do not (Bremner & McCaffery, 2008; O'Reilly et al., 2008). As it can cross the blood brain barrier, it can cause effects on CNS. There has been a significant amount of research conducted on the role that RA plays in the regulation of CNS development. Yet until very recently, it was hardly ever recognized that RA has the potential to cause changes in the way neurons in the adult brain function. The adult brain, on the other hand, is where RA signaling has been found to take place, according to the growing body of research, indicating that the brain of an adult, just like the brain of an embryo, may be sensitive to an excessive amount of RA. This developing body of knowledge is pertinent to claims of depression and suicide in acne patients who were treated with 13-cis-RA (Isotretinoin) (Hull & D'arcy, 2003). When all the evidence is looked at together, it points to the possibility of an unrecognized

neural signaling pathway. This pathway could, among other things, help explain why serotonin, dopamine, and norepinephrine are not enough to explain mood disorders (O'Reilly et al., 2008). Moreover, this pathway may help explain about affective disorders. It is well established that that retinoid can attach to retinoid receptors in the brain and alter gene transcription in that way. There is a high concentration of retinoid receptors in the limbic regions that have been linked to depression. These limbic regions include the amygdala, the prefrontal cortex, and the hippocampus. Specially Dopamine, as well as serotonin and norepinephrine to a lesser extent, are among the neurochemicals that can be affected by retinoids, which are known to have a part in the formation of depressive symptoms and disorders (Bremner & McCaffery, 2008; O'Reilly et al., 2008). Retinoids, such as all-trans retinol A (the active form of vitamin A), which is an isomeric variation of 13-cis retinol A, have psychiatric consequences at high dosages and a lack of it can lead to impairment in learning and memory (Bremner & McCaffery, 2008). 13-cis-RA has been shown in research conducted on both humans and animals to be capable of inducing depressed tendencies. The principles presented in this study suggest that these effects can lead to changes in behavior, such as the signs of affective disorders.

1.7 Aim

The aim of this project is to conduct a review on the association between the treatment of Isotretinoin in acne patients and affective disorders.

1.8 Objective

i) Isotretinoin use: To understand the use of Isotretinoin in acne patients- dose, frequency and its effect or side effect on patients.

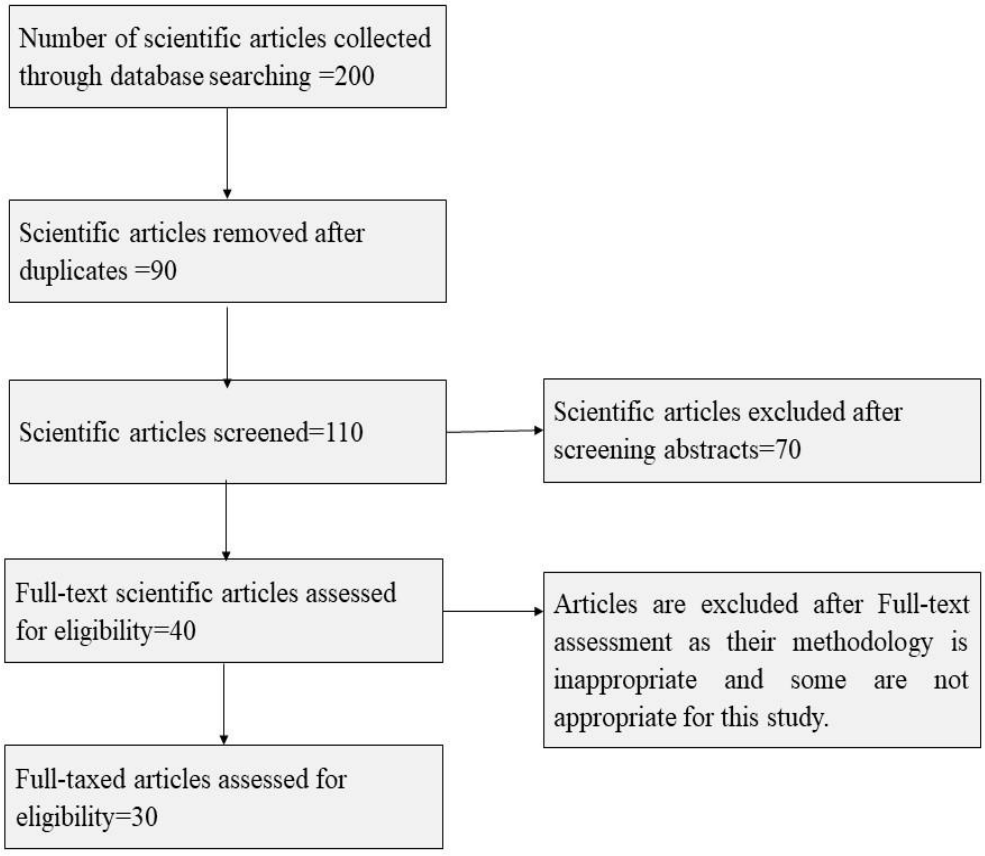
ii) Different forms of Isotretinoin: To evaluate weather use of Isotretinoin is related to affective disorders observed in the patients.

Chapter 2

Methodology

The review task included the selection of relevant literature, the analysis of scientific articles and summary of this paper. Facts and statistics of this review were gathered from many scientific articles. The information has been collected from the recently published articles of choice; a plan prepared to convey the assembled material in accordance with the requirements of the project objectives. The main objective of this review is to gather core information about the drug and also briefly understand its pharmacological activity. A comprehensive search of Pubmed, Google Scholar, Sciencedirect, Elsevier, Natures, Spriners for studies investigating the relationship between Isotretinoin and affective disorders has been conducted. The time frame for the search will be limited to the period from 1999 to 2022, and the language used in the articles will be restricted to English.

Table 3: Selection of scientific articles



Chapter 3

Result:

3.1 Studies not in support of Isotretinoin association with affective disorder

i. According to McGrath et al., 2010, a study has been conducted where the comparison group consisted of 94 individuals, 50 of whom were male (representing 53% of the total) (age range 13-32 years). There was not a clear shift in depression ratings over the course of time, nor was there a distinction between the genders in terms of shifts in depression.

ii. In addition, Ferahbas et al., 2004, report suggests that the final evaluation was finished by twenty-three different patients. There was a drop in anxiety levels that was significant according to the statistics. Moreover, depression scores dropped, but this decline was not statistically significant. There was not a single patient who committed suicide or attempted it (Ferahbas et al., 2004).

iii. According to the findings of the research presented in the scientific publication authored by Cohen et al., 2007, a total of 200 participants took part in this investigation. Patients who had given their informed consent and were starting Isotretinoin treatment for acne were included in the cohort that was exposed. In a Canadian prospective cohort study, researchers did not find any correlation between individuals taking Isotretinoin for acne and an increased risk of developing depression (Cohen et al., 2007).

iv. A study made by Metekoglu et al., 2019, suggest that 112 acne patients who went to the Dermatology Clinic of Beyazit Medico Social Center of Istanbul University were given tests to measure their anxiety and depression, as well as the severity and quality of their acne. In this study, 72 people with acne (61 women and 11 men) were looked

at. At the end of the therapy, the HAD-D, GAGS, and CADI scores all went down by a lot. There was no clear link between a patient having history of depression and their HAD-D scores at the end of the first month of therapy or at the end of treatment. Even though psychiatrists are worried about the possible mental side effects of Isotretinoin, there is no evidence that acne patients who take Isotretinoin are more likely to become depressed (Metekoglu et al., 2019).

v. According to Rehn et al., 2009, Isotretinoin does not appear to be generally related with treatment-emergent depression or suicidal ideation in young men. However, it is not possible to rule out the potential that certain individuals, on an individual basis, may be more susceptible to the mood effects of Isotretinoin as a result of a rare idiosyncratic reaction (Rehn et al., 2009).

vi. According to Nevoralová et al., 2013, one hundred different patients were a part of this single center study. The study was completed by each and every patient. Before they began receiving treatment, six percent of the patients had shown indications of depression. In none of these individuals did any increase of depressive problems occur while taking therapy with Isotretinoin, according to the findings of the study. On the other hand, the majority of patients did not exhibit any signs of depression after treatment. In the two individuals who exhibited depressive symptoms, it was determined that the cause was a combination of previous conditions and environmental circumstances. There was not a single instance of suicide thoughts discovered (Nevoralová et al., 2013).

vii. A study of Ng et al., 2002, stated that, there were 215 patients that participated in the trial, and their mean age was 20 years. From the beginning of the study, there has not been much of a shift in the proportion of Isotretinoin patients who report having moderate depressive symptoms. The differences in the scores of the quality-of-life

measures that were measured before and after therapy did not demonstrate any significant differences. There was found to be no connection between the amount of Isotretinoin taken and the depression score. Despite of the fact that, five Isotretinoin patients were taken out of the trial due to a worsening of mood during the course of the research, no conclusive link between the two was found. According to the results of this pilot investigation, there does not appear to be any kind of direct connection between Isotretinoin and depression (Ng et al., 2002).

viii. According to Jacobs et al., 2001, the reports of suicidal thoughts, clinical depression, or depressed symptoms that are said to be connected with Isotretinoin do not satisfy these criteria for causality. There is no evidence to support the hypothesis that, Isotretinoin is either a necessary or sufficient factor in the development of depression or suicide (Jacobs et al., 2001).

3.2 Studies with no conclusion for Isotretinoin association with affective disorder

i) The paper of Suuberg, 2019, suggests a review of drug-induced depression and suicidal behavior reported in the United Kingdom from 1998 to 2011 found that, Isotretinoin was one of the five drugs most commonly associated with such reports. The review covered the years 1998 through 2011. In the year 2015, 59 patients reported Isotretinoin and was rated among the top 10 medications in the database maintained by the FDA that were connected with reports of patients experiencing depression and attempting suicide in the United States. But the paper also said that there was either no link to depression or that treatment improved depressive or anxious symptoms. This led to the idea that there may be patients who are uniquely vulnerable or that individuals who

have a background of mental illness in their family or have experienced mental health issues themselves could be at risk (Suuberg, 2019). So, conclusion has not been found.

ii) According to Borovaya et al., 2013, the findings of clinical research fall throughout a rather large spectrum of possible outcomes. Isotretinoin, for example, was used to treat 700 individuals, and one percent of those patients experienced reversible depression as a side effect of the treatment. 45 Another clinical research involving 121 individuals treated with Isotretinoin found that 4% of them experienced depression. 29 Depression was identified in 10% of the total 94 individuals who participated in the third study. However, the research was unable to discover any connection between Isotretinoin and depression-related symptoms. Further studies with a high level of evidence are required to resolve situation (Borovaya et al., 2013).

iii) Another report of Wysowski et al., 2001, stat that, from the time that Isotretinoin was first marketed in 1982 until May of the year 2000, the FDA received reports of a total of 431 patients who had been treated with Isotretinoin. Of these patients, 37 had committed suicide, 110 had been admitted to hospital for suicidal ideation, depression or an attempt at suicide, and 284 suffered from depression but were not hospitalized. A correlation in time between the use of the medicine and the onset of depression is one of the indicators that point to the possibility of a connection between Isotretinoin and depression. The Food and Drug Administration has received reports of treated patients with Isotretinoin suffering from depression, suicidal ideation, attempted suicide, and completed suicide. But there is no concrete evidence to prove that Isotretinoin was responsible for this event. There is a need for additional research to discover whether or not Isotretinoin causes depression and to identify people who are susceptible to its effects (Wysowski et al., 2001).

iv) According to Singer et al., 2019, during 1997-2017, the FDA received 17,829 reports of psychiatric adverse events associated with the use of Isotretinoin. The most commonly reported side effects were changes in mood (depressive disorders), changes in personality (emotional lability), and changes in anxiety levels (anxiety disorders). Numerous psychiatric side events were recorded with Isotretinoin usage, including depression and suicidality, but it is unknown if these occurrences were caused by the drug. Although there has been no definitive research establishing a causal relationship between Isotretinoin and psychiatric risk, persons on the medication appear to be at a higher risk of developing psychiatric issues (Singer et al., 2019).

v) According to Marqueling & Zane, 2007, Isotretinoin users who had no prior history of depression were included in a study, which was a retrospective assessment of 877 patients. At the conclusion of treatment, the participants in the study had a reduced mean MADRS score, which indicates fewer depressed symptoms. These data give support to the hypothesis that treatment with Isotretinoin can alleviate depressive symptoms. A different research project utilized diagnostic codes to recognize instances of depression or psychosis among individuals with acne who were undergoing treatment with Isotretinoin or oral antibiotics. The databases employed for this study were the Canadian Saskatchewan Health Database (CSHD) and the United Kingdom General Practice Research Database (UKGPRD). The CSHD is a vast and thorough database due to the fact that it has been collecting data for more than 20 years, during which time it has accumulated patient information for all citizens of Saskatchewan. The CSHD determined that a total of 20,895 individuals were eligible to participate in this trial; of those patients, 7,195 were treated with isotretinoin (Marqueling & Zane, 2007). The UK General Practice Research Data Collection (UKGPRD) is a research database that currently has more than 4 million patients enrolled and only 1016 of these patients

fulfilled the requirements to take part in the trial and 340 of those patients were given Isotretinoin. In neither of the two databases, there was a statistically significant difference in the ARR of depression or psychosis when Isotretinoin was used to treat acne patients who were being treated with either Isotretinoin or who had been treated with it previously. For these findings to be verified, a more extensive study is required (Marqueling & Zane, 2007).

3.3 Studies in support for Isotretinoin association with affective disorder

Based on Bray et al., 2019, a study states that, there was a total of 56 patients that participated, with an average age of 21. At the beginning of the study, the scores on the questionnaire for all of the criteria that were measured indicated a lower mood than the norms that were published. Throughout therapy and afterward, data indicating that mood was either remaining the same or improving were displayed across all surveys. Three individuals reported a considerable deterioration in their emotions, and two of these patients also experienced serious ill consequences physically (Bray et al., 2019).

Chapter 4

Discussion

When the link between Isotretinoin and affective disorder is being studied, it is important to consider the impact of retinoids in the CNS. It is a significant factor that can affect the results. In this study on the affective disorder of Isotretinoin has been examined by evaluating the scientific articles which are based on group of individuals who also had significant acne and Isotretinoin was used to treat them. There was little noticeable variation in depressive symptoms among those who used Isotretinoin. Additionally, the study did not uncover any noticeable increase in the occurrence of depressive symptoms. The results of the study indicates that there is no proof to back up the idea that Isotretinoin use and depression are linked. For this study almost 30 articles have been analyzed where most of them have claimed that there may have been connection between Isotretinoin and affective disorder but there is not enough data to support this point.

In section 3.1, the evidence indicates that isotretinoin does not cause emotional disorder. More than 600 patients have been enrolled. The number of patients suffering from affective disorder in this study is relatively low, and the reason is also unknown.

Another observable part is acne is more vulnerable for teenage people. During poverty hormonal changes occurs. The adolescent years are defined by a great deal of change, both psychologically and physically. One example of such a transformation is the manner in which an individual reacts to various sources of stress. To be more specific, adolescence is characterized by major alterations in the reactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which results in increased stress-induced hormonal responses (Romeo, 2013). It was estimated that 8.8% of acne patients suffered from clinical depression, making the prevalence of depression among acne patients two to three times higher than it was in the

general population. The vast majority of depression cases and the use of antidepressant medication were seen in acne patients 18 and older, with the highest proportion being seen in patients in the age group of 36–64 (Ng et al., 2002). So, the depression can occur from this side also. The medication helped the majority of the patients. It is because the patients in this study did not provide enough statistics showing that Isotretinoin causes affective disorder.

On the other hand, in 3.2, there are not enough clinical data to prove the Isotretinoin has an effect on CNS. Symptomatically the patient should show neurological imbalance characteristics such as depression, bipolar disorder, anxiety, suicidal attempt etc. In section 4.1, it is discussed that the mental disorder can also be explained due to the effect of severe acne on the skin and the vulnerability of teenage people towards depression. The outlook change and severe skin damage can cause patient to have lowered mood and depression. Rising rates of depression, anxiety, aggression, and thoughts of suicide are some of the psychological impairments that are associated with acne. Patients who suffer from skin disorders and mental health disorders are frequent users of dietary supplements, despite the limited availability of clinical research in these areas (Rubin et al., 2008).

The effect of the Isotretinoin can cure acne and which may result in an elevated mood. But the Isotretinoin can cross the blood brain barrier to affect the CNS (Bray et al., 2019). Though very few patients have shown following symptoms, there is no clinical proof. A wide range of research is needed to established the relationship. Due to lack of significant number of patients being affected by depression, bipolar disorder, anxiety, suicidal attempt it cannot be concluded that Isotretinoin can cause affective disorder.

In 3.3 section, information was gathered on patients who were affected by disorder pertaining to Isotretinoin consumption. Though it is found patients suffering from mental disorders, few patients have shown significant improvement after therapy. Only 3 of the 56 patients had

deviated mood and required help. Which means 5.35% patients were seen to have affective disorder.

In section 1.6 the possible adverse effect mechanism is also been discussed. Many studies have shown that the adult brain has the molecular parts that are needed for retinoic acid signaling. The overlap of brain areas linked in retinoic acid function with stress and depression suggests that retinoids may have an impact in affective disorders (Bremner & McCaffery, 2008). Retinoids are able to pass through the blood–brain barrier and influence a variety of cellular processes, some of which include but are not limited to ATRA and RAR-mediated gene transcription. Yet, until very recently, it was almost never recognized that RA may potentially change neuronal function in the adult brain. This recognition only came about very lately. It has been discovered that RA signaling occurs, which suggests that the brain of an adult, similar to the brain of an embryo, may be sensitive to an excessive quantity of RA. This growing amount of evidence is relevant to assertions that acne sufferers who were treated with Isotretinoin. A neurological signaling pathway that could, among other things, offer insight on the insufficient explanation of mood problems utilizing the already accessible neurochemical systems of serotonin, dopamine, and norepinephrine. Moreover, at least in part, this pathway may help explain the signs and symptoms of affective disorders (Bremner & McCaffery, 2008; Hull & D'arcy, 2003; O'Reilly et al., 2008).

Chapter 5

Conclusion

Isotretinoin is used to treat acne that is very bad and has not gotten better with other treatments. Even though isotretinoin works well to treat acne, there has been a lot of talk about how safe it is, especially when it comes to its potential to cause psychiatric disorders like depression, anxiety, and suicidal thoughts. The goal of this review was to look at the research that has already been done on Isotretinoin and how it is linked to mood disorders like depression and suicide. The review found that there is evidence linking isotretinoin to an increased risk of depression and suicide attempts or completed suicides (Bremner & McCaffery, 2008).

The review looked at studies on depression, suicide, anxiety, bipolar disorder, psychosis, retinoic acid (RA), vitamin A, and Isotretinoin. Several studies have found that people who take Isotretinoin are more likely to feel depressed and think about killing themselves. Also, Isotretinoin therapy was linked to a higher risk of a clinical worsening of symptoms in people with bipolar disorder. These results show how important it is for doctors to keep an eye on their patients for signs of depression and thoughts of killing themselves during and after treatment with Isotretinoin (Damsky & King, 2017; Thürmann, 2001).

It is important to note that, the review found some problems with the research that has already been done on Isotretinoin and affective disorders. Many studies, for example, had small sample sizes or did not have enough control groups. Even though there were not much evidence, many study suggests that there is a link between Isotretinoin and affective disorders, especially depression and thoughts of suicide. Before giving Isotretinoin to a patient, doctors need to think carefully about the risks and benefits. They also need to keep a close eye on the patient for signs of depression and suicidal thoughts during and after treatment (Damsky & King, 2017; Shin et al., 2018; Thürmann, 2001).

In conclusion, Isotretinoin is a good way to treat severe acne, but both doctors and patients should be aware of the risks that come with the drug. There is evidence that Isotretinoin may increase the risk of depression and suicidal thoughts, especially in people who have had psychiatric problems in the past. So, it is important for doctors to carefully weigh the possible benefits and risks of Isotretinoin and keep a close eye on patients during and after treatment for signs of mood disorders. More research needs to be done to learn more about the link between Isotretinoin and affective disorders and to come up with effective ways to reduce the risks of this medication.

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