# Evaluation of the Safety and Efficacy of Oral Isotretinoin in the Treatment of Acne

By

Ankita Bose
19146010

A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy

BRAC University

October 2023

© 2023. BRAC University
All rights reserved.

## 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.

**Student's Full Name & Signature:**

**Ankita Bose**
**19146010**

# Approval

The project titled "Evaluation of the Safety and Efficacy of Oral Isotretinoin in the Treatment of Acne" submitted by Ankita Bose (19146010), of Spring 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

**Supervised By:** _____

Farzana Islam
Lecturer
School of Pharmacy
BRAC University

**Approved By:**

Program Director: _____

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean: _____

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

## Ethics Statement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

## Abstract

Acne is a prevalent skin disorder. Isotretinoin is an FDA-approved retinoic acid isomer frequently used to cure or remission this obstinate condition when other procurable approaches and antibiotics fail. However, the oral form is reportedly responsible for some unusual side effects in some patients. This systematic review is intended to summarize the findings regarding safety, efficacy and any observed side effects throughout the oral Isotretinoin treatment. Data about acne pathogenesis, epidemiology and mechanism of action of Isotretinoin was also synthesized. According to the tabular representation of information, it can be considered that incident of side effects and adverse drug reaction occurrence is typically dose-dependent and sometimes reversible with some specific precautions. Severe adverse incidents such as teratogenicity are quite uncommon and can be avoided by adhering to safety regulations or using contraception. However, considering the negligible occurrence of adverse events and adequate patient satisfaction, isotretinoin can be an economical and efficient choice for the First-line treatment for acne treatment and reduce the use of oral or topical antibiotics in this antibiotic resistance awareness era.

**Keywords:** Acne; Retinoid; Isotretinoin; Teratogenicity.

## Dedication

*Dedicated to my parents who instilled a love of learning in my mind and continuously have inspired me to reach the stars and chase my ambitions.*

## Acknowledgment

I am thankful to the Almighty Creator for granting me the wonderful opportunity to gain experience with such lovely, optimistic and supportive individuals from the School of Pharmacy throughout my entire journey.

First of all, I would like to extend my gratitude to my project supervisor, Farzana Islam (Lecturer, School of Pharmacy, BRAC University), for allowing me to work under her guidance. On top of that, her advice, instructions, enthusiasm and expertise in this field ignited my interest in the project work and encouraged me to do my research successfully.

Most importantly, I want to convey my profound thanks to Professor Dr. Eva Rahman Kabir (Dean, School of Pharmacy, BRAC University) and Professor Dr. Hasina Yasmin (Program Director and Assistant Dean, School of Pharmacy, BRAC University) for their encouragement, support and kind words. Additionally, I would like to express my gratitude to all the faculty members of School of Pharmacy, BRAC University for their tireless efforts to accomplish my graduation successfully. Last but not least, I would like to convey my sincere appreciation to my friends and seniors for their assistance and my family for their enormous support throughout the years.

.

# Table of Contents

## List of Tables

# List of Figures

## List of Acronyms

| | |
|---|---|
| FDA | Food and Drug Administration |
| GBD | Global Burden of Disease |
| AAAD | American Academy of Dermatology |
| RAR | Retinoic Acid Receptor |
| RXR | Retinoic X Receptor |
| FOXO1 | Forkhead Box Protein O1 |
| TLR | Toll-like receptor |
| Th cell | T helper cell |
| PPP | Pregnancy Prevention Program |
| GAGS | Global Acne Grading System |
| FAERS | FDA Adverse Event Reporting System |
| AQol | Assessment of Quality of Life |

# Chapter 1

# Introduction

Retinoids are vitamin A derivatives that can be organic or physiologically active or can be synthetic retinol analogues and they are FDA approved agents as topical treatments. (Zasada & Budzisz, 2019). Oral Isotretinoin, (2,6,6-trimethyl cyclohexen-1-yl) is a prescription-only authorized oral retinoid drug for the treatment of serious, resilient, nodular, recalcitrant to traditional therapy acne. It is also named as 13-cis retinoic acid (Kapała et al., 2022).

## 1.1 Acne

Acne is a multifactorial, chronic, persistent, inflammatory and immunological disease of the pilosebaceous unit that incudes hair shaft, hair follicle, erector pili muscle and sebaceous gland (Costa et al., 2018). Acne can progress to the formation of refractory cysts, nodules, and subcutaneous fistulas that are recalcitrant to treatment. Nodular acnes are tougher, solid-knot-like lumps that form beneath the skin (Kurokawa & Nakase, 2020).

It may cause scars and impose a detrimental effect on a person's quality of life affecting the face, trunk, and back. Early, efficient, and safe treatment is essential for disease resolution (Alyamani et al., 2022).

### 1.1.1 Etiology

A variety of factors as well as hormonal, microbiological and immune systems are considered to have a vital influence on the development of acne (Sadeghzadeh-Bazargan et al., 2021).

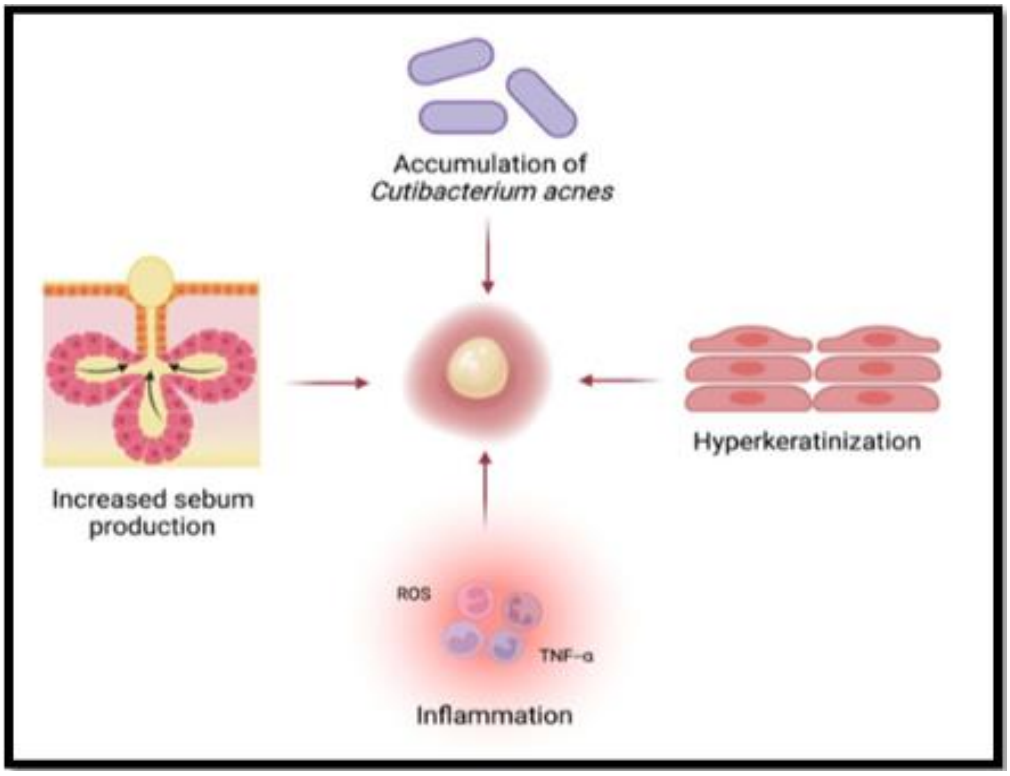


*Figure 1: Acne pathogenesis* (*Peyravian et al., 2022)*

Some significant factors for the etiology of acne are the following:

- Seborrhoea, increased sebum secretion by sebaceous glands within the hair follicle (Costa et al., 2018).
- Microcomedone, a plug of sebum and keratin formation due to follicular hyperkeratinisation and blockage of fat follicles(Costa et al., 2018).
- Proliferation and hypercolonisation by several micro-organisms, mostly by *Propionibacterium acnes* within the pilosebaceous unit (Costa et al., 2018).
- Inflammation caused by subsequent innate and acquired immune responses in affected follicles (Costa et al., 2018).
- Production of more viscous oil because of raised endocrinological factors like androgens (Kurokawa & Nakase, 2020).

However, it is found that cytokines can trigger the evolution of inflammatory acne as well as its persistence is believed to play a key role in the progression of chronic diseases from severe acne (Sadeghzadeh-Bazargan et al., 2021).

Even the role of hypercaloric food and dairy products has been documented as possible reason of acne pathogenesis without a clear result. Different external and internal parameters such as air pollution, proactive dermatological products, medicine, genetic factors and currently lifestyles and stress also have been postulated as having an impact on acne (Claudel et al., 2018).

### 1.1.2 Epidemiology

Acne is regarded as the 8th position among the most widespread diseases around the globe. It is also reported that about 9.4% population extensively suffers because of this (J. K. L. Tan & Bhate, 2015). As well as epidemiological studies throughout the globe, state acne as the most frequent cause for consulting a dermatologist (Stern, 2004). According to The Global Burden of Disease (GBD) Report 2013, acne was the second major cause of impairment among different skin illnesses (Karimkhani et al., 2017).

A rise in incidences of acne occurs within 16 and 20 years (Augustin et al., 2011; Shen et al., 2012). Population-based epidemiology studies focused on adolescents' state that acne affects 80% of teenagers (Amado et al., 2006; Ghodsi et al., 2009; H. H. Tan et al., 2007). Earlier investigations have found that females have a higher incidence of acne than males (Janani & Sureshkumar, 2019; Lynn et al., 2016).

Additionally, the Global Burden of Disease Study, 2010 projected that the prevalence of acne in men (8.96%) was lower than the anticipated prevalence in women (9.81%) (Lynn et al., 2016).

However, the earlier beginning of puberty of females compared to boys is also estimated as the cause of girls having greater acne prevalence at their younger age (Rombouts et al., 2007). Besides, 20 years or above-aged females are suffering more than males (Collier et al., 2008).

Acne should no longer be regarded as a teen condition, based upon the prevalence research over the previous 15 years (Goulden et al., 1999). At present, excellent evidence is also there that shows acne can persist beyond the adolescent years in up to 50% of people (Thiboutot et al., 2009). Consequently, acne continues throughout the 20s and the 30s in approximately 64 and 43% of people (Bhate & Williams, 2013).

Heredity not only has an impact on acne susceptibility, but it is also a predictor (Ghodsi et al., 2009). Infact, acne is over 80% heritable among first-degree relative (Bhate & Williams, 2013). An earlier onset of acne, increased number of comedones and treatment complications are believed to be associated with family history (Ballanger et al., 2006). Whether ethnicity affects acne is a matter of debate but from ethnic groups involved studies, ethnicity is found somehow to affect the degree and intensity of acne. Adolescent Caucasians have a greater incidence of acne than the African or Asian adolescents. Nevertheless, black persons tend to be more susceptible to post-inflammatory hyperpigmentation and particular subtypes like 'pomade acne'(Bhate & Williams, 2013).

Though acne causes substantial physical and psychological morbidity such as lasting scars, negative self-esteem and anxiety, it is not associated with mortality. It is estimated that the condition costs more than $3 billion in direct expenses per year (Zaenglein et al., 2016).

### 1.1.3 Oral Isotretinoin as treatment of choice

Depending on the severity of the lesions, there are various common treatments (Faghihi et al., 2017). Several topical acne treatments are available and three systemic treatments are also available: antibiotics, antiandrogens (combined oral contraceptives and spironolactone), and Isotretinoin (Bagatin & Costa, 2020). Studies have shown that the treatment with Isotretinoin results in significant improvement (Faghihi et al., 2017). Among all available numerous treatments, oral Isotretinoin is the most effective treatment that impacts all aspects involved in

the disease's etiology and development. It tends to produce the best results (Ghalamkarpour & Nasiri, 2006).

Moreover, Isotretinoin heals or enhances recovery of moderate and severe acne as well as lowers psychosocial consequences and visible scarring. The oral form of it is considered more significant for improved bioavailability (Bagatin & Costa, 2020).

Infact, according to the American Academy of Dermatology (AAD), Isotretinoin should be the initial treatment choice for mild to chronic inflammatory acne as it is considered as a 'Gold Standerd Drug' for acne treatment (Zaenglein et al., 2016).

## 1.2 Isotretinoin

Oral Isotretinoin is a member of the retinoid family. It was synthesized in 1955, while it was licensed for use in severe acne in 1982 by the Food and Drug Administration (FDA) in the United States, 1983 in Europe and 1990 in Brazil (Bagatin & Costa, 2020).

The drug is best taken with an entire glass of water along with a fatty meal because it is extremely lipophilic and has limited bioavailability. Based on the patient tolerance and body weight, the starting dose is recommended to be 0.5 mg/kg/day, then increasing gradually to 1.0 mg/kg/day for a 15- to 20-week course (Bagatin et al., 2020; Pile & Sadiq, 2023).

### 1.2.1 Mechanism of action

Isotretinoin's specific mechanism of action is still questionable. It is found that oral Isotretinoin does not directly affect microbial cells like antibiotics (Layton, 2009). Since, Isotretinoin has no or little capacity to bind with retinoic acid nuclear receptors (RARs and RXRs) like tretinoins, it functions as a prodrug and after metabolism, it is transformed intracellularly into RAR and RXR agonist metabolites. (Allenby et al., 1993; Fex et al., 1996; Fogh et al., 1993; Ott et al., 1996).

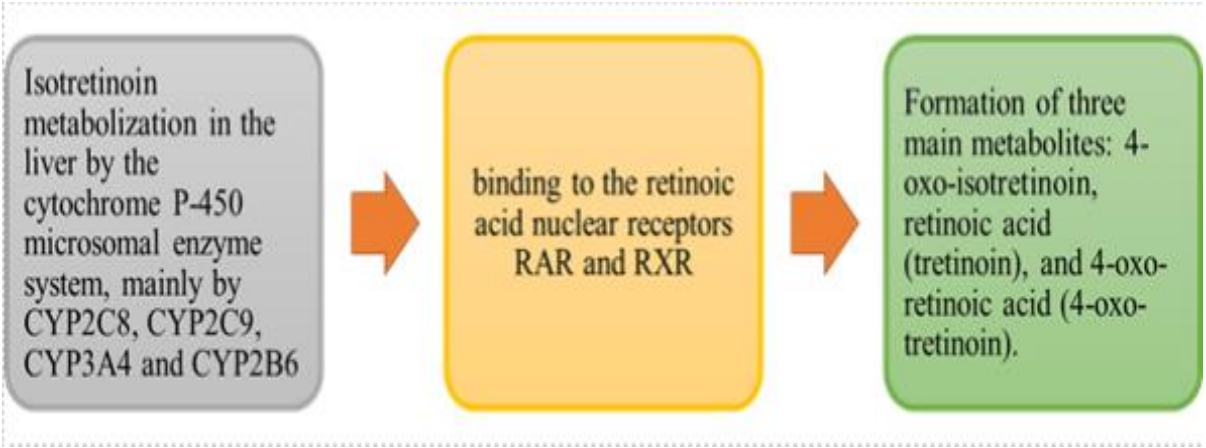


*Figure 2: Metabolism and active metabolite formation of Isotretinoin adapted from (Kapała et al., 2022)*

According to a recent investigation, oral Isotretinoin causes sebaceous gland contractions, which ends up resulting in decreased sebum production, via initiating sebocytes' apoptosis. These outcomes are not directly related with activation of RAR receptor rather considered to relate to the produced metabolites (Nelson et al., 2006). Only 4-oxo-isotretinoin, an active metabolite of Isotretinoin is found to reduce sebum excretion at 70% average rate. Then, tretinoin and 4-oxo-tretinoin attach to a significant receptor, RAR-γ, which is crucial for retinoid therapy of acne (A. Layton, 2009).

Besides, Isotretinoin brings about a significant reduction in comedogenesis by lowering hyperkeratinisation (DALZIEL et al., 1987; Knutson, 1974; Plewig et al., 2004). As there is no proof that indicates the Isotretinoin alters the metabolic processes of the keratinocytes, the specific mechanism is quite unclear through which this is accomplished (DALZIEL et al., 1987).

In addition, greater suppression *Propionibacterium acnes* (P. acnes) and consequent decrease in the follicular hyperkeratinisation can be seen due to duct microenvironment alteration by Isotretinoin and this effect is much more than that can be observed by topical or antibiotics ( King et al., 1982). Then, the reduced P. acnes population results in reduction in acne inflammation (Coates et al., 1997).

Meanwhile, it is claimed that Isotretinoin, similarly all-trans retinoic acid, may boost host defence systems and alter monocyte chemotaxis (Seguin-Devaux et al., 2005).

By down-regulation of TLR 2 and 4 and Th cells, Isotretinoin can exert both the anti-inflammatory and immunoregulatory properties ( Chen et al., 2019; Dispenza et al., 2012). Cellular inflammatory activity is also modified by oral Isotretinoin (Falcon et al., 1986).

However, off-label use of the drug is found to influence nuclear transcription factors reducing proliferation and inducing differentiation, apoptosis and cell renewal and regulates gene expression also. A variety of undiscovered functions of the drug can be clarified by its interaction with Forkhead Box Protein O1 (FOXO1) (Bagatin et al., 2020; Kochhar & Penner, 1987; Nau, 2001).

### 1.2.2 Safety

Isotretinoin can be the only solution whenever other available acne treatments fail. Even oral Isotretinoin can be used for the successful treatment of patients with major systemic disorders (A. Layton, 2009).

Though it requires a longer time for acne clearance, the result seems permanent in most cases. However, the drug is so potent that there could be some severe adverse effects as a result. Therefore, a thorough assessment of each case by dermatologists is a must to ensure patient safety before Isotretinoin prescribing. Besides, close monitoring is needed to assess the pros and cons of the drug (Goldsmith et al., 2004).

Dryness of the skin, eye irritation, painful joints and cracked lips are typical Isotretinoin side effects and mostly they are reversible when the medication is stopped. Issues related to Muscle, blood, and immune system are among the serious adverse effects of Isotretinoin, however, these are quite uncommon. Moreover, if administered during pregnancy, Isotretinoin can cause substantial harm to developing fetuses but not every time. Additionally, Isotretinoin has been linked to mental health issues like anxiety and depression. These reported issues are referred

to as psychological side effects. Some sexual difficulties such as trouble achieving and keeping an erection, dryness of vagina, and decreased libido. Isotretinoin rarely has serious adverse effects, and not all patients experience them.

According to the 'Report of the Commission on Human Medicines' Isotretinoin Expert Working Group' the following is a summary of the key suggestions:

- Stricter regulations are needed while prescribing the drug to young patients aged 12-18 to make sure that it is only initiated when other conventional treatments have been unsuccessfully attempted adequately.
- Detailed knowledge regarding the potential risks of Isotretinoin should be provided to patients as well as their families before starting the dose. Then after beginning routine monitoring of the patient's mental and sexual functioning is required to identify any unwanted issues earlier (Strauss et al., 2007)

One of the most severe, concerning and dose-dependent risks of prescribing the drug to women of reproductive age is teratogenicity. The usage of two secure contraceptives including an average monthly beta-HCG prescription must be imposed (Brzezinski et al., 2017; Tkachenko et al., 2019).

In this respect, a significant term should be mentioned that is iPLEDGE. The iPLEDGE is a complete teratogenic drug distribution system that involves not only the registration of patients, but also the registration of medical professionals, pharmacy chains as well as wholesalers (Honein et al., 2007).In addition, it is a compulsory safety policy needed by the U.S. Food and Drug Administration (FDA) to address the risk of Isotretinoin-associated teratogenicity and to decrease fetal exposures. Actually, it is a process to guarantee that the advantages of Isotretinoin outnumber its hazards (Lowery et al., 2020). This initiative gathers all the vulnerable medical data of patients with reproductive potential and maintains its confidentiality (Cockerell & Thiboutot, 2006).

To finish the entire process, patients will be requested to sign a variety of paperwork. It requires the registered patients to utilize two contraceptive methods concurrently. Each time prior to the prescription renewal, they have to respond to a few questions and reapply the pledge. Also, over the period of treatment, they must remain dedicated to the continued prohibition (Barbieri et al., 2020; Lowery et al., 2020).

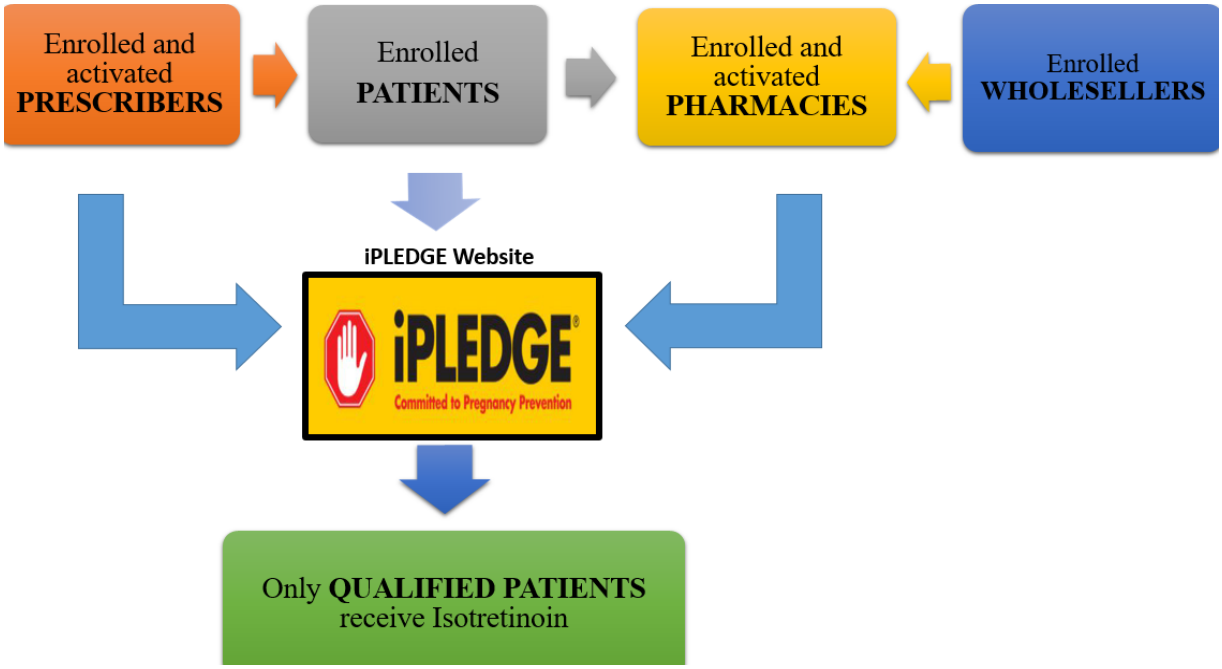


*Figure 3: iPLEDGE REMS process flowchart adapted from 'iPLEDGE REMS Prescriber Guide', October, 2021*

Besides, an initiative named the Pregnancy Prevention Program (PPP) has been endorsed by the regulatory body in each nation that offers guidance on-

- Drug supply control: A female patient can only be provided 30 days of oral Isotretinoin at a time with a prescription of one week validity.
- Therapeutic management: Contraception recommendations and Pregnancy testing under physician supervision prior to, during, and after 5 weeks of adhering to a course of medication.

- Educational initiatives: Teratogenicity must be properly acknowledged by patients as well as prescribing physicians and accept detailed guidance from the physician before and throughout therapy (A. Layton, 2009).

Though the ratio between the advantages and drawbacks of Isotretinoin for serious acne treatment always remained pleasing, it is believed that providing more knowledge, greater tracking, and further supervision may reduce the risk to a higher extent.

To summarize, Isotretinoin rarely has serious adverse effects, and not all patients experience them. Even its frequently not clear if Isotretinoin is to blame for alleged side effects. (Strauss et al., 2007)

### 1.2.3 Efficacy

While treating acne regardless of severity level, oral Isotretinoin is unquestionably more effective than prescription antibiotics. In fact, after 3-5 years of treatment, Isotretinoin-treated patients were determined to be totally cured of their acne (A. Layton, 2009).

Approximately 85% of patients getting this dose notice acne clearance within 16 weeks of treatment (Nast et al., 2010). Majority of the rest of people require about 5-6 months to experience a complete response at that specific dose (Lehucher-Ceyrac et al., 1999) whereas less than 1% may need up to 12 months of regular therapy to be acne-free (Zouboulis & Piquero-Martin, 2003).

To yield 90% removal of acne lesions, the duration of treatment is modified up to four weeks of maintenance and the treatment requires consolidation before withdrawal of the drug (Harms et al., 1986). Within two weeks of discontinuing treatment, Isotretinoin and its metabolites recover to endogenous levels (Wiegand & Chou, 1998).

Though Isotretinoin was approved in 1982 by FDA for the first time, initial guidelines for the optimum dosage of isotretinoin for acne-related treatments were released in 1992 (A. M. Layton & Cunliffe, 1992). The clinical trials, consensus and dermatological practice all follow

the label-recommended maximum dose, which lies between 120 and 150 mg/kg (Bagatin et al., 2020; Pile & Sadiq, 2023). It is found that exceeding 150mg/kg gives no extra benefit. Strong alcohol consumption is found to be related to decreased efficacy of Isotretinoin (A. Layton, 2009).

It was revealed into a study performed in India in 2014 that for moderate to severe acne patients, low-dose Isotretinoin was beneficial with fewer problems and a higher cost-effectiveness. Patients in this research were given 0.3-0.4 mg/kg/day Isotretinoin (Rao et al., 2014).

Furthermore, a study (2012) found that low-dose Isotretinoin (0.1-0.3 mg/kg/day) was successful in treating severe acne (Mehra et al., 2012). Since, the adverse effects of this medicine are dose dependent, administering 0.25 mg/kg/day Isotretinoin for 6 months appears more logical (Faghihi et al., 2017). Hence, low-dose treatment is just as effective as normal therapy in terms of efficacy (Sardana & Garg, 2010).

## 1.3 Aim and Objectives

The purpose of this review is to highlight the safety and efficacy of oral Isotretinoin in the treatment of nodular acne by assessing-

- Whether the occurrence of adverse events can outweigh the benefit of the drug
- Whether satisfactory result can be obtained while assuring safe use of the drug
- Whether the drug is highly efficient for the intended treatment

# Chapter 2

# Methodology

This literature review study and assessment is mainly focused on the safety and efficacy of oral Isotretinoin for the recalcitrant nodular acne treatment. It is the most approved therapy of most prevalent condition (acne) but had been reported to be associated with some side-effects and undesirable consequences. As a result, this topic has become highly pertinent to analyze the safety and efficacy of the drug in comparison with its negative impacts. That's why, this topic was chosen for this thesis. After choosing the topic, it was decided to do a review. Therefore, this review was performed systemically using the most recent and relevant studies. English language literatures were searched regarding my topic using following keywords: "acne", "acne epidemiology", "pathogenesis of acne", "isotretinoin", "Oral isotretinoin", "nodular acne", "safety of isotretinoin", "isotretinoin efficacy", "acne treatment", "treatment with isotretinoin." till 2022 without any limitations about demography, sex, age or origin of patients. Numerous sorts of published articles including reviews, guidelines, case reports, peer reviewed journals, expert reviews, clinical trials, consensus were considered during information evaluation about the chosen issue and for generating a good, quality review about oral isotretinoin's safety and efficacy. High impact databases like PubMed, The Cochrane Library, ResearchGate, ScienceDirect, Google Scholar, Willey-online library, Journal of American Academy and Dermatology (JAAD), Taylor and Francis Online, International Journal of Pharmaceutical Sciences and Research (IJPSR), British Journal of Dermatology (BJD), National Institutes of Health (NIH) were thoroughly searched to enrich this review paper with fundamental and supplemental information.

## 2.1 Study flow diagram

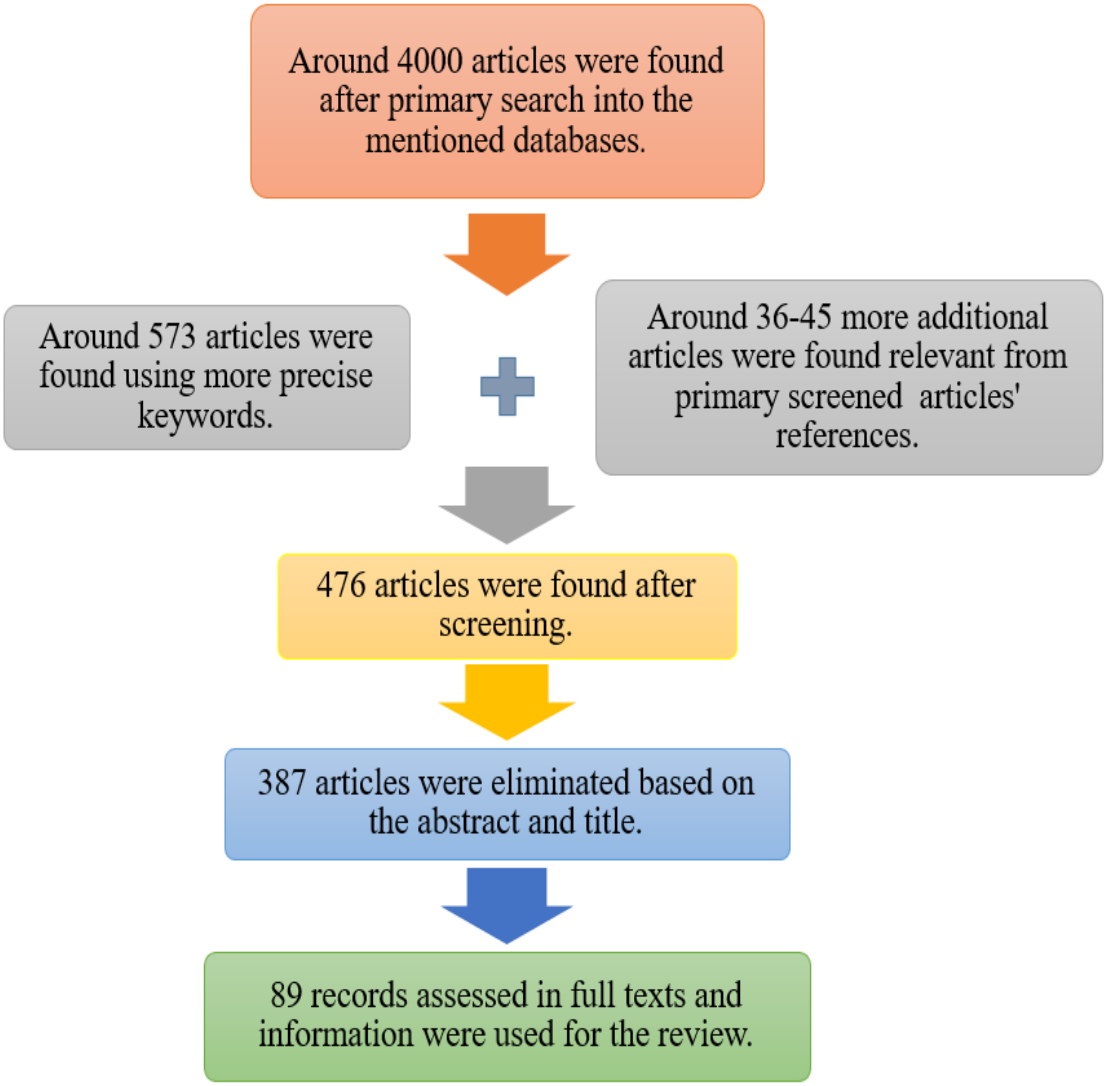


*Figure 4: Flow diagram of studies selection*

# Chapter 3

# Result

## 3.1 Tabular representation of the outcomes and adverse effects of several studies

From all the found papers the information has been organized into a table considering study methods, sample size, results after using Isotretinoin and observed adverse effects.

| No. of entity | Title, authors and year | Sample size and description | Method | Result | Adverse effect |
|---|---|---|---|---|---|
| 1 | **Efficacy and safety of systemic isotretinoin treatment for moderate to severe acne (insights from the real-life clinical setting)** (Tolino et al., 2020). | Total patients: 100<br>Male: 59<br>Female: 41<br>Nodulocystic acne: 32<br>Papulopustular acne: 68<br>Moderate acne: 64 (Male: 59%, Female: 71%)<br>Severe acne: 36<br>Male: 41%, Female: 29%<br>Mean Age :<br>Male: 22.2 with the range of 16-40<br>Female: 26.5 with the range of 17-40 | • Observational real-life monocentric study.<br>• 3 cycles of course with quite equal dosage distribution regardless of gender.<br>• The mean dose of regular administration: 0.41 mg/kg<br>• Male patients: 0.40 mg/kg/day<br>• Female patients: 0.43 mg/kg/day | • Reduction of GAGS (Global Acne Grading System) mean score from 27 to 3<br>• Increased Mean AQoL (Assessment of Quality of Life) score from 60 to 90<br>• Indication of satisfactory result.<br>• Treatment response was indifferent to gender. | • ≤ 1 adverse effect: 80%<br>• Skin xerosis and cheilitis, headache etc.: 87%<br>• No psychological adverse incidents were noticed.<br>• Acne recurrence: 9% |

| | | | | | |
|---|---|---|---|---|---|
| **2** | **Efficacy of fixed low-dose isotretinoin (20 mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris** (Sardana et al., 2009). | Moderate papulopustular acne: 305 patients<br>Males: 107<br>Females: 198<br>Mean age: 17.7 ±9.6 years | • Non-comparative study<br>• Duration of treatment: 6 months,<br>• Dose: About 20 mg on daily basis which corresponds to 0.15 to 0.28 mg/kg/day. | • Highly satisfactory outcome: 68.20% (208)<br>• Satisfactory outcome: 19.34% (59)<br>• Treatment failure: 12.46% (38)<br>• Treatment relapses: 16.39% (50) | Most common adverse effects:<br>• Mild cheilitis: 91%<br>• Xerosis: 43% |
| **3** | **Can oral isotretinoin be safely initiated and monitored in primary care? A case series** (Buckley & Yoganathan, 2017). | Total patients: 100<br>Male: 62<br>Female: 38 | • Retrospective cohort study<br>• Duration of treatment: 5 months<br>• Dose: 0.5-1 mg/kg/day till their acne cleansed up. | • Significant improvement: Acne patients:94<br>Rosacea patient:1<br>Relapsed patients: 5 | • Dry skin, backache, dry nose, mood swings and tiredness<br>• Dry lips: 100%<br>• Suicidal thoughts and needed additional consultancy. |

| | | | | | |
|---|---|---|---|---|---|
| **4** | **Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris** (Rao et al., 2014). | Total patients: 50<br>Male: 38 (76%)<br>Female: 12 (24%)<br>Mean age: 26.36 years<br>Nodulocystic acne: 22 (44%)<br>Resistant acne: 20 (40%)<br>Treatment relapse: 8 (16%). | • Prospective, non-comparative study<br>• Dose: 20 mg/day (about 0.3-0.4 mg/kg/day) for 3 months. | • Complete lesion clearance: 90% | • Cheilitis was quite prevalent among 98% of the patients as adverse effect.<br>• A very uncommon side effect, vitiligo was reported in only 1 patient. |
| **5** | **Comparing the Efficacy of Low Dose and Conventional Dose of Oral Isotretinoin in Treatment of Moderate and Severe Acne Vulgaris** (Faghihi et al., 2017). | Total patients: 60<br>All had moderate to severe acne vulgaris<br>Two separate groups. | • Clinical trial<br>• Dose: 0.5 mg/kg/day and 0.25 mg/kg/day<br>• Duration of treatment: 6 months. | • The improvement of the patients was significantly positive.<br>• The average level of acne severity in the two therapy groups did not differ extensively. | • Dry nose and hair thinning was quite common.<br>• Every patient had dry lips. |
| **6** | **A Randomized-Controlled Trial of Oral Low-Dose Isotretinoin for Difficult-To-Treat Papulopustular Rosacea** ( (Sbidian et al., 2016). | Total patients: 156<br>Male: 35.9<br>Female: 64.1%<br>Median age: 47.5<br>Difficult-to-treat papulopustular rosacea | • Double-blind, randomized-placebo-controlled investigation<br>• Dose: 0.25 mg/kg/day.<br>• Duration of treatment: 4-months. | • Improvement in the rate of response.<br>• Decreased number of acnes: 90%. | • Adverse event: ≥1% participants.<br>• Eczema, dry skin, cheilitis, abdominal pain etc. |

| | | | | | |
|---|---|---|---|---|---|
| **7** | **Long-term safety of isotretinoin as a treatment for acne vulgaris** ( GOULDEN et al., 1994) | Total patients: 720<br>Males: 447<br>Females: 273 | • Long term follow-up investigation<br>• One or more courses of isotretinoin.<br>• The range of follow-up visit: 4 to 6 months.<br>• Mean follow-up period: 4.9 years. | • The improvement of the patients was highly positive | • Adverse symptoms: 52 patients (7.4%)<br>• Mild and infrequent symptoms.<br>• Xeroderma, eczema, dry eye syndrome, arthralgia. |
| **8** | **A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris** (Dhaked et al., 2016) | Total patients: 240<br>Mean age: 18.88 ± 2.46 years<br>Two groups with 120 patients in each<br>Medium to serious acne vulgaris<br>Two groups of patients. | • Prospective randomized comparative study.<br>• Dose: 20mg<br>• One group: daily dose<br>• Another group: alternative day dose<br>• Duration of treatment: 24 weeks. | • An excellent response:<br>• Group A (98.3%)<br>• Group B (93.96%)<br>• Reduction of total acne counts.<br>• The two isotretinoin regimens proved to be successful. | • No significant adverse effect. |
| **9** | **Low-dose isotretinoin in the treatment of acne vulgaris** (Amichai et al., 2006) | Total patients: 638<br>Group 1: (12-20 years)<br>Patients: 495<br>Female/male ratio: 2:1<br>Group 2: (21-35 years)<br>Patients: 122<br>Female/male ratio: 3.5:1<br>Papulopustular acne: 96%<br>Papulocystic acne: 4% | • Open, prospective, noncomparative study<br>• Dose: 20 mg/d (about 0.3-0.4 mg/kg/day).<br>• Duration of treatment: 6 months<br>• Follow-up duration: 4 years. | • Highly positive outcome:<br>• Group1:94.8<br>• Group 2: 92.6% | • Hyper-lipidemia and increased liver enzyme.<br>• No depression or other severe effects. |

| | | | | | |
|---|---|---|---|---|---|
| **10** | **Oral isotretinoin for acne, adjusting treatment according to patient's response (** Ghaffarpour et al., 2006) | Total patients: 132<br>Mean age: 22.9 +/- 6.2 years<br>Severe nodulocystic acne. | • Clinical trial<br>• Starting dose: 0.75 mg/kg per day<br>• Maintenance dose: 20 mg/kg per day<br>• Duration of treatment: 1 month. | • Rate of ultimate recovery: 96.7%.<br>• Gender, age, the period of therapy or total dosage had no effect on the pace of improvement. | • Most side effects were minor and were managed gently. |
| **11** | **Retrospective case series of isotretinoin outcomes for acne in 393 female patients at Baylor College of Medicine during 2012-2016**(Fernandez et al., 2020) | All Female patients.<br>Total patients: 393<br>Mean age: 34.6 years | • Retrospective study.<br>• Cumulative dosage: 103.83 ± 52.78 mg/kg<br>• Duration of treatment: Around 4 months | • Positive response: 95.4%<br>• Complete acne clearance: 43.3%<br>• Improvement without full resolution: 52.2% | • The most typical side effects were cheilitis and xerosis in 97.3% participants. |
| **12** | **Comparison of safety and efficacy of low dose isotretinoin versus the conventional dosing regimen in the treatment of acne vulgaris (**Hafeez et al., 2020) | Total patients:140<br>Two groups of 70 with Acne vulgaris | • Randomized controlled trial study<br>• Group A (Low dose): 20mg/day<br>• Group B (Conventional dose): 80mg/ day<br>• Duration of treatment: 12 weeks | Efficacy<br>• Group A: 50%<br>• Group B: 71.4% | Group A:<br>• Dry eyes: 31.4%<br>• Headache: 14.3%<br><br>Group B:<br>• Dry eyes: 42.9%<br>• Headache: 17.1% |

| | | | | | |
|---|---|---|---|---|---|
| **13** | **Isotretinoin is safe and efficacious in Asians with acne vulgaris (** Gan et al., 2013) | Total: 2,255<br>Mean age: 22.5 years<br>Male:female: 2.5:1.<br>Nodulocystic acne: 65.4%<br>Moderate acne:11.9%<br>Mild relapsing acne: 22.7% | • Initial dose: 0.4 ± 0.1 mg/kg.<br>• Mean dose: 0.5 ± 0.2 mg/kg<br>• Duration of treatment: 7.8 months | • Full acne remission: 93.9% | • Chelitis, headache and photo-sensitivity were common side effects. |
| **14** | **The safety of isotretinoin in patients with acne and systemic diseases (**Hull & Cunliffe, 1989) | Total: 21<br><br>Associated with other systemic disease: gastrointestinal disease, Crohn's disease, multiple epilepsy; renal disease, endocrine disease, diabetes, hyperlipidaemia. | • Dose: 0.5 mg/kg/day -1 mg/kg/day<br>• Duration of treatment: 4-5 months. | • All the patients showed high improvement<br>• Only a patient with Crohn's disease needed 3 courses of treatment. | • Not any severe side effects or drug interaction was recorded. |

*Table 1: A few studies that outline the adverse effects of Isotretinoin*

# Chapter 4

# Discussion

It may be possible to achieve a quick and positive response rate with few side effects by beginning therapy with a high dose and adjusting the duration of treatment depending on the level of response in each patient. Low-dose Isotretinoin therapy for acne is an appealing alternative since the adverse effects are dose-related. With a low incidence of major side effects, low-dose Isotretinoin (20 mg/day) was shown to be beneficial in the treatment of medium to severe acne vulgaris. In addition, this dosage was less expensive than the larger levels. The outcomes of the low-dosage regimen with those of the conventional regimen since Isotretinoin at a dose of 1 mg/kg/day is compared and considered the gold standard for the treatment of severe acne. Since the effectiveness and recurrence rates were shown to be equal, people with mild to severe acne can benefit from low-dose treatment (0.5 mg/kg/day). Additionally, administering the recommended amount of 1 mg/kg/day in cases of mild to severe acne is pharmacologically inappropriate and thus results in additional adverse effects. Therefore, according to Hafeez et al, while treating acne vulgaris, a typical dosage regimen was found more effective but less safe than low-dose Isotretinoin (Ghaffarpour et al., 2006; Hafeez et al., 2020; Rao et al., 2014; Sardana & Garg, 2010).

In addition, according to Hull and Cunliffe, no report for drug- drug interaction or incidence of deterioration of patients was observed in the Isotretinoin treated patients associated with other systemic disorders (Hull & Cunliffe, 1989).

The most common side effects of Isotretinoin found investigating the mentioned studies was some mild cutaneous side effects, like dry skin, xerosis, rashes, dry lips, dry mouth, dehydration, cheilitis, and dry nose. Although it is sometimes difficult to tolerate these, gladly, they are all in frequent, transient, well-controlled with topical treatments, and not deadly. For instance, emollients are effective in treating xerosis successfully, which is found to be the most

prevalent adverse event. However, Isotretinoin's effectiveness at 0.5 to 1.0 mg/kg per day in the treatment of acne is well established and is considered safe (Amichai et al., 2006; Kapała et al., 2022; Tolino et al., 2020).

Besides, contraceptive methods can be used at the time when Isotretinoin is being used to prevent teratogenicity, and the worst cases are infrequent and symbolizes unique drug response. Oral contraceptive pills were used as a means of contraception by patients, according to Fernandez et al, no case of treatment stopping was observed because to cheilitis or xerosis, despite their high incidence. So, Isotretinoin should be regarded as a safe, effective choice for clinicians to take into account even for the treatment of adult female patients also (Fernandez et al., 2020; Kapała et al., 2022).

In order to facilitate the post-marketing risk monitoring program of the FDA for pharmacological and therapeutic biologic products, a database has been developed named FDA Adverse Event Reporting System, 'FAERS' in short. This database includes records of adverse effects reports and prescription-related mistakes that have been reported to the FDA. This can't be considered as an indication of the drug or biological causing the recorded adverse effects, even though FAERS includes reports on those. In fact, this information can be extremely beneficial for acknowledging risk indicators and further investigations on those specific items. In addition, FDA's assumption is that improved transparency encourages every public health-related individual to submit more thorough and detailed new case reports.

Therefore, in light of this FAERS database, all total 70,207 Isotretinoin related cases are reported from 1982 to 30 June, 2023. Among those, 49,168 are crucial cases including deaths and 1,512 cases are total death cases.

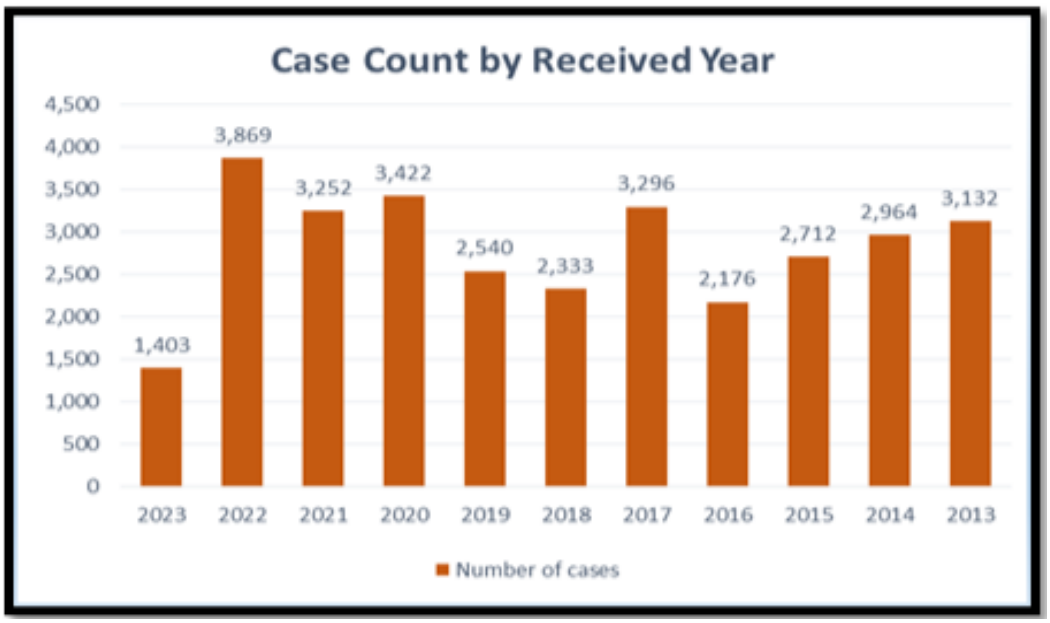


*Figure 5: Isotretinoin associated adverse event reports adapted from FAERS Database from 2013-2023(30, June)*

According to the graph, in 2022 the highest number of adverse events are reported among the recent 10 years and 1403 cases are reported in this year up to 30 June of 2023.

To describe more elaborately, among the total reported adverse events till now 8,010 cases (11%) are for depression;5,254 cases (8%) are for Inflammatory Bowel Disease; 3,846 cases (6%) are for Colitis Ulcerative; 3,795 cases (5%) are for Dry skin; 3,726 cases (5%) are for Headache and many more miscellaneous effects.

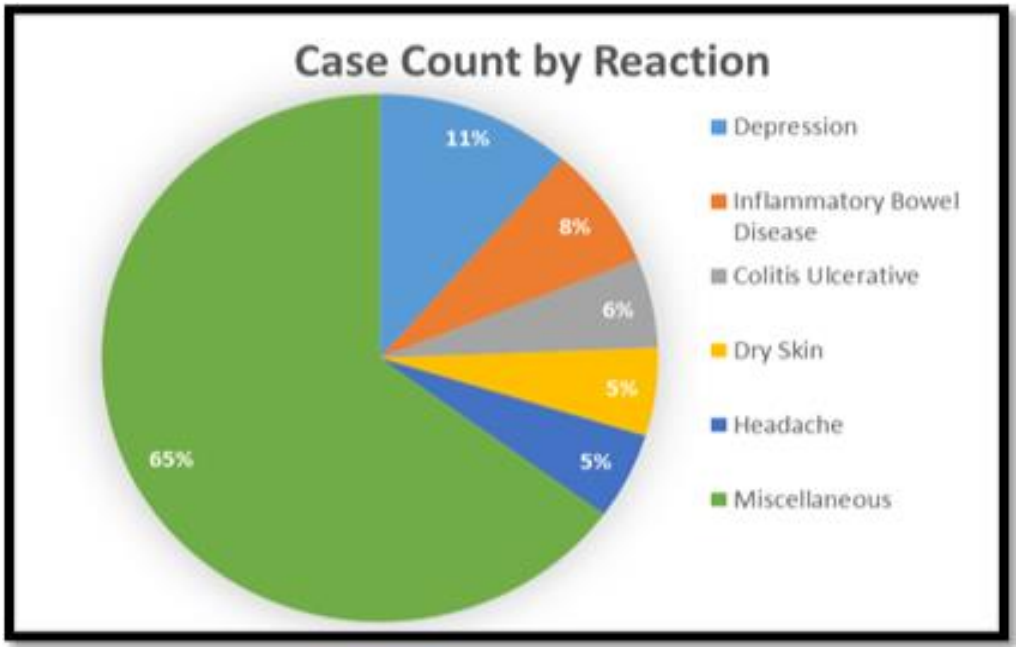


*Figure 6: Isotretinoin associated adverse case count by reaction adapted from FAERS Database*

It is yet unclear why certain individuals have a higher or lower chance of developing an incident. Some of the variation can be linked to a patient's capacity of side effect tolerance required to gain advantages from the drug (McLane, 2001).

To sum up, the results of all investigations show that Isotretinoin is a widely recognized, quite safe, and efficient drug in the treatment of moderate to severe acne with outstanding outcomes: better performance, a lower risk of recurrence of acne and no severe permanent adverse consequences without teratogenicity (GOULDEN et al., 1994; Tolino et al., 2020).

# Chapter 5

# Conclusion

Isotretinoin expertise spanning over three decades has culminated in more precisely defined safety and efficacy identities. Hence, Isotretinoin is predicted to remain the mainstay of medium to severe, resistant acne management. Isotretinoin has a number of adverse effects; however, the majority of these effects are anticipated and barely disrupt the treatment of patients. Besides, the most frequent mucocutaneous adverse effects tend to be dose-dependent and can be mitigated by modifying the dose or supplementing compensatory medication. However, patients and healthcare professionals are obligated to follow drug safety precautions, including discussions based on evidence and incidental dangers (Bauer et al., 2016; A. Layton, 2009; Leyden et al., 2014).

Experts also make additional recommendations, such as discussing the risks of congenital birth defects and spontaneous abortion with female patients; and prohibiting blood donation for both male and female patients till one month after the completion of the Isotretinoin course. Then, while there is insufficient evidence that Isotretinoin has any direct association with depression or suicidality, patients need to be informed of these anecdotal or anticipated consequences. Throughout the course of treatment, patients should be asked about their mental health on a regular basis. Finally, people must be informed and compelled to have their condition evaluated if any pregnancy difficulties or transaminase or triglyceride elevations develop (Bauer et al., 2016). In fact, awareness and clarification of the adverse effects to the patients can enhance the possibility of their prescribed dose regimen adherence (Kapała et al., 2022).

## 5.1 Future Prospect

There is a probability that new medications will be developed to target diverse routes of inflammation because many dermatoses, including acne, are persistent and inflammatory in

nature. Their use along with oral Isotretinoin might prove capable of shortening the course of treatment and lessen the chance of side effects. Regarding the usage of Isotretinoin, safety, side effects, and monitoring, there is adequate literature available. Moreover, Isotretinoin when used off-label is now thought to successfully treat other dermatological disorders aside from acne. Nevertheless, to figure out when and how to recommend Isotretinoin for maximal efficacy and safety, additional prospective research is required (Alyamani et al., 2022; Bagatin & Costa, 2020; Chu et al., 2021; Dhaked et al., 2016).

Another significant fact of concern is that there are no established guidelines for oral isotretinoin administration or its combination with other treatments. As a result, it is essential to identify the right patient and to follow a patient specific customized treatment plan with precisely scheduled sessions based on the extent and sort of acne lesions to accomplish the finest results. Hence, future investigations with higher sample sizes, randomized clinical trials and longer monitoring intervals are required to make an essential contribution to the research and assist in developing safer and more efficient Isotretinoin therapy guidelines (Alyamani et al., 2022; Villani et al., 2022).

Undoubtedly, future treatments with precise molecular targets will be introduced soon. However, a combination of medications might be required, since inflammatory illnesses tend to be complicated. Oral retinoids such as Isotretinoin mixed with immunobiological medications may become the standard treatment of choice for moderate to severe acne. Perhaps the usage of topical and oral antibiotics will come to an end (Bagatin & Costa, 2020).

Therefore, in this modern era, when there is a growing concern about antibiotic resistance plus a huge number of patients have developed allergic reactions or at a high risk of acquiring scars, earlier oral isotretinoin therapy for acne may be regarded as an appealing therapeutic choice ( Tolino et al., 2020).

## References


[1] Allenby, G., Bocquel, M. T., Saunders, M., Kazmer, S., Speck, J., Rosenberger, M., Lovey, A., Kastner, P., Grippo, J. F., Chambon, P., & Levin, A. A. (1993). Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. *Proceedings of the National Academy of Sciences of the United States of America*, *90*(1), 30–34. https://doi.org/10.1073/PNAS.90.1.30

[2] Alyamani, N. R., Alharbi, A. S., Alghamdi, T. A., Althagafi, O. A., Alsenadi, Y. J., Abdulrahman, A. A., Almomen, F. A., Mahmood, K. A., Aljawder, M. S., Alamer, A. M., & Alharbi, W. F. (2022). Indication, Contraindication, Complication and Monitoring of Isotretinoin. *Journal of Pharmaceutical Research International*, 10–15. https://doi.org/10.9734/jpri/2022/v34i47a36392

[3] Amado, J. M., Matos, M. E., Abreu, A. M., Loureiro, L., Oliveira, J., Verde, A., & Massa, A. (2006). The prevalence of acne in the north of Portugal. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *20*(10), 1287–1295. https://doi.org/10.1111/J.1468-3083.2006.01791.X

[4] Amichai, B., Shemer, A., & Grunwald, M. H. (2006). Low-dose isotretinoin in the treatment of acne vulgaris. *Journal of the American Academy of Dermatology*, *54*(4), 644–646. https://doi.org/10.1016/J.JAAD.2005.11.1061

[5] Augustin, M., Herberger, K., Hintzen, S., Heigel, H., Franzke, N., & Schäfer, I. (2011). Prevalence of skin lesions and need for treatment in a cohort of 90 880 workers. *The British Journal of Dermatology*, *165*(4), 865–873. https://doi.org/10.1111/J.1365-2133.2011.10436.X

[6] Bagatin, E., & Costa, C. S. (2020). The use of isotretinoin for acne–an update on optimal dosing, surveillance, and adverse effects. In *Expert Review of Clinical Pharmacology* (Vol.

13, Issue 8, pp. 885–897). Taylor and Francis Ltd. https://doi.org/10.1080/17512433.2020.1796637

[7] Bagatin, E., Costa, C. S., Rocha, M. A. D. da, Picosse, F. R., Kamamoto, C. S. L., Pirmez, R., Ianhez, M., & Miot, H. A. (2020). Consensus on the use of oral isotretinoin in dermatology - Brazilian Society of Dermatology. *Anais Brasileiros de Dermatologia*, *95*, 19–38. https://doi.org/10.1016/J.ABD.2020.09.001

[8] Ballanger, F., Baudry, P., N'Guyen, J. M., Khammari, A., & Dréno, B. (2006). Heredity: a prognostic factor for acne. *Dermatology (Basel, Switzerland)*, *212*(2), 145–149. https://doi.org/10.1159/000090655

[9] Barbieri, J. S., Roe, A. H., & Mostaghimi, A. (2020). Simplifying Contraception Requirements for iPLEDGE: A Decision Analysis. *Journal of the American Academy of Dermatology*, *83*(1), 104. https://doi.org/10.1016/J.JAAD.2020.02.022

[10] Bauer, L. B., Ornelas, J. N., Elston, D. M., & Alikhan, A. (2016). Isotretinoin: controversies, facts, and recommendations. *Expert Review of Clinical Pharmacology*, *9*(11), 1435–1442. https://doi.org/10.1080/17512433.2016.1213629

[11] Bhate, K., & Williams, H. C. (2013). Epidemiology of acne vulgaris. *British Journal of Dermatology*, *168*(3), 474–485. https://doi.org/10.1111/BJD.12149

[12] Brzezinski, P., Borowska, K., Chiriac, A., & Smigielski, J. (2017). Adverse effects of isotretinoin: A large, retrospective review. *Dermatologic Therapy*, *30*(4). https://doi.org/10.1111/DTH.12483

[13] Bubna, A. K. (2020). Isotretinoin: In acne and beyond – An overview. *Indian Journal of Drugs in Dermatology*, *6*(2), 59. https://doi.org/10.4103/IJDD.IJDD_11_19

[14] Buckley, D., & Yoganathan, S. (2017). Can oral isotretinoin be safely initiated and monitored in primary care? A case series. *Irish Journal of Medical Science*, *186*(2), 315–319. https://doi.org/10.1007/S11845-016-1540-5

[15] Chen, W., Zhao, S., Zhu, W., Wu, L., & Chen, X. (2019). Retinoids as an Immunity-modulator in Dermatology Disorders. *Archivum Immunologiae et Therapiae Experimentalis*, *67*(6), 355–365. https://doi.org/10.1007/S00005-019-00562-5

[16] Chu, S., Michelle, L., Ekelem, C., Sung, C. T., Rojek, N., & Mesinkovska, N. A. (2021). Oral isotretinoin for the treatment of dermatologic conditions other than acne: a systematic review and discussion of future directions. *Archives of Dermatological Research*, *313*(6), 391–430. https://doi.org/10.1007/S00403-020-02152-4/METRICS

[17] Claudel, J. P., Auffret, N., Leccia, M. T., Poli, F., & Dréno, B. (2018). Acne and nutrition: hypotheses, myths and facts. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *32*(10), 1631–1637. https://doi.org/10.1111/JDV.14998

[18] Coates, P., Adams, C. A., Cunlijfe, W. J., Mc Ginley, K. T., Eady, E. A., Leyden, J. J., Ravenscroft, J., Vyakrnam, S., & Vowels, B. (1997). Does oral isotretinoin prevent Propionibacterium acnes resistance? *Dermatology (Basel, Switzerland)*, *195 Suppl 1*(1), 4–9. https://doi.org/10.1159/000246012

[19] Cockerell, C. J., & Thiboutot, D. M. (2006). Ipledge: A report from the front lines of dermatologic practice. *Virtual Mentor*, *8*(8), 524–528. https://doi.org/10.1001/VIRTUALMENTOR.2006.8.8.PFOR1-0608

[20] Collier, C. N., Harper, J. C., Cantrell, W. C., Wang, W., Foster, K. W., & Elewski, B. E. (2008). The prevalence of acne in adults 20 years and older. *Journal of the American Academy of Dermatology*, *58*(1), 56–59. https://doi.org/10.1016/J.JAAD.2007.06.045

[21] Costa, C. S., Bagatin, E., Martimbianco, A. L. C., da Silva, E. M. K., Lúcio, M. M., Magin, P., & Riera, R. (2018). Oral isotretinoin for acne. In *Cochrane Database of Systematic Reviews* (Vol. 2018, Issue 11). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD009435.pub2

[22] DALZIEL, K., BARTON, S., & MARKS, R. (1987). The effects of isotretinoin on follicular and sebaceous gland differentiation. *The British Journal of Dermatology*, *117*(3), 317–323. https://doi.org/10.1111/J.1365-2133.1987.TB04138.X

[23] Dhaked, D., Meena, R., Maheshwari, A., Agarwal, U., & Purohit, S. (2016). A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris. *Indian Dermatology Online Journal*, *7*(5), 378. https://doi.org/10.4103/2229-5178.190505

[24] Dispenza, M. C., Wolpert, E. B., Gilliland, K. L., Dai, J. P., Cong, Z., Nelson, A. M., & Thiboutot, D. M. (2012). Systemic Isotretinoin Therapy Normalizes Exaggerated TLR-2-Mediated Innate Immune Responses in Acne Patients. *Journal of Investigative Dermatology*, *132*, 2198–2205. https://doi.org/10.1038/jid.2012.111

[25] Faghihi, G., Mokhtari, F., Fard, N., Motamedi, N., & Hosseini, S. (2017a). Comparing the efficacy of low dose and conventional dose of oral isotretinoin in treatment of moderate and severe acne vulgaris. *Journal of Research in Pharmacy Practice*, *6*(4), 233. https://doi.org/10.4103/jrpp.jrpp_17_30

[26] Faghihi, G., Mokhtari, F., Fard, N., Motamedi, N., & Hosseini, S. (2017b). Comparing the Efficacy of Low Dose and Conventional Dose of Oral Isotretinoin in Treatment of Moderate and Severe Acne Vulgaris. *Journal of Research in Pharmacy Practice*, *6*(4), 233. https://doi.org/10.4103/JRPP.JRPP_17_30

[27] Falcon, R. H., Lee, W. L., Shalita, A. R., Suntharalingam, K., & Fikrig, S. M. (1986). In vitro effect of isotretinoin on monocyte chemotaxis. *The Journal of Investigative Dermatology*, *86*(5), 550–552. https://doi.org/10.1111/1523-1747.EP12355006

[28] Fernandez, J., Lee, B., Patel, J. M., Weiss, E., Jiang, J., Dao, H., & Kim, S. J. (2020). Retrospective case series of isotretinoin outcomes for acne in 393 female patients at Baylor

College of Medicine during 2012-2016. *Journal of the American Academy of Dermatology*, *82*(5), 1218–1219. https://doi.org/10.1016/j.jaad.2019.06.1293

[29] Fex, G. A., Andréasson, S., & Ehinger, B. (1996). Serum retinoids in retinitis pigmentosa patients treated with vitamin A. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *234*(SUPPL. 1), S18–S21. https://doi.org/10.1007/BF02343043/METRICS

[30] Fogh, K., Voorhees, J. J., & Åström, A. (1993). Expression, purification, and binding properties of human cellular retinoic acid-binding protein type I and type II. *Archives of Biochemistry and Biophysics*, *300*(2), 751–755. https://doi.org/10.1006/ABBI.1993.1104

[31] Gan, E. Y., Koh, W. P., Jin, A. Z., Tan, A. W. H., Tan, H. H., & Tang, M. B. Y. (2013). Isotretinoin is safe and efficacious in Asians with acne vulgaris. *Journal of Dermatological Treatment*, *24*(5), 387–391. https://doi.org/10.3109/09546634.2012.672708

[32] Ghaffarpour, G., Mazloomi, S., Soltani-Arabshahi, R., & Soltani Arabshahi Seyed, K. (2006). Oral isotretinoin for acne, adjusting treatment according to patient's response - PubMed. *J Drugs Dermatol* , 878–882. https://pubmed.ncbi.nlm.nih.gov/17039654/

[33] Ghalamkarpour, F., & Nasiri, S. (2006). Isotretinoin in treatment of acne: its efficacy, side effects, and recurrence rate of disease - PubMed. *Arch Iran Med.*, 228–230. https://pubmed.ncbi.nlm.nih.gov/16859056/

[34] Ghodsi, S. Z., Orawa, H., & Zouboulis, C. C. (2009a). Prevalence, severity, and severity risk factors of acne in high school pupils: a community-based study. *The Journal of Investigative Dermatology*, *129*(9), 2136–2141. https://doi.org/10.1038/JID.2009.47

[35] Ghodsi, S. Z., Orawa, H., & Zouboulis, C. C. (2009b). Prevalence, severity, and severity risk factors of acne in high school pupils: a community-based study. *The Journal of Investigative Dermatology*, *129*(9), 2136–2141. https://doi.org/10.1038/JID.2009.47

[36] Goldsmith, L. A., Bolognia, J. L., Callen, J. P., Chen, S. C., Feldman, S. R., Lim, H. W., Lucky, A. W., Reed, B. R., Siegfried, E. C., Thiboutot, D. M., & Wheeland, R. G. (2004). Erratum: American Academy of Dermatology Consensus Conference on the Safe and Optional Use of Isotredtinoin: Summary and recommendations (Journal of the American Academy of Dermatology (June 2004) 51 (900-906)). *Journal of the American Academy of Dermatology*, *51*(3), 348. https://doi.org/10.1016/j.jaad.2004.06.005

[37] GOULDEN, V., LAYTON, A. M., & CUNLIFFE, W. J. (1994). Long-term safety of isotretinoin as a treatment for acne vulgaris. *The British Journal of Dermatology*, *131*(3), 360–363. https://doi.org/10.1111/J.1365-2133.1994.TB08524.X

[38] Goulden, V., Stables, G. I., & Cunliffe, W. J. (1999). Prevalence of facial acne in adults. *J Am Acad Dermatol* , 577–580. https://pubmed.ncbi.nlm.nih.gov/10495379/

[39] Hafeez, L., Khan, A. N., Aslam, A., Tahir, R., Shafi, A., & Akhtar, A. (2020). Comparison of safety and efficacy of low dose isotretinoin versus the conventional dosing regime in the treatment of acne vulgaris. *Journal of Pakistan Association of Dermatologists*, *30*(3), 423–427. https://www.jpad.com.pk/index.php/jpad/article/view/1484

[40] Harms, M., Masouyé, I., & Radeff, B. (1986). The relapses of cystic acne after isotretinoin treatment are age-related: a long-term follow-up study. *Dermatologica*, *172*(3), 148–153. https://doi.org/10.1159/000249320

[41] Honein, M. A., Lindstrom, J. A., & Kweder, S. L. (2007). Can we ensure the safe use of known human teratogens? The iPLEDGE$^{TM}$ test case. *Drug Safety*, *30*(1), 5–15. https://doi.org/10.2165/00002018-200730010-00002/METRICS

[42] Hull, S. M., & Cunliffe, W. J. (1989). The safety of isotretinoin in patients with acne and systemic diseases. *Journal of Dermatological Treatment*, *1*(1), 35–37. https://doi.org/10.3109/09546638909086687

[43] Janani, S. K., & Sureshkumar, R. (2019). *A COMPREHENSIVE REVIEW ON ACNE, ITS PATHOGENESIS, TREATMENT, IN-VITRO AND IN-VIVO MODELS FOR INDUCTION AND EVALUATION METHODS | INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH*. 3155–3177. https://doi.org/10.13040/IJPSR.0975-8232.10(7).3155-77

[44] Kapała, J., Lewandowska, J., Placek, W., & Owczarczyk-Saczonek, A. (2022). Adverse Events in Isotretinoin Therapy: A Single-Arm Meta-Analysis. In *International Journal of Environmental Research and Public Health* (Vol. 19, Issue 11). MDPI. https://doi.org/10.3390/ijerph19116463

[45] Karimkhani, C., Dellavalle, R. P., Coffeng, L. E., Flohr, C., Hay, R. J., Langan, S. M., Nsoesie, E. O., Ferrari, A. J., Erskine, H. E., Silverberg, J. I., Vos, T., & Naghavi, M. (2017). Global Skin Disease Morbidity and Mortality: An Update From the Global Burden of Disease Study 2013. *JAMA Dermatology*, *153*(5), 406–412. https://doi.org/10.1001/JAMADERMATOL.2016.5538

[46] King, K., Jones, D. H., Daltrey, D. C., & Cunliffe, W. J. (1982). A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population. *The British Journal of Dermatology*, *107*(5), 583–590. https://doi.org/10.1111/J.1365-2133.1982.TB00410.X

[47] Knutson, D. D. (1974). Ultrastructural observations in acne vulgaris: the normal sebaceous follicle and acne lesions. *The Journal of Investigative Dermatology*, *62*(3), 288–307. https://doi.org/10.1111/1523-1747.EP12676804

[48] Kochhar, D. M., & Penner, J. D. (1987). Developmental effects of isotretinoin and 4-oxo-isotretinoin: The role of metabolism in teratogenicity. *Teratology*, *36*(1), 67–75. https://doi.org/10.1002/TERA.1420360110

[49] Kurokawa, I., & Nakase, K. (2020). Recent advances in understanding and managing acne. In *F1000Research* (Vol. 9). F1000 Research Ltd. https://doi.org/10.12688/f1000research.25588.1

[50] Layton, A. (2009a). The use of isotretinoin in acne. *Dermato-Endocrinology*, *1*(3), 162. https://doi.org/10.4161/DERM.1.3.9364

[51] Layton, A. (2009b). The use of isotretinoin in acne. *Dermato-Endocrinology*, *1*(3), 162–169. https://doi.org/10.4161/DERM.1.3.9364

[52] Layton, A. M., & Cunliffe, W. J. (1992). Guidelines for optimal use of isotretinoin in acne. *Journal of the American Academy of Dermatology*, *27*(6), S2–S7. https://doi.org/10.1016/S0190-9622(08)80252-6

[53] Lehucher-Ceyrac, D., De La Salmonière, P., Chastang, C., & Morel, P. (1999). Predictive factors for failure of isotretinoin treatment in acne patients: results from a cohort of 237 patients. *Dermatology (Basel, Switzerland)*, *198*(3), 278–283. https://doi.org/10.1159/000018130

[54] Leyden, J. J., Rosso, J. Q. Del, Baum, E. W., & Mcguigan, K. A. (2014). The Use of Isotretinoin in the Treatment of Acne Vulgaris: Clinical Considerations and Future Directions. *The Journal of Clinical and Aesthetic Dermatology*, *7*(2 Suppl), S3. /pmc/articles/PMC3970835/

[55] Lowery, K., Rosen, T., & Malek, J. (2020). iPLEDGE Must Abstain from Abstinence. *The Journal of Clinical and Aesthetic Dermatology*, *13*(6), 54. /pmc/articles/PMC7442303/

[56] Lynn, D. D., Umari, T., Dunnick, C. A., & Dellavalle, R. P. (2016). The epidemiology of acne vulgaris in late adolescence. *Adolescent Health, Medicine and Therapeutics*, *7*, 13–25. https://doi.org/10.2147/AHMT.S55832

[57] McLane, J. (2001). Analysis of common side effects of isotretinoin. *Journal of the American Academy of Dermatology*, *45*(5), S188–S194. https://doi.org/10.1067/MJD.2001.113719

[58] Mehra, T., Borelli, C., Burgdorf, W., Röcken, M., & Schaller, M. (2012). Treatment of severe acne with low-dose isotretinoin. *Acta Dermato-Venereologica*, *92*(3), 247–248. https://doi.org/10.2340/00015555-1325

[59] Nast, A., Bayerl, C., Borelli, C., Degitz, K., Dirschka, T., Erdmann, R., Fluhr, J., Gieler, U., Hartwig, R., Meigel, E. M., Möller, S., Ochsendorf, F., Podda, M., Rabe, T., Rzany, B., Sammain, A., Schink, S., Zouboulis, C. C., & Gollnick, H. (2010). [S2k-guideline for therapy of acne]. *Journal Der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, *8 Suppl 2*(SUPPL. 2). https://doi.org/10.1111/J.1610-0387.2010.07466.X

[60] Nau, H. (2001). Teratogenicity of isotretinoin revisited: Species variation and the role of all-trans-retinoic acid. *Journal of the American Academy of Dermatology*, *45*(5), S183–S187. https://doi.org/10.1067/mjd.2001.113720

[61] Nelson, A. M., Gilliland, K. L., Cong, Z., & Thiboutot, D. M. (2006). 13-cis Retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. *The Journal of Investigative Dermatology*, *126*(10), 2178–2189. https://doi.org/10.1038/SJ.JID.5700289

[62] Ott, F., Bollag, W., & Geiger, J. M. (1996). Oral 9-cis-retinoic acid versus 13-cis-retinoic acid in acne therapy. *Dermatology (Basel, Switzerland)*, *193*(2), 124–126. https://doi.org/10.1159/000246226

[63] Peyravian, N., Deo, S., Daunert, S., & Jimenez, J. J. (2022). The Anti-Inflammatory Effects of Cannabidiol (CBD) on Acne. *Journal of Inflammation Research*, *15*, 2795–2801. https://doi.org/10.2147/JIR.S355489

[64] Pile, H. D., & Sadiq, N. M. (2023). Isotretinoin. *Handbook of Systemic Drug Treatment in Dermatology: Second Edition*, 184–193. https://doi.org/10.1201/b18491-23

[65] Plewig, G., Dressel, H., Pfleger, M., Michelsen, S., & Kligman, A. M. (2004). Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne. *Journal Der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, *2*(1), 31–45. https://doi.org/10.1046/J.1439-0353.2004.03739.X

[66] *Position Statement on Isotretinoin Page 2 of 2*. (n.d.).

[67] Rao, P. K., Bhat, R. M., Nandakishore, B., Dandakeri, S., Martis, J., & Kamath, G. H. (2014a). Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. *Indian Journal of Dermatology*, *59*(3), 316. https://doi.org/10.4103/0019-5154.131455

[68] Rao, P. K., Bhat, R. M., Nandakishore, B., Dandakeri, S., Martis, J., & Kamath, G. H. (2014b). Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. *Indian Journal of Dermatology*, *59*(3), 316. https://doi.org/10.4103/0019-5154.131455

[69] Rombouts, S., Nijsten, T., & Lambert, J. (2007). Cigarette smoking and acne in adolescents: results from a cross-sectional study. *Journal of the European Academy of Dermatology and Venereology*, *21*(3), 326–333. https://doi.org/10.1111/J.1468-3083.2006.01915.X

[70] Sadeghzadeh-Bazargan, A., Ghassemi, M., Goodarzi, A., Roohaninasab, M., Najar Nobari, N., & Behrangi, E. (2021). Systematic review of low-dose isotretinoin for treatment of acne vulgaris: Focus on indication, dosage, regimen, efficacy, safety, satisfaction, and follow up, based on clinical studies. *Dermatologic Therapy*, *34*(1). https://doi.org/10.1111/dth.14438

[71] Sardana, K., & Garg, V. (2010). Efficacy of low-dose isotretinoin in acne vulgaris. *Indian Journal of Dermatology, Venereology and Leprology*, *76*(1), 7. https://doi.org/10.4103/0378-6323.58672

[72] Sardana, K., Garg, V. K., Sehgal, V. N., Mahajan, S., & Bhushan, P. (2009). Efficacy of fixed low-dose isotretinoin (20 mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris. *Journal of the European Academy of Dermatology and Venereology*, *23*(5), 556–560. https://doi.org/10.1111/J.1468-3083.2008.03022.X

[73] Sbidian, E., Vicaut, É., Chidiack, H., Anselin, E., Cribier, B., Dréno, B., & Chosidow, O. (2016). A Randomized-Controlled Trial of Oral Low-Dose Isotretinoin for Difficult-To-Treat Papulopustular Rosacea. *Journal of Investigative Dermatology*, *136*(6), 1124–1129. https://doi.org/10.1016/J.JID.2016.01.025

[74] Seguin-Devaux, C., Hanriot, D., Dailloux, M., Latger-Cannard, V., Zannad, F., Mertes, P. M., Longrois, D., & Devaux, Y. (2005). Retinoic acid amplifies the host immune response to LPS through increased T lymphocytes number and LPS binding protein expression. *Molecular and Cellular Endocrinology*, *245*(1–2), 67–76. https://doi.org/10.1016/J.MCE.2005.10.006

[75] Shen, Y., Wang, T., Zhou, C., Wang, X., Ding, X., Tian, S., Liu, Y., Peng, G., Xue, S., Zhou, J., Wang, R., Meng, X., Pei, G., Bai, Y., Liu, Q., Li, H., & Zhang, J. (2012). Prevalence of acne vulgaris in Chinese adolescents and adults: a community-based study of 17,345 subjects in six cities. *Acta Dermato-Venereologica*, *92*(1), 40–44. https://doi.org/10.2340/00015555-1164

[76] Stern, R. S. (2004). Dermatologists and office-based care of dermatologic disease in the 21st century. *The Journal of Investigative Dermatology. Symposium Proceedings*, *9*(2), 126–130. https://doi.org/10.1046/J.1087-0024.2003.09108.X

[77] Strauss, J. S., Krowchuk, D. P., Leyden, J. J., Lucky, A. W., Shalita, A. R., Siegfried, E. C., Thiboutot, D. M., Van Voorhees, A. S., Beutner, K. A., Sieck, C. K., & Bhushan, R. (2007). Guidelines of care for acne vulgaris management. *Journal of the American Academy of Dermatology*, *56*(4), 651–663. https://doi.org/10.1016/J.JAAD.2006.08.048

[78] Tan, H. H., Tan, A. W. H., Barkham, T., Yan, X. Y., & Zhu, M. (2007). Community-based study of acne vulgaris in adolescents in Singapore. *The British Journal of Dermatology*, *157*(3), 547–551. https://doi.org/10.1111/J.1365-2133.2007.08087.X

[79] Tan, J. K. L., & Bhate, K. (2015). A global perspective on the epidemiology of acne. *British Journal of Dermatology*, *172*(S1), 3–12. https://doi.org/10.1111/BJD.13462

[80] Thiboutot, D., Gollnick, H., Bettoli, V., Dréno, B., Kang, S., Leyden, J. J., Shalita, A. R., Lozada, V. T., Berson, D., Finlay, A., Goh, C. L., Herane, M. I., Kaminsky, A., Kubba, R., Layton, A., Miyachi, Y., Perez, M., Martin, J. P., Ramos-e-Silva, M., … Wolf, J. (2009). New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. *Journal of the American Academy of Dermatology*, *60*(5), S1–S50. https://doi.org/10.1016/J.JAAD.2009.01.019

[81] Tkachenko, E., Singer, S., Sharma, P., Barbieri, J., & Mostaghimi, A. (2019). US Food and Drug Administration Reports of Pregnancy and Pregnancy-Related Adverse Events Associated With Isotretinoin. *JAMA Dermatology*, *155*(10), 1175–1179. https://doi.org/10.1001/JAMADERMATOL.2019.1388

[82] Tolino, E., Skroza, N., Proietti, I., Bernardini, N., Balduzzi, V., Anzalone, A., la Torre, G., Marchesiello, A., Mambrin, A., & Potenza, C. (2020). Postacne scarring: which factors are involved? *Giornale Italiano Di Dermatologia e Venereologia : Organo Ufficiale, Societa Italiana Di Dermatologia e Sifilografia*, *155*(6), 793–794. https://doi.org/10.23736/S0392-0488.19.06154-6

[83] Tolino, E., Skroza, N., Proietti, I., Mambrin, A., Balduzzi, V., Marchesiello, A., Maddalena, P., Michelini, S., Volpe, S., Bernardini, N., & Potenza, C. (2020a). Efficacy and safety of systemic isotretinoin treatment for moderate to severe acne (insights from the real-life clinical setting). *Dermatologic Therapy*, *33*(6), e14392. https://doi.org/10.1111/DTH.14392

[84] Tolino, E., Skroza, N., Proietti, I., Mambrin, A., Balduzzi, V., Marchesiello, A., Maddalena, P., Michelini, S., Volpe, S., Bernardini, N., & Potenza, C. (2020b). Efficacy and safety of systemic isotretinoin treatment for moderate to severe acne (insights from the real-life clinical setting). *Dermatologic Therapy*, *33*(6), e14392. https://doi.org/10.1111/DTH.14392

[85] Villani, A., Nastro, F., Di Vico, F., Fabbrocini, G., Annunziata, M. C., & Genco, L. (2022). Oral isotretinoin for acne: a complete overview. In *Expert Opinion on Drug Safety* (Vol. 21, Issue 8, pp. 1027–1037). Taylor and Francis Ltd. https://doi.org/10.1080/14740338.2022.2102605

[86] Wiegand, U. W., & Chou, R. C. (1998). Pharmacokinetics of oral isotretinoin. *Journal of the American Academy of Dermatology*, *39*(2 III), S8–S12. https://doi.org/10.1016/s0190-9622(98)70438-4

[87] Zaenglein, A. L., Pathy, A. L., Schlosser, B. J., Alikhan, A., Baldwin, H. E., Berson, D. S., Bowe, W. P., Graber, E. M., Harper, J. C., Kang, S., Keri, J. E., Leyden, J. J., Reynolds, R. V., Silverberg, N. B., Stein Gold, L. F., Tollefson, M. M., Weiss, J. S., Dolan, N. C., Sagan, A. A., … Bhushan, R. (2016). Guidelines of care for the management of acne vulgaris. *Journal of the American Academy of Dermatology*, *74*(5), 945-973.e33. https://doi.org/10.1016/j.jaad.2015.12.037

[88] Zasada, M., & Budzisz, E. (2019). Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments. *Advances in Dermatology*

*and Allergology/Postępy Dermatologii i Alergologii*, *36*(4), 392. https://doi.org/10.5114/ADA.2019.87443

[89] Zouboulis, C. C., & Piquero-Martin, J. (2003). Update and future of systemic acne treatment. *Dermatology (Basel, Switzerland)*, *206*(1), 37–53. https://doi.org/10.1159/000067821

## Project Summer 2023

ORIGINALITY REPORT

| 15% | 13% | 10% | 4% |
|---|---|---|---|
| SIMILARITY INDEX | INTERNET SOURCES | PUBLICATIONS | STUDENT PAPERS |

PRIMARY SOURCES

| | | |
|---|---|---|
| 1 | pubmed.ncbi.nlm.nih.gov<br>Internet Source | 2% |
| 2 | www.ncbi.nlm.nih.gov<br>Internet Source | 1% |
| 3 | ogma.newcastle.edu.au<br>Internet Source | 1% |
| 4 | worldwidescience.org<br>Internet Source | 1% |
| 5 | www.researchgate.net<br>Internet Source | 1% |
| 6 | www.tandfonline.com<br>Internet Source | 1% |
| 7 | Aoife U. Daly, Rui Baptista Gonçalves, Eva Lau, Joanne Bowers et al. "A systematic review of isotretinoin dosing in acne vulgaris", JEADV Clinical Practice, 2023<br>Publication | 1% |
| 8 | jrpp.net<br>Internet Source | 1% |

| | | |
|---|---|---|
| 9 | K Sardana. "Efficacy of fixed low-dose isotretinoin (20mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris", Journal of the European Academy of Dermatology and Venereology, 05/2009<br>Publication | <1% |
| 10 | www.dovepress.com<br>Internet Source | <1% |
| 11 | Submitted to Cardiff University<br>Student Paper | <1% |
| 12 | Submitted to University of Western Sydney<br>Student Paper | <1% |
| 13 | rxstars.net<br>Internet Source | <1% |
| 14 | www.science.gov<br>Internet Source | <1% |
| 15 | Submitted to University Of Tasmania<br>Student Paper | <1% |
| 16 | athenaeumpub.com<br>Internet Source | <1% |
| 17 | Joan Fernandez, Brigette Lee, Jay M. Patel, Emma Weiss, Jiating Jiang, Harry Dao, Soo Jung Kim. "Retrospective case series of isotretinoin outcomes for acne in 393 female | <1% |

patients at Baylor College of Medicine during 2012-2016", Journal of the American Academy of Dermatology, 2020
Publication

| | | |
|---|---|---|
| 18 | ebin.pub<br>Internet Source | <1 % |
| 19 | Muhammad Shahzeb Khan, Haolin Xu, Gregg C. Fonarow, Dominik Lautsch et al. "Applicability of Vericiguat to Patients Hospitalized for HeartFailure in the United States", JACC: Heart Failure, 2023<br>Publication | <1 % |
| 20 | "Subject index", Journal of the American Academy of Dermatology, 200606<br>Publication | <1 % |
| 21 | aacrjournals.org<br>Internet Source | <1 % |
| 22 | www.gov.uk<br>Internet Source | <1 % |
| 23 | www.termedia.pl<br>Internet Source | <1 % |
| 24 | www.medicaljournals.se<br>Internet Source | <1 % |
| 25 | d.docksci.com<br>Internet Source | <1 % |

hal.science

| | | |
|---|---|---|
| 26 | Internet Source | <1% |
| 27 | "Abstracts grouped per topic", European Journal of Nuclear Medicine, 1998<br>Publication | <1% |
| 28 | Ersilia Tolino, Nevena Skroza, Ilaria Proietti, Alessandra Mambrin et al. "Efficacy and safety of systemic isotretinoin treatment for moderate to severe acne (insights from the real-life clinical setting)", Dermatologic Therapy, 2020<br>Publication | <1% |
| 29 | Gan, Emily Yiping, Woon-Puay Koh, Ai Zhen Jin, Audrey Wei Hsia Tan, Hiok Hee Tan, and Mark Boon Yang Tang. "Isotretinoin is safe and efficacious in Asians with acne vulgaris", Journal of Dermatological Treatment, 2013.<br>Publication | <1% |
| 30 | news.unboundmedicine.com<br>Internet Source | <1% |
| 31 | patents.google.com<br>Internet Source | <1% |
| 32 | www.scielo.br<br>Internet Source | <1% |
| 33 | Hiok Hee Tan. "Minocycline and its extended-release formulation for the treatment of | <1% |

moderate-to-severe acne vulgaris", Expert Review of Dermatology, 2014
Publication

| | | |
|---|---|---|
| 34 | laegemiddelstyrelsen.dk<br>Internet Source | <1 % |
| 35 | www.karger.com<br>Internet Source | <1 % |
| 36 | Ayman Abdelmaksoud, Torello Lotti, Rana Anadolu, Mohamed Goldust et al. "Low dose of isotretinoin: A comprehensive review", Dermatologic Therapy, 2020<br>Publication | <1 % |
| 37 | Edileia Bagatin, Caroline Sousa Costa. "The use of isotretinoin for acne – an update on optimal dosing, surveillance, and adverse effects", Expert Review of Clinical Pharmacology, 2020<br>Publication | <1 % |
| 38 | Nadia El-Sherif, Azza Greiw, Amal Benamer. "Efficacy of daily low dose versus intermittent isotretinoin regimens in patients with moderate acne vulgaris: A randomized-controlled trial", Ibnosina Journal of Medicine and Biomedical Sciences, 2022<br>Publication | <1 % |
| 39 | Lin Liu, Peng Liu, Guo Wei, Liya Meng, Chunmin Zhang, Chunhong Zhang. "Combination of 5-Aminolevulinic acid photodynamic therapy and isotretinoin to treat moderate-to-severe acne", Photodiagnosis and Photodynamic Therapy, 2021<br>Publication | <1 % |

Exclude quotes Off
Exclude bibliography Off
Exclude matches Off