

Review Article

Efficacy and Safety of Topical Versus Systemic Isotretinoin for Acne Vulgaris Treatment: A Systematic Review

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Abstract

Introduction: Oral Isotretinoin has been used for years to successfully treat and manage severe acne. Topical isotretinoin has also been used to manage acne. However there exist very few studies that assess the safety and efficacy of topical isotretinoin. The aim of this systematic review is to evaluate available literature that report on the safety and efficacy of topical isotretinoin particularly in the management of acne.

Methods: A systematic review of existing literature. Online searches were conducted on various databases including PubMed, PubMed Central, Embase, CINAHL, the Cochrane Central Register of Controlled Trials, Web of Knowledge, PsycINFO and Scopus. Studies were assessed for eligibility using the specified inclusion and exclusion criteria. The researchers independently reviewed the abstracts and differences were settled by a consensus. Relevant data was extracted from eligible studies, including author and year of publication, study type, research design, number of participants, study aim and main findings from each study.

Results: Out of the 274 studies identified through search of databases and registers, 11 studies met the criteria for inclusion in the systematic review. A total of 1129 patients were included in the systematic review. The studies were from different geographical regions and countries. The studies found that topical isotretinoin was used in the management of acne and other dermatological conditions.

Conclusion: Topical isotretinoin is comparatively effective for the treatment of acne vulgaris of various degrees of severity, with minimal side effects. Further research is needed to understand its long-term safety, especially for high-risk populations. With appropriate monitoring, primary care clinicians should consider it for moderate to severe acne, especially in high-risk populations for whom the use of oral isotretinoin could be problematic or is contraindicated.

Keywords: Dermatological Conditions; Skin Disease; Isotretinoin; Acne Vulgaris Treatment

Introduction

Acne vulgaris is a common chronic skin disease that affects millions of people worldwide. It affects approximately 9% of the population worldwide and approximately 85% of those aged 12 to 24 years [1]. Acne also affects people in early adulthood [2,3]. Statistically, approximately 50 million people living in the United States are affected by acne [4]. The disease can significantly impact a person's self-image causing anxiety and depression due to permanent scarring [5]. This can lead to significant psychological distress and impairment of quality of life and may increase suicide risk [6-9]. In moderate, severe and/or persistent forms, acne vulgaris can significantly impair different dimensions of quality of life of affected persons [10-12]. The impairment of quality of life, however, does not directly correlate with the severity of the disease [13].

Acne lesions are primarily observed on the face, neck, upper back and chest. The financial burden of the disease is approximated

at above \$3 billion per year [14]. The management of acne involves targeting one or more pathways in its pathogenesis using effective therapies. Combining therapies has proven to be more successful than using just one treatment method [15]. For mild to moderate acne, topical therapies are the standard of care. However, for moderate to severe acne, systemic therapies are typically utilized [16]. In women with acne, hormonal therapies are an effective second-line treatment, irrespective of the presence or absence of androgen excess [17-19].

Isotretinoin, chemically known as 13-cis-retinoic acid and a derivative of vitamin A, is a highly effective drug for the treatment of severe and persistent forms of acne. It works by regulating the growth and differentiation of skin cells. Isotretinoin is available in different forms, including tablets (taken orally) and creams, gels and lotions (applied topically). In most clinical settings, however, primary care physicians are not privileged to prescribe systemic (oral) isotretinoin which, though very effective, is known to cause several adverse effects directly attributable to its use making its initiation and/or continuation at both primary and higher care levels potentially problematic for many patients [20,21].

Topical isotretinoin is used to treat mild to moderate acne. When applied topically, isotretinoin reduces inflammation and the clogging of pores, which are two of the primary factors in the occurrence of acneiform lesions. It is also thought to help normalize the growth and differentiation of skin cells, which can reduce the appearance of acne lesions over time. Topical isotretinoin can be used in combination with other topical acne treatments, such as benzoyl peroxide, salicylic acid or oral medications such as antibiotics [22,23]. It is usually prescribed for moderate to severe cases of acne that have not responded to other treatments. However, few studies exist that assess its efficacy and safety in the treatment and management of acne vulgaris. This systematic review aims at evaluating available literature to determine how safe and effective topical isotretinoin is in the management of acne vulgaris of varying degrees of severity, compared to oral (systemic) isotretinoin and other topical medications used in the treatment of acne vulgaris.

Objectives

To evaluate available literature on the efficacy and safety of topical isotretinoin compared to oral (systemic) isotretinoin, vis-a-vis its suitability for the treatment of patients with various degrees of acne severity in the primary care setting.

PICO Research question

P: Population - Individuals with mild to moderate acne or conditions manifesting with acne

I: Intervention - Topical isotretinoin

C: Comparison - Oral isotretinoin, other topical treatments and placebo

O: Outcome - Efficacy and safety of topical isotretinoin compared to oral isotretinoin, other topical treatments and placebo used in the treatment of acne

Methods

Prior to the commencement of data extraction, this systematic review was registered on Prospero (registration ID CRD42023421332). The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guided our methodology and reporting, to ensure consistency [23].

Inclusion Criteria

1. Study design: Randomized Controlled Trials (RCTs), Clinical Trials (CTs), retrospective studies, observational studies and cross-sectional studies
2. Participants: Individuals with acne vulgaris (various degrees of severity) as well as specific dermatological conditions such as melasma and photodamaged skin
3. Intervention: Topical isotretinoin treatment
4. Control: Systemic isotretinoin treatments, other topical treatments and placebo
5. Outcome measures: Efficacy and safety of topical isotretinoin in the treatment of acne vulgaris and dermatological conditions and the associated side effects as compared to systemic isotretinoin, other topical acne medications and placebo

Exclusion Criteria

1. Studies that do not evaluate the effectiveness or safety of topical isotretinoin or systemic isotretinoin in the treatment of acne and other dermatological conditions
2. Studies that do not include participants with acne and other dermatological conditions such as melasma and photodamaged skin
3. Studies with inadequate data or poor methodological quality
4. Studies that are not published in English

Search Criteria

The search was conducted across multiple online databases including PubMed, PubMed Central, Embase, CINAHL, the Cochrane Central Register of Controlled Trials, Web of Knowledge, PsycINFO and Scopus. Google Scholar was utilized as a search engine. The bibliographic databases, especially Medline and CENTRAL, were found to be highly valuable due to their millions of references with Medical Subject Headings (MeSH). The search string used across multiple databases included: (("topical isotretinoin" OR "isotretinoin cream" OR "isotretinoin gel" OR "isotretinoin lotion") AND ("acne vulgaris" OR "acneiform eruptions" OR "pimples" OR "zits" OR "comedones") AND ("efficacy" OR "effectiveness" OR "safety" OR "adverse effects" OR "side effects" OR "tolerability" OR "clinical trial" OR "randomized controlled trial"))).

Search Results

The search for this study was conducted across multiple databases and registers, resulting in a total of 274 records. Before screening, 99 duplicate records and 69 ineligible records flagged by automation tools were removed, while no records were removed for other reasons. Of the 106 remaining records screened, 44 were excluded, leaving 62 reports sought for retrieval. Of these, 27 reports were not retrieved and the remaining 35 reports were assessed for eligibility. Of the eligible reports, 19 were excluded because they were literature reviews, 2 because they discussed other dermatological conditions and 3 were excluded because they were not available in English. Finally, the review included a total of 11 studies, with 11 reports associated with these included studies (Fig. 1).

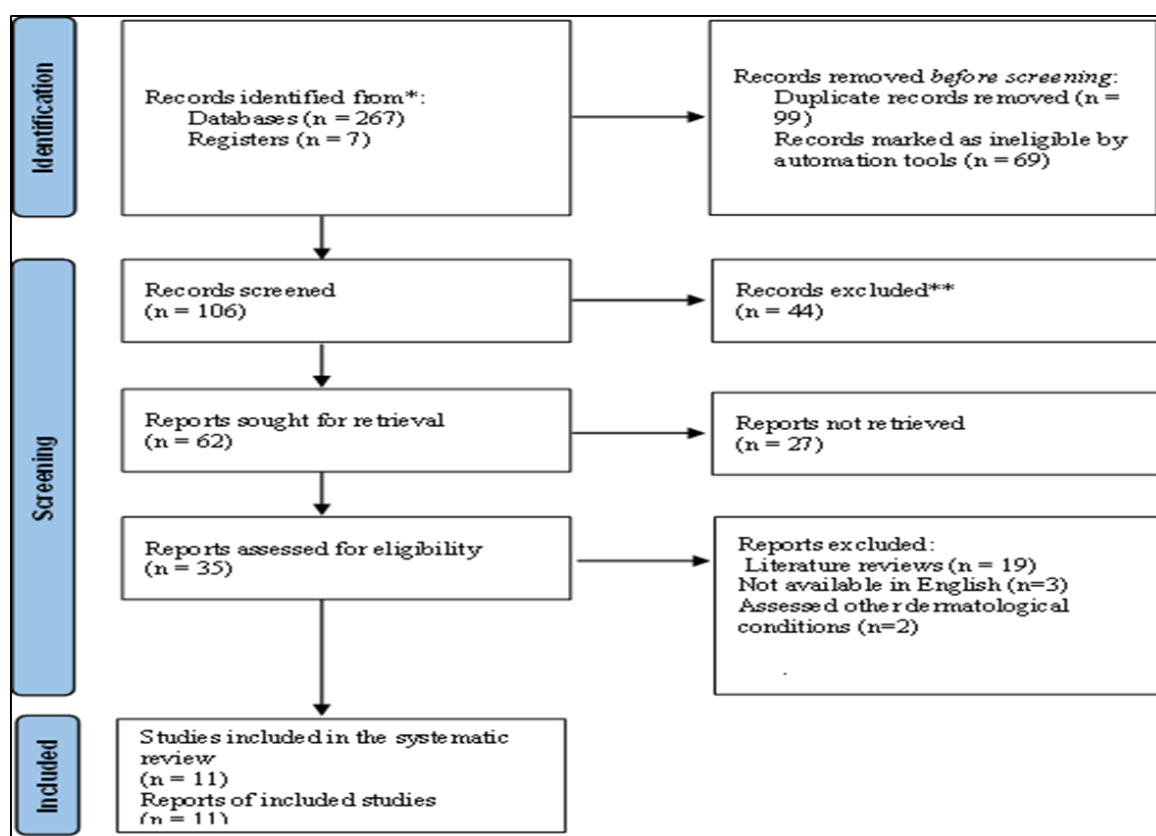


Figure 1: Prisma flow diagram.

Data Extraction

A standard data extraction form was used to extract relevant data from tables, including author and year of publication, study type, research design, number of participants, study aim and main findings from each study.

Results

Table of summaries are discussed in Table 1.

Author and Year	Study Design	Country	Aim	Participants	Type of Isotretinoin	Treatment Outcome	Author's Conclusion
Domínguez, et al.,	Clinical, prospective and longitudinal study	Mexico	The study compared the safety and efficacy of topical isotretinoin vs topical retinoic acid in acne vulgaris management. The researchers examined the efficacy of each treatment and side effects associated with each treatment.	30 patients	Topical	After 12 weeks of treatment, both groups showed a good response to treatment, with a reduction in inflammatory and noninflammatory lesions. The efficacy of both drugs was similar. However, patients in the retinoic acid group reported more adverse effects, such as stinging, erythema and desquamation, while patients in the isotretinoin group reported only mild irritation.	Efficacy was determined by the reduction in the number of lesions between weeks 0 and 12 of treatment. The authors found that both topical isotretinoin and topical retinoic acid were effective in treating acne vulgaris, with no significant differences in efficacy between the two treatments. However, the authors noted that topical isotretinoin was associated with fewer side effects than topical retinoic acid, suggesting that topical isotretinoin may be a safer treatment option for acne vulgaris.
Chalker, et al.,	RCT	USA	The study aimed to evaluate the effectiveness of topical isotretinoin in reducing the severity of acne lesions, both inflammatory	268 patients	Topical	The results showed that isotretinoin gel was significantly more effective than the placebo in reducing inflammatory lesions after 5 weeks and noninflammatory lesions and acne	The study found that the topical isotretinoin gel was effective in reducing the severity of acne vulgaris. The participants who received the isotretinoin gel showed a

			and non-inflammatory and to assess any adverse effects associated with the treatment.			severity grade after 8 weeks. Overall, the treatment was well-tolerated, with only two patients dropping out due to irritation.	significant improvement in their acne compared to those who received the placebo gel. The treatment was well-tolerated and no serious adverse effects were reported.
Aslan Bayhan, et al.,	Prospective study	Turkey	The authors evaluated the effectiveness of isotretinoin as a treatment for severe acne and the potential side effects associated with the use of this medication.	43 patients	Topical	Certain topical acne treatments such as tretinoin and benzoyl peroxide, were associated with dry eye syndrome and other ocular surface problems while isotretinoin was reported to be highly effective in the treatment of severe acne, particularly when used systemically but patients receiving it experienced side effects, such as dry skin, nosebleeds and ocular surface problems.	Patients receiving topical treatment for acne should be evaluated regularly to ensure the timely detection and treatment of pathologic signs on the ocular surface due to significant signs and symptoms of dry eye caused by topical retinoid-antibiotic combination treatment.
Elbaum	RCT	The USA	The study's main aim was to compare the stability of topical isotretinoin and topical tretinoin when exposed to different types of light (incandescent and fluorescent) and to assess their efficacy in treating moderate acne	18 patients	Topical	The study reports that isotretinoin, when administered topically, improved acne and caused a significant drop in lesion counts. The patients using topical isotretinoin also experienced no irritation and had lowered skin surface lipid levels by up to 30% and more	Isotretinoin and tretinoin were unstable when exposed to room lighting and the efficacy of the two preparations in treating acne was similar.
Hughes, et al.,	RCT	England	To evaluate and compare the efficacy of	77 patients	Topical	The isotretinoin group experienced more side effects than	After eight weeks of treatment, the researchers found

			topical isotretinoin 0.05%, benzoyl peroxide gel 5% and a placebo in the treatment of moderate to severe acne in patients.			the benzoyl peroxide group, although they were generally mild and reversible.	that both the isotretinoin and benzoyl peroxide groups showed significant improvement in acne compared to the placebo group. However, there was no statistically significant difference between the isotretinoin and benzoyl peroxide groups in terms of effectiveness.
Pandey and Agrawal	RCT	India	To evaluate the efficacy and safety of combining isotretinoin and antihistamine compared to isotretinoin alone in patients with moderate to severe acne at week 12.	100 patients	Oral (systemic)	The efficacy of isotretinoin improved when combined with antihistamine in providing a synergic effect while minimizing the side effects of isotretinoin and achieving greater clearance of the lesion and scars.	The combination of isotretinoin and an antihistamine group resulted in a statistically significant decrease in the score of the global acne grading system and acne lesion counts compared to isotretinoin alone group at week 12. Flaring up of acne occurred less frequently and adverse effects were more tolerable in the antihistamine group.
Özkoca, et al.,	Cross-sectional study	Turkey	To investigate the incidence of fatigue, myalgia and low back pain in individuals undergoing systemic isotretinoin treatment and determine their relation to age, gender, treatment	180 patients	Oral (systemic)	Among the patients, fatigue was reported by 4.4%, myalgia by 2.8% and low back pain by 25%. Further analysis revealed that 2.2% experienced inflammatory low back pain, while 22.8% had mechanical low back pain. Interestingly, no patients had sacroiliitis. The study	The study's findings suggest that the reported side effects, namely fatigue, myalgia and low back pain, are not as common as initially feared. This is particularly reassuring for patients and physicians who may have concerns about the potential

			duration, daily isotretinoin dose and isotretinoin-naiveness of the patient.			found that age, gender, isotretinoin dosage, treatment duration and prior isotretinoin use did not significantly affect the occurrence of these side effects.	adverse effects of systemic isotretinoin. Based on these results, healthcare professionals should feel confident in prescribing isotretinoin for indicated cases, without undue hesitation.
Tolino, et al.,	Observational study	Italy	To assess the effectiveness of isotretinoin in treating moderate and severe acne	100 patients	Oral (systemic)	Baseline Global Acne Grading System (GAGS) mean score was 27 and was reduced to 3 at the end of treatment. Mean AQL (Assessment of Quality of Life) score was 60 at baseline and 90 after treatment.	This study highlights that systemic isotretinoin could be used in treatment of moderate acne with excellent results: higher effectiveness, less recurrence risk with only few transient adverse effects.
Mülkoğlu and Karaosmanoğlu	Prospective controlled studies	Turkey	To assess the musculoskeletal side effects in patients treated with oral isotretinoin for acne vulgaris	30 patients	Oral (systemic)	Compared to the control group, which was treated with local treatment, there was no significant difference in muscle strength between the two groups.	The research concluded that systemic isotretinoin does not alter muscle strength in patients with acne vulgaris
Ibrahim, et al.,	Cross-sectional study	Sudan	To assess the rate of relapse of acne vulgaris after oral isotretinoin treatment and predictive factors that contribute to relapse.	225 patients	Oral (systemic)	At the 2-year follow-up, approximately 36% of patients experienced acne relapse. The relapses were commonly observed within 6 to 18 months after the last oral isotretinoin therapy. Early discontinuation of oral isotretinoin treatment was a positive predictor of acne relapse. Patients who discontinued	The researchers attributed acne relapse to several risk factors such as early discontinuation and low cumulative doses of oral isotretinoin. About a third of the study population experienced relapse. The study recommended long term therapy of oral isotretinoin with

						oral isotretinoin early were 3.99 times more likely to experience relapse compared to those who completed the planned course of treatment.	cumulative doses of 120–159 mg/kg to reduce relapse rates.
Dixit, et al.,	Randomized prospective study		To assess how effective combined treatment oral isotretinoin with salicylic acid and mandelic peel against acne tarda (adult acne)	58 patients	Oral (systemic)	The combined treatment showed significant improvements in acne severity, as assessed by MASI and VAS scores and had a positive impact on scarring and inflammatory components. These findings suggest that the addition of SM peeling to oral isotretinoin treatment may enhance the therapeutic outcomes for acne patients.	The study concluded that combining oral isotretinoin with SM peeling was highly effective and shows no serious side effects.

Table 1: Table of summaries.

Discussion

This systematic review included a range of studies evaluating the efficacy and safety of topical and oral (systemic) isotretinoin in the treatment of acne vulgaris. The studies varied in design, including clinical prospective studies, Randomized Controlled Trials (RCTs), observational studies and cross-sectional studies, providing a comprehensive overview of the available evidence. Acne vulgaris is a common skin condition that affects a large proportion of the global population. Oral (systemic) isotretinoin has been widely used in the management of severe acne but concerns regarding its safety have been raised. This systematic review comparatively evaluates the safety and efficacy of both topical and oral isotretinoin in the treatment of acne vulgaris.

Efficacy of Topical Isotretinoin vs Oral (Systemic) Isotretinoin

Topical isotretinoin has been shown to be effective in the treatment of mild to moderate acne vulgaris. Domínguez, et al., found that both topical isotretinoin and topical retinoic acid were effective in reducing inflammatory and noninflammatory lesions [25]. Chalker, et al., conducted an RCT and reported that the isotretinoin gel was significantly more effective than the placebo in reducing inflammatory and noninflammatory lesions, as well as acne severity grade [22]. Elbaum compared the efficacy of topical isotretinoin and tretinoin and found that isotretinoin improved acne and caused a significant drop in lesion counts. These studies suggest that topical isotretinoin is an effective treatment option for acne vulgaris [27].

Oral/systemic isotretinoin has also demonstrated acceptable effectiveness in treating moderate to severe acne. Pandey and Agrawal conducted an RCT and found that the combination of oral (systemic) isotretinoin and antihistamine resulted in greater clearance of lesions and scars compared to isotretinoin alone [29]. Tolino, et al., conducted an observational study and reported excellent results in the treatment of moderate acne with oral (systemic) isotretinoin, with higher effectiveness and less recurrence risk [31]. However, Ibrahim, et al., found that approximately 36% of patients experienced acne relapse at the 2-year follow-up, with early discontinuation of isotretinoin treatment being a positive predictor of relapse [33]. These findings suggest that oral (systemic) isotretinoin is effective in treating acne, but completion of the planned course of treatment and long-term therapy may

be necessary to reduce relapse rates.

Safety of Topical vs Oral (Systemic) Isotretinoin

Based on the reviewed studies, topical isotretinoin was generally considered safe for the treatment of acne vulgaris. Domínguez et al., in their study which compared the safety and efficacy of topical isotretinoin with topical retinoic acid, found that patients in the isotretinoin group reported only mild irritation as a side effect, while the retinoic acid group experienced more side effects such as stinging, erythema and desquamation [25]. Chalker, et al., conducted a Randomized Controlled Trial (RCT) and reported that the topical isotretinoin gel was well-tolerated, with only two patients dropping out due to irritation [22]. Overall, these studies suggest that topical isotretinoin has a favorable safety profile, with mild and reversible side effects.

The safety of oral (systemic) isotretinoin was assessed in some studies. Özkoca, et al., conducted a cross-sectional study and found that fatigue, myalgia and low back pain were reported by a minority of patients, with no significant impact from factors such as age, gender, dosage, treatment duration or prior isotretinoin use [30]. Mülkoğlu and Karaosmanoğlu conducted a prospective controlled study and reported that muscle strength was not significantly affected by oral isotretinoin treatment [32]. These findings indicate that systemic isotretinoin is generally well-tolerated, with only a small percentage of patients experiencing mild side effects.

Topical vs Oral (Systemic) Isotretinoin in the Management of Other Dermatological Conditions

Isotretinoin is a medication commonly used in the treatment of severe acne, but it has also been explored for other dermatological conditions like lamellar congenital ichthyosis, plane warts and facial lichen planopilaris [35]. For instance, Giustina, et al., in their study demonstrated better and significant improvement in oral lichen planus lesions in patients treated with topical applications of isotretinoin, compared to those treated with a placebo [36]. In addition, though not statistically significant, treatment of a group of patients in a randomized clinical trial with 0.05% topical isotretinoin revealed a 68.2% reduction in Melasma Area Severity Index (MASI) after 40-weeks compared to a 60% reduction in the control group [37]. In a similar vein, topical isotretinoin was also demonstrated to provide cosmetic improvements in people with photodamaged skin [38].

In the study by Kaur et al., the efficacy and safety of oral versus topical isotretinoin were compared in the treatment of plane warts. The results showed that oral isotretinoin demonstrated better, and earlier response compared to topical isotretinoin [39]. After 3 months of treatment, 69% of patients in the oral isotretinoin group achieved complete remission, while only 38% in the topical isotretinoin group achieved complete remission. The difference between the two groups was statistically significant. However, it is important to note that the study had a small sample size of 40 patients.

Saber, et al., on the other hand, conducted a study to compare the effectiveness of systemic and topical isotretinoin in treating facial lichen planopilaris [40]. The study found that both systemic and topical isotretinoin were effective in improving the symptoms of facial lichen planopilaris. Systemic isotretinoin showed superior efficacy in reducing erythema and scaling compared to topical isotretinoin. However, topical isotretinoin was associated with fewer side effects, indicating a better safety profile.

These studies suggest that isotretinoin can be effective in treating certain dermatological conditions, but the route of administration (oral or topical) and the specific condition being treated can influence its efficacy. Oral isotretinoin demonstrated better outcomes in the treatment of plane warts, as well as superior efficacy in reducing erythema and scaling in facial lichen planopilaris.

The outcomes of interest from the evaluated studies were overall efficacy and safety of topical isotretinoin in comparison with oral (systemic) isotretinoin, other topical treatments, and placebo for acne vulgaris and other dermatologic conditions. Findings from the review suggest that topical isotretinoin is effective in reducing inflammatory and noninflammatory acne lesions and sebum production and has a relatively better safety profile than oral (systemic) isotretinoin and some other topical anti-acne medications.

Although isotretinoin is known to be a lipophilic substance, a related study demonstrated that its systemic availability following

topical administration is negligible; this property might be a plausible explanation for its comparatively better safety profile [41]. In addition, topical isotretinoin can be used in combination with other topical therapies but requires ongoing monitoring and, unlike systemic isotretinoin, requires a more prolonged (ongoing) treatment to maintain results.

Apart from its reported efficacy and safety, it is imperative to also note that therapy with topical isotretinoin resulted in improved overall patient satisfaction and global aesthetic improvement score, as reported by a study on its use in the treatment of another dermatologic condition [40]. This is noteworthy considering the significant impact acne vulgaris and other dermatologic conditions have on the quality of life of affected persons.

Limitations

1. The studies included in the review had varying sample sizes, treatment regimens and outcome measures, which may limit the ability to draw definitive conclusions
2. Some studies may be subject to bias, particularly those with small sample sizes or those that did not use a randomized controlled design
3. A huge limitation of this systematic review was that it included relatively old studies. This was due to literature gap in the use of topical isotretinoin in the treatment and management of acne
4. The systematic review points to the paucity of literature on studies comparing the effectiveness of topical vs oral isotretinoin in treating acne

Conclusion

The review highlights the potential benefits of topical isotretinoin over other acne treatments, particularly in terms of fewer side effects. Patients using topical isotretinoin experienced milder side effects compared to those using oral isotretinoin, indicating its safety profile. This systematic review suggests that topical isotretinoin is an effective treatment option for moderate, severe or persistent acne vulgaris, with minimal reported or demonstrated adverse effects. The review highlights the potential benefits of topical isotretinoin over some other acne treatments, particularly in terms of fewer side effects. However, it is important to note that the studies included in the review had varying sample sizes, treatment regimens and outcome measures, which may limit the ability to draw definitive conclusions.

In view of its efficacy and relatively better safety profile, primary care physicians should consider isotretinoin as a viable treatment option for patients with moderate to severe acne and thus consider incorporating topical isotretinoin early in the management of patients with moderate and severe or persistent acne vulgaris, with appropriate monitoring for adverse effects, especially for people with underlying conditions that are contra-indications or that may be aggravated by systemic isotretinoin. Further research is needed to understand its long-term efficacy and safety in comparison to systemic isotretinoin, especially for high-risk patients.

Recommendations

1. Future studies should strive to use standardized treatment regimens and outcome measures to increase the comparability of results across studies
2. More randomized controlled trials should be conducted to reduce the risk of bias in the findings
3. Researchers should consider conducting studies in different populations to determine the generalizability of the findings
4. Future systematic reviews should aim to include more recent studies to provide an up-to-date summary of the evidence base
5. Primary care physicians should consider topical isotretinoin as a potential treatment option for patients with acne, particularly those who have not responded well to other treatments

Conflict of Interest

The author has no conflict of interest to declare.

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