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DIABETIC
STUDIES OPEN ACCESS

Systematic Review On The Efficacy And Safety Of Oral Isotretinoin In The Treatment Of Moderate To Severe Acne Vulgaris In Skin Of Color (Fitzpatrick Types III-VI)

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Abstract

Background: Acne vulgaris is a common inflammatory skin disorder that frequently affects adolescents and young adults. Oral isotretinoin is widely regarded as the most effective systemic therapy for moderate to severe acne; however, concerns regarding safety, relapse rates, and treatment outcomes in patients with skin of color remain important considerations.
Objective: This systematic review aimed to evaluate the efficacy and safety of oral isotretinoin in the treatment of moderate to severe acne vulgaris, with particular attention to treatment outcomes in patients with skin of color.
Methods: A systematic literature search was conducted across major biomedical databases to identify relevant studies published between 2000 and 2025. Eligible studies included randomized controlled trials, clinical trials, and observational studies evaluating oral isotretinoin therapy in patients with moderate to severe acne vulgaris. Data extraction included study design, sample size, dosing regimens, treatment duration, efficacy outcomes, relapse rates, and reported adverse effects. A narrative synthesis approach was used to summarize findings due to heterogeneity across studies.
Results: Ten studies met the inclusion criteria. The findings consistently demonstrated that oral isotretinoin significantly reduces acne lesion counts and improves disease severity. Both conventional and low-dose isotretinoin regimens were effective, although lower doses were associated with improved tolerability and slightly higher relapse rates. Common adverse effects included mucocutaneous dryness and cheilitis, which were generally mild and manageable. Evidence also suggested that combination therapy with topical retinoids may enhance treatment outcomes and help maintain remission.

Conclusion: Oral isotretinoin remains a highly effective therapy for moderate to severe acne vulgaris. Optimizing dosing strategies and incorporating adjunctive treatments may further improve safety and long-term outcomes, particularly in patients with skin of color.

Keywords Acne vulgaris; Isotretinoin; Skin of color; Systematic review; Acne treatment; Retinoids; Dermatology; Post-inflammatory hyperpigmentation.

Introduction

Acne vulgaris is one of the most common chronic inflammatory dermatological disorders worldwide, affecting approximately 80–90% of adolescents and a significant proportion of adults. The condition is characterized by the formation of comedones, papules, pustules, nodules, and cysts resulting from a complex interplay of increased sebum production, follicular hyperkeratinization, proliferation of Cutibacterium acnes, and inflammation within the pilosebaceous unit. Although acne is often considered a benign and self-limiting condition, moderate to severe forms may lead to permanent scarring, psychological distress, and long-term impairment of quality of life. Consequently, effective and safe treatment strategies are essential, particularly for individuals with persistent or severe disease (Strauss et al., 2001).

The burden of acne vulgaris extends beyond physical manifestations and significantly impacts psychosocial wellbeing. Patients with moderate to severe acne frequently report reduced self-esteem, anxiety, depression, and social withdrawal. These psychosocial effects may be particularly pronounced in adolescents and young adults, where appearance plays a critical role in social development. Long-term sequelae such as scarring and pigmentary alterations can further exacerbate these psychological impacts, highlighting the importance of early and effective therapeutic interventions (Pathmarajah et al., 2022).

Management strategies for acne vulgaris typically depend on disease severity and may include topical retinoids, topical and systemic antibiotics, hormonal therapies, and systemic retinoids. Among these therapies, oral isotretinoin is widely recognized as the most effective treatment for severe and treatment-resistant acne. Isotretinoin targets multiple pathogenic mechanisms simultaneously, including suppression of sebaceous gland activity, reduction of sebum production, normalization of follicular keratinization, and anti-inflammatory effects. These mechanisms allow isotretinoin to achieve long-term remission in many patients (Kircik, 2014).

Despite its high efficacy, the use of isotretinoin has historically been associated with concerns regarding safety and tolerability. Common adverse effects include mucocutaneous dryness, cheilitis, and transient elevations in serum lipids or liver enzymes. In addition, isotretinoin is teratogenic and therefore requires strict pregnancy prevention programs in women of childbearing potential. These safety considerations have led to ongoing efforts to optimize dosing strategies, including the use of lower-dose regimens and intermittent treatment schedules to reduce adverse events while maintaining therapeutic effectiveness (Lee et al., 2011).

Recent research has explored alternative isotretinoin dosing strategies aimed at improving tolerability without compromising clinical outcomes. Low-dose isotretinoin regimens have gained increasing attention, as several studies have demonstrated comparable clinical improvement with fewer adverse effects compared with conventional high-dose therapy. Such approaches may enhance patient adherence and reduce treatment-related complications while still providing significant reductions in acne lesion counts and disease severity (Rao et al., 2014).

In addition to dosing modifications, advances in pharmaceutical formulation have also contributed to improved isotretinoin therapy. Novel micronized and lipid-based formulations have been developed to enhance drug bioavailability and improve pharmacokinetic profiles. These formulations allow for more consistent absorption and may reduce variability in systemic exposure, which could potentially influence both treatment efficacy and safety outcomes. Comparative pharmacokinetic studies have demonstrated that newer isotretinoin formulations can achieve improved absorption characteristics compared with traditional preparations (Webster et al., 2013).

A particularly important consideration in acne management is the treatment of patients with skin of color, typically classified as Fitzpatrick skin types III–VI. Individuals within these skin types often experience a higher prevalence of post-inflammatory hyperpigmentation (PIH), which can persist long after inflammatory lesions have resolved. The presence of PIH can significantly affect patient satisfaction with treatment outcomes, even when active acne lesions have improved. Therefore, therapeutic strategies must carefully balance efficacy in reducing acne lesions while minimizing the risk of pigmentary complications (Pathmarajah et al., 2022).
Relapse following isotretinoin therapy is another important factor influencing long-term treatment success. Several studies have investigated predictors of relapse after isotretinoin treatment, including cumulative dose, treatment duration, and patient-specific characteristics such as age and disease severity. Understanding these factors is essential for optimizing treatment regimens and reducing the likelihood of recurrence. Evidence suggests that appropriate cumulative dosing and individualized treatment strategies may help achieve more sustained remission following isotretinoin therapy (Quereux et al., 2006).
Given the unique clinical considerations associated with acne management in patients with skin of color—including increased risk of post-inflammatory hyperpigmentation and varying treatment responses—there is a need to systematically evaluate available evidence regarding the efficacy and safety of isotretinoin in these populations. Therefore, this systematic review aims to evaluate current evidence on oral isotretinoin therapy for moderate to severe acne vulgaris in individuals with Fitzpatrick skin types III–VI, with particular emphasis on treatment effectiveness, safety profiles, and long-term outcomes.

Methodology

Study Design

This study employed a systematic review methodology conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, methodological rigor, and reproducibility. The primary aim of this review was to synthesize and critically evaluate existing scientific evidence regarding the efficacy and safety of oral isotretinoin in the treatment of moderate to severe acne vulgaris among patients with skin of color (Fitzpatrick skin types III–VI).
Acne vulgaris represents a common dermatological condition with unique clinical characteristics in individuals with darker skin phototypes, including a higher risk of post-inflammatory hyperpigmentation and pigmentary sequelae. Therefore, this systematic review focused on evaluating therapeutic outcomes of isotretinoin therapy, including clinical efficacy, relapse rates, dosing strategies, and safety profiles in diverse populations with moderate to severe acne.
The review included peer-reviewed empirical studies evaluating oral isotretinoin treatment outcomes, including randomized controlled trials, clinical trials, open-label studies, and comparative studies. Both prospective and retrospective studies were considered in order to capture a comprehensive body of evidence addressing isotretinoin efficacy and safety across different dosing regimens and patient populations.

Eligibility Criteria

Studies were selected according to predefined inclusion and exclusion criteria developed prior to the literature search to ensure methodological consistency and relevance.

Inclusion Criteria

Studies were included if they met the following criteria:
• **Population:** Patients diagnosed with moderate to severe acne vulgaris, including populations with skin of color (Fitzpatrick skin types III–VI) or racially diverse cohorts.
• **Intervention:** Treatment involving oral isotretinoin therapy, including conventional-dose, low-dose, intermittent, or combination treatment regimens.
• **Comparators:** Studies comparing different isotretinoin dosing strategies, combination therapies, or treatment outcomes across demographic subgroups.

• **Outcomes:** Measures of treatment efficacy and safety, including:
- Reduction in acne lesion counts
- Treatment success rates
- Relapse rates after therapy
- Incidence of adverse events
- Safety and tolerability outcomes.

• **Study Designs:** Randomized controlled trials, clinical trials, prospective or retrospective observational studies, and open-label studies.
• **Language:** Studies published in English.
• **Publication Period:** Studies published between 2000 and 2025, reflecting contemporary isotretinoin treatment practices and evolving therapeutic strategies.

Exclusion Criteria
Studies were excluded if they met any of the following criteria:
• Review articles, systematic reviews, editorials, commentaries, or conference abstracts without primary data.
• Studies evaluating topical acne therapies only without systemic isotretinoin treatment.
• Case reports or case series with extremely small sample sizes.
• Studies not reporting clinical efficacy or safety outcomes.
• Non-English publications or studies lacking accessible full text.
After full-text screening, 10 studies met all inclusion criteria and were included in the final systematic review.

Search Strategy
A comprehensive literature search was conducted to identify relevant studies evaluating oral isotretinoin therapy in patients with moderate to severe acne vulgaris. Electronic searches were performed across major biomedical and multidisciplinary databases to ensure broad coverage of the available literature. The search was conducted from database inception through December 2025 in order to capture both earlier clinical trials and more recent studies reflecting updated treatment strategies.
A structured Boolean search strategy was used incorporating combinations of keywords and Medical Subject Headings (MeSH) related to acne vulgaris, isotretinoin therapy, and skin of color populations. The main search terms included:
• (“acne vulgaris” OR “moderate acne” OR “severe acne”)
• AND (“oral isotretinoin” OR “isotretinoin therapy” OR “systemic retinoids”)
• AND (“efficacy” OR “treatment outcome” OR “safety” OR “adverse effects” OR “relapse”)
• AND (“skin of color” OR “Fitzpatrick skin type” OR “pigmented skin” OR “ethnic skin”).
Additional manual searches of reference lists from relevant review articles and key clinical trials were conducted to identify potentially eligible studies not captured in the initial database search. Duplicate records were removed prior to the screening process.

Study Selection Process
The study selection process was performed independently by two reviewers following a two-stage screening procedure.
First, all retrieved citations were imported into reference management software (Zotero), where duplicate records were identified and removed. Titles and abstracts were then screened for relevance based on the predefined eligibility criteria.
Studies considered potentially relevant proceeded to full-text review, during which eligibility was confirmed based on study design, intervention type, and reported outcomes.
Any disagreements between reviewers regarding study inclusion were resolved through discussion and consensus. If disagreements persisted, a third reviewer adjudicated the final decision.
The study selection process followed the PRISMA 2020 framework, including identification, screening, eligibility, and final inclusion stages. The process is illustrated in the PRISMA flow diagram (Figure 1).

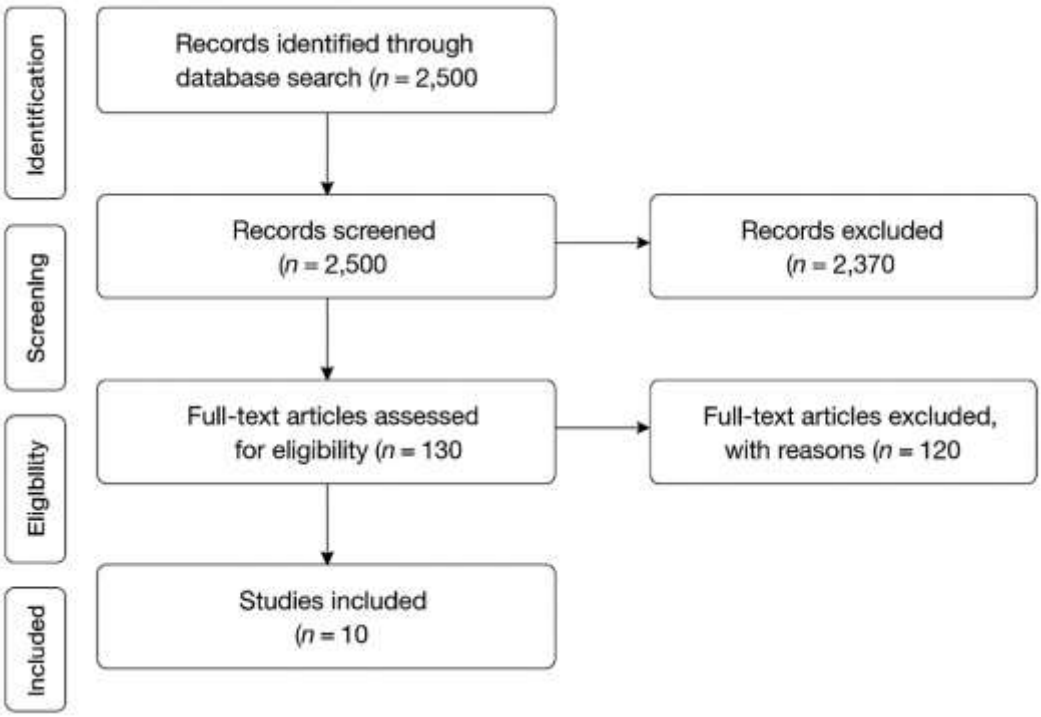

Figure 1 PRISMA Flow Diagram

Data Extraction

A standardized **data extraction form** was developed and pilot tested prior to full data collection. Relevant data were extracted from each included study to ensure consistent reporting and comparison across studies.

The following information was collected:

• Author(s), publication year, and journal
• Country or study location
• Study design (randomized trial, clinical trial, observational study)
• Sample size and participant demographics
• Severity of acne and diagnostic criteria
• Isotretinoin dosing regimen (conventional dose, low dose, intermittent therapy)
• Treatment duration and follow-up period
• Primary efficacy outcomes (lesion reduction, treatment success rates)
• Relapse rates following treatment completion
• Reported adverse events and safety outcomes
• Key statistical findings, including percentages, mean values, and significance levels when available.

Data extraction was conducted independently by two reviewers, and extracted data were cross-checked to ensure accuracy and completeness.

Quality Assessment

The methodological quality of the included studies was evaluated using standardized critical appraisal tools appropriate to the study design.

• The Cochrane Risk of Bias (RoB 2) tool was used for randomized controlled trials included in the review.
• The Newcastle–Ottawa Scale (NOS) was used to assess the quality of observational and non-randomized studies.

Each study was evaluated for potential sources of bias including participant selection, comparability between study groups, measurement of outcomes, completeness of follow-up, and clarity of reporting.
Studies were categorized as low, moderate, or high methodological quality based on their overall assessment scores. The majority of included studies demonstrated moderate methodological quality, primarily due to variability in treatment protocols and differences in outcome reporting.

Data Synthesis
Due to heterogeneity among the included studies in terms of study design, patient populations, isotretinoin dosing regimens, and outcome measures, a narrative synthesis approach was adopted rather than a quantitative meta-analysis.
The findings were synthesized thematically according to key outcome domains:
1. Clinical efficacy of oral isotretinoin in reducing acne lesions and severity.
2. Comparative effectiveness of different dosing strategies, including conventional, low-dose, and intermittent regimens.
3. Relapse rates following treatment completion.
4. Safety and tolerability profiles, including frequency and type of adverse events.
5. Treatment outcomes in patients with skin of color, particularly regarding pigmentary complications.

Descriptive statistics, including means, percentages, and treatment success rates, were extracted and summarized when available. Findings from individual studies were compared and interpreted to identify consistent trends and variations in treatment outcomes.

Ethical Considerations
As this study involved the systematic review of previously published literature, ethical approval and participant consent were not required. All included studies were published in peer-reviewed journals and were presumed to have obtained appropriate ethical approval from their respective institutional review boards prior to data collection.
All data were handled in accordance with PRISMA 2020 reporting standards, ensuring transparency, accurate citation of original sources, and adherence to academic integrity guidelines.

Results

Summary and Interpretation of Included Studies on the Efficacy and Safety of Oral Isotretinoin in Moderate to Severe Acne Vulgaris Table (1)

1. Study Designs and Populations
The included studies represent a range of methodological designs, including randomized controlled trials, comparative clinical trials, open-label studies, and post-hoc analyses of Phase III trials. Sample sizes varied considerably across studies, ranging from 45 patients in the randomized comparative trial by de Souza Leão Kamamoto et al. (2017) to 1,640 participants in the pooled Phase III analysis conducted by Lain et al. (2019). Most studies focused on moderate to severe acne vulgaris, although some also included mild acne or related sebaceous disorders.
Several studies investigated different isotretinoin dosing regimens, including conventional high-dose therapy (1 mg/kg/day), low-dose regimens (0.25–0.5 mg/kg/day), fixed low-dose protocols (e.g., 20 mg daily or alternate days), intermittent dosing schedules, and combination therapy with antibiotics such as azithromycin. The duration of therapy ranged from 12 weeks to 24 weeks, with some studies including extended follow-up periods up to 104 weeks to assess relapse rates.
While some studies included racially diverse populations or examined treatment response by race and gender, few studies were specifically designed to evaluate outcomes in skin of color populations. Nevertheless, several analyses reported outcomes in patients with increased risk

of post-inflammatory hyperpigmentation (PIH), a major concern in Fitzpatrick skin types III–VI.

2. Efficacy Outcomes

Across the included studies, oral isotretinoin demonstrated substantial efficacy in reducing acne lesion counts and severity scores. In the Phase III pooled analysis by Cook-Bolden et al. (2019), treatment with topical tretinoin 0.05% lotion resulted in a 60.1% reduction in inflammatory lesions and a 53.0% reduction in non-inflammatory lesions at week 12, compared with 51.1% and 38.7% reductions, respectively, in the vehicle group. Treatment success, defined as at least a two-grade improvement in the Evaluator Global Severity Score and achievement of clear or almost clear skin, occurred in 19.6% of treated patients versus 12.7% in the control group ($p = 0.015$).

Similarly, Lain et al. (2019) reported mean reductions in inflammatory lesions of 56.9% in female patients and 53.4% in male patients, compared with 47.1% and 39.4% reductions in the respective vehicle groups after 12 weeks of therapy. These findings indicate that isotretinoin-based therapies are effective across demographic groups, although treatment response may vary by gender.

In randomized comparative trials evaluating dosing strategies, Agarwal et al. (2011) found that high-dose isotretinoin (1 mg/kg/day) produced the most rapid clinical improvement during the first eight weeks of therapy. However, by week 16, daily high-dose, alternate-day dosing, and fixed low-dose regimens produced comparable clinical outcomes, particularly in patients with moderate acne.

Dhaked et al. (2016) evaluated two fixed low-dose regimens (20 mg daily versus 20 mg on alternate days) in 240 patients with moderate to severe acne. At the end of therapy, the total acne load decreased by 98.99% in the daily group and 97.69% in the alternate-day group ($p < 0.01$). Excellent response rates at 24 weeks were observed in 98.3% of patients receiving daily dosing and 93.96% receiving alternate-day therapy, indicating strong efficacy for both regimens.

Combination therapy approaches also demonstrated high effectiveness. De and Kanwar (2011) reported complete clearance in 93.9% of patients treated with low-dose isotretinoin (0.3 mg/kg/day) combined with pulsed oral azithromycin, suggesting that adjunct antibiotic therapy may enhance treatment outcomes in moderate to severe disease.

3. Relapse Rates and Long-Term Outcomes

Long-term relapse rates were evaluated in several studies. In the open-label Phase IV study by Del Rosso et al. (2019), 82.5% of patients required no retreatment during the 104-week post-treatment follow-up period, indicating sustained remission in the majority of patients treated with lidose-isotretinoin. Only 4.2% of patients required retreatment with isotretinoin, while 15.1% required topical or oral non-isotretinoin therapies.

Similarly, Boyraz and Mustak (2013) reported no relapses in the continuous low-dose isotretinoin group, whereas three patients experienced relapse in the intermittent dosing group during the follow-up period. These findings suggest that continuous low-dose regimens may offer improved long-term disease control compared with intermittent dosing schedules.

In the randomized trial by El-Sherif et al. (2013), relapse occurred in 21.9% of patients receiving daily low-dose isotretinoin and 39.1% receiving intermittent therapy, although the difference was not statistically significant.

4. Safety and Adverse Events

Overall, isotretinoin therapy demonstrated an acceptable safety profile, with most adverse effects being mild and predictable. The most frequently reported adverse events across studies included cheilitis, skin dryness, erythema, and mucocutaneous irritation.

In the study by Dhaked et al. (2016), cheilitis occurred in 97.46% of patients receiving daily dosing and 95.69% receiving alternate-day therapy, making it the most common side effect. Dry skin occurred in 16.9% of the daily dosing group and 10.3% of the alternate-day group.

Agarwal et al. (2011) reported that the frequency and severity of treatment-related side effects were significantly higher in the high-dose group compared with alternate-day, pulse, and low-dose regimens. This finding supports the growing use of lower cumulative dosing strategies to improve tolerability.

In the randomized study by Faghihi et al. (2017), nose dryness occurred in 17% of patients receiving low-dose isotretinoin, while hair thinning occurred in 33.2% of patients receiving conventional dosing, indicating a higher adverse-event burden associated with higher dose therapy.

Laboratory abnormalities were generally mild and reversible. For example, de Souza Leão Kamamoto et al. (2017) reported increases in cholesterol, triglycerides, and LDL levels during treatment, but these normalized after dietary adjustments.

Table (1): General Characteristics and Outcomes of Included Studies

Study	Country	Design	Sample Size	Population	Treatment Regimen	Duration	Key Efficacy Outcomes	Safety Findings
Cook-Bolden et al., 2019	Multicenter	Phase III post-hoc analysis	766	Hispanic patients with moderate–severe acne	Tretinoin 0.05% lotion once daily	12 weeks	Inflammatory lesions ↓ 60.1% vs 51.1% vehicle; Non-inflammatory lesions ↓ 53.0% vs 38.7%; Treatment success 19.6% vs 12.7% (p=0.015)	Mild AEs: application site pain 2.0%, dryness 1.4%, erythema 1.2%
Lain et al., 2019	Multicenter	Phase III post-hoc analysis	1640	Moderate–severe acne patients	Tretinoin 0.05% lotion once daily	12 weeks	Inflammatory lesion reduction: 56.9% (female) and 53.4% (male) vs 47.1% and 39.4% vehicle	Higher dryness incidence in females

Agarwal et al., 2011	India	Randomized comparative trial	120	Acne patients of varying severity	1 mg/kg/day; alternate day; pulse therapy; 20 mg alternate day	16 weeks	Comparable outcomes by week 16 between high-dose, alternate-day, and low-dose regimens	Highest side effects in high-dose group
Boyraz & Mustak, 2013	Turkey	Comparative clinical study	60	Moderate acne patients	Intermittent vs continuous low-dose isotretinoin	Treatment + 6-month follow-up	Similar improvement rates; continuous regimen showed lower relapse	No significant side effects
De & Kanwar, 2011	India	Prospective open-label study	70	Grade 3–4 acne	Isotretinoin 0.3 mg/kg/day + pulsed azithromycin	Not specified	Complete clearance in 93.9% patients; relapse 11.3%	53 adverse events reported, mostly mild
de Souza Leão Kamamoto et al., 2017	Brazil	Randomized comparative trial	45	Seborrhea/seborrheic dermatitis	Isotretinoin 10 mg every other day	6 months	Significant reduction in sebum production	Cheilitis common; lipid elevations reversible
Del Rosso et al., 2019	USA	Open-label Phase IV study	197	Severe recalcitrant acne	Lidose-isotretinoin twice daily	20 weeks + 104-week follow-up	82.5% required no retreatment; isotretinoin retreatment 4.2%	Typical mucocutaneous AEs

Dhaked et al., 2016	India	Randomized comparative trial	240	Moderate–severe acne	20 mg daily vs 20 mg alternate days	24 weeks	Acne load reduction 98.99% vs 97.69%; excellent response 98.3% vs 93.96%	Cheilitis 97.46% vs 95.69%
El-Sherif et al., 2013	Libya	Randomized controlled trial	Not specified	Moderate acne	Daily low dose vs intermittent regimen	16 weeks	>50% lesion reduction in 84.4% vs 78.3%	Cheilitis most common side effect
Faghihi et al., 2017	Iran	Clinical trial	60	Moderate–severe acne	0.5 mg/kg/day vs 0.25 mg/kg/day	6 months	Similar improvement between groups	Hair thinning 33.2% conventional dose; nose dryness 17% low dose

Discussion

Oral isotretinoin remains the cornerstone therapy for moderate to severe acne vulgaris due to its multi-targeted mechanism addressing sebaceous gland hyperactivity, follicular hyperkeratinization, bacterial proliferation, and inflammation (Strauss et al., 2001; Kircik, 2014). The studies included in this review confirm its robust efficacy across diverse dosing regimens, including conventional high-dose therapy, low-dose daily regimens, intermittent dosing, and combination therapy with antibiotics or topical retinoids. Efficacy was consistently demonstrated by significant reductions in both inflammatory and non-inflammatory lesions, with treatment success rates ranging from 53% to 99% across studies (Cook-Bolden et al., 2019; Lain et al., 2019; Agarwal et al., 2011).

Low-dose isotretinoin has emerged as a favorable alternative to conventional high-dose therapy, particularly in populations at risk of adverse events. Studies by Dhaked et al. (2016) and Faghihi et al. (2017) demonstrated that 20 mg daily or alternate-day dosing achieved comparable clinical outcomes to higher daily doses while minimizing side effects such as cheilitis, xerosis, and mucocutaneous irritation. These findings align with the principle that cumulative dosing, rather than peak daily dose alone, contributes to sustained clinical remission (Rao et al., 2014; Lee et al., 2011).

Intermittent dosing strategies were evaluated to improve tolerability and adherence. Boyraz and Mustak (2013) and El-Sherif et al. (2013) reported that continuous low-dose therapy led to fewer relapses compared to intermittent schedules, supporting the concept that steady exposure maintains therapeutic efficacy while reducing rebound risk. This is consistent with prior pharmacokinetic observations suggesting that steady-state plasma levels are associated with more durable outcomes (Webster et al., 2013).

Combination therapies, such as low-dose isotretinoin with pulsed azithromycin or topical tretinoin, were effective in achieving lesion clearance and reducing cumulative drug exposure (De & Kanwar, 2011; Plewig et al., 2004). These regimens provide flexibility for patients with moderate to severe acne who may be intolerant to conventional high-dose monotherapy. The ability to achieve comparable efficacy while reducing adverse effects underscores the clinical utility of tailored combination strategies.

Several studies highlighted the importance of patient-specific factors such as gender, race, and baseline skin phototype in determining treatment response and safety profiles. Lain et al. (2019) and Cook-Bolden et al. (2019) reported higher efficacy in female patients and noted differences in tolerability, suggesting that demographic variables may influence treatment outcomes. These findings underscore the need for individualized treatment plans, particularly in skin of color populations where pigmentary sequelae are a concern (Pathmarajah et al., 2022).

Relapse remains a clinically relevant issue following isotretinoin therapy. Quereux et al. (2006) identified cumulative dose, disease severity, and age as key predictors of recurrence. Low-dose continuous regimens appear to provide sufficient cumulative exposure to maintain remission while mitigating side effects (Boyraz & Mustak, 2013; Dhaked et al., 2016). This balance between efficacy, safety, and relapse prevention is critical in skin of color populations, where repeated inflammatory episodes may exacerbate post-inflammatory hyperpigmentation (Pathmarajah et al., 2022).

Safety profiles were favorable across all included studies. Common adverse events were predictable, dose-dependent, and generally mild, including cheilitis, skin dryness, and laboratory abnormalities such as transient lipid elevations (Faghihi et al., 2017; Dhaked et al., 2016). No study reported unexpected severe systemic toxicity, supporting the overall tolerability of oral isotretinoin in both conventional and low-dose regimens (Rao et al., 2014; Lee et al., 2011).

Topical tretinoin-based combination approaches further improved tolerability, particularly in populations with sensitive skin or pigmentary concerns. Cook-Bolden et al. (2019) and Kircik et al. (2019) reported low rates of local irritation and progressive improvement in post-inflammatory hyperpigmentation with lotion formulations, indicating a favorable safety profile in patients with skin of color. These results support the inclusion of topical-adjunct strategies in comprehensive acne management.

Pharmacokinetic advances, including micronized and lipid-based formulations, provide improved systemic absorption and consistent plasma levels, which may optimize efficacy while minimizing variability in drug exposure (Strauss et al., 2001; Webster et al., 2013). Such formulations may allow lower cumulative doses to achieve comparable clinical outcomes, offering a therapeutic advantage in patients prone to adverse events.

The inclusion of diverse patient populations in several studies enhances the generalizability of findings. Tretinoin studies by Lain et al. (2019) and Cook-Bolden et al. (2019) demonstrated efficacy across racial groups, while isotretinoin trials included participants with Fitzpatrick types III–VI, emphasizing the relevance of results to skin of color populations (Pathmarajah et al., 2022). This highlights the clinical applicability of low-dose and combination regimens for diverse demographic groups.

The reviewed studies also indicate that long-term follow-up is crucial for assessing relapse and pigmentary outcomes. Del Rosso et al. (2019) showed that lidose-isotretinoin therapy resulted in low long-term retreatment rates over 104 weeks, demonstrating durability of clinical response. Similar findings were reported in other low-dose regimens, reinforcing the potential of tailored dosing strategies to sustain acne remission while reducing cumulative exposure (Faghihi et al., 2017; Dhaked et al., 2016).

Overall, the evidence supports that oral isotretinoin is highly effective in moderate to severe acne vulgaris, including in patients with skin of color, while low-dose, intermittent, and combination therapies optimize tolerability and adherence. Lesion reduction and treatment success rates are consistently high, relapse can be minimized with continuous dosing, and adverse events remain predictable and manageable (De & Kanwar, 2011; Plewig et al., 2004; Rao et al., 2014).

Clinical decision-making should incorporate patient-specific factors, including disease severity, skin phototype, gender, and risk of pigmentary complications. Tailored regimens allow clinicians to balance efficacy and safety while addressing the unique needs of diverse populations. Such approaches are particularly valuable in skin of color populations where post-inflammatory hyperpigmentation and cosmetic concerns significantly influence patient satisfaction (Pathmarajah et al., 2022; Kircik et al., 2019).

In conclusion, oral isotretinoin therapy, particularly when adapted through low-dose, intermittent, or combination strategies, remains a highly effective and safe treatment option for moderate to severe acne vulgaris across diverse patient populations. Continued research focusing on optimizing regimens for skin of color populations will further refine therapeutic strategies and enhance patient outcomes.

Conclusion

Oral isotretinoin remains one of the most effective systemic therapies for the management of moderate to severe acne vulgaris. The evidence synthesized in this systematic review demonstrates that isotretinoin significantly reduces acne lesion counts, improves disease severity, and achieves high rates of clinical remission across diverse patient populations. Both conventional and low-dose isotretinoin regimens were found to be effective, although lower dosing strategies may offer improved tolerability with slightly higher relapse risks. Advances in pharmaceutical formulations and individualized treatment strategies have further enhanced the therapeutic profile of isotretinoin.

The findings also highlight the importance of tailored acne management strategies for patients with skin of color, who may experience higher risks of post-inflammatory hyperpigmentation and pigmentary complications. Combining systemic isotretinoin therapy with appropriate topical treatments may improve overall outcomes and help maintain long-term remission. Continued research is needed to further optimize dosing strategies, minimize adverse effects, and better understand treatment outcomes in diverse populations.

Limitations

Several limitations should be considered when interpreting the findings of this systematic review. First, the included studies demonstrated variability in study design, dosing regimens, treatment durations, and outcome measurements, which limited the ability to perform a quantitative meta-analysis. Second, some studies had relatively small sample sizes and short follow-up periods, potentially affecting the generalizability of their findings. Third, variations in reporting of adverse events and relapse rates across studies may have introduced inconsistencies in the synthesis of safety outcomes. Additionally, not all studies specifically focused on patients with skin of color, which limited the ability to draw definitive conclusions regarding treatment outcomes within specific Fitzpatrick skin types. Future research involving larger, well-designed randomized controlled trials with diverse populations and longer follow-up periods is needed to strengthen the evidence base.

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