

MESTRADO INTEGRADO EM MEDICINA

Spironolactone in the treatment of acne in adult women: Systematic review

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M

2025

ÁREA: Medicina Clínica

TIPOLOGIA: Dissertação

TRABALHO EFETUADO SOBRE A ORIENTAÇÃO DE:

Professora Doutora Sofia Magina

TRABALHO ORGANIZADO DE ACORDO COM AS NORMAS DA REVISTA:

International Journal of Dermatology

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Dermatologia e doenças venéreas

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Spironolactone in the treatment of acne in adult women: Systematic review

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Dedicatória

O caminho foi longo, mas nunca solitário.

À minha família por estarem sempre do meu lado. Aos meus amigos por todos os momentos partilhados. À minha orientadora pela orientação e confiança.

Este trabalho também é vosso,

Obrigada

Spironolactone in the treatment of acne in adult women: Systematic review

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Conflicts of interest: The authors declare no conflicts of interest.

Funding Sources: This study was not supported by any grants or funding.

Running Head: Spironolactone in the treatment of acne in adult women: Systematic review

Keywords: Spironolactone (MeSH), Acne vulgaris (MeSH), Acne (MeSH), Facial acne (MeSH), Women (MeSH), Female (MeSH), Adult (MeSH), Anti-androgenic (MeSH), Systematic review (MeSH).

Total Word Count: 4625

Figure count: 3

Table count: 3

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Abstract

Acne, the eighth most prevalent disease globally, significantly impacts quality of life, particularly in adult women, where hormonal factors play a key role. Spironolactone, an androgen receptor antagonist, has emerged as a promising treatment for acne by reducing sebum production and inflammation. Despite its off-label use, spironolactone is increasingly recommended as an alternative to antibiotics, especially amid rising antimicrobial resistance. This systematic review synthesizes evidence from studies published between 2010 and 2024 to evaluate spironolactone's efficacy in treating adult female acne.

High-quality, studies, such as the 2023 Santer/SAFA trial have provided robust evidence for spironolactone's efficacy at doses below 200 mg/day, resolving prior uncertainties identified in the 2017 review by Layton. Current findings indicate significant improvements in acne severity, particularly in moderate to severe cases, with doses near 100 mg/day.

Despite these advancements, methodological limitations, including varied assessment tools and high follow-up loss, hinder definitive conclusions. Future research should prioritize standardized methodologies, long-term maintenance studies, and subgroup analyses, particularly in populations with polycystic ovary syndrome (PCOS) or cyclical acne. Spironolactone's unique profile as a hormonal and anti-inflammatory agent positions it as a first-line option for antibiotic-resistant or recurrent female acne. This review underscores its potential for on-label approval and highlights the need for further research to optimize its use in clinical practice.

KEYWORDS: Spironolactone (MeSH), Acne vulgaris (MeSH), Acne (MeSH), Facial acne (MeSH), Women (MeSH), Female (MeSH), Adult (MeSH), Anti-androgenic (MeSH), Systematic review (MeSH).

Acne-QoL - Acne-Specific Quality of Life Questionnaire; AE – Adverse Effects; AFSAT – Acne-Free Self-Assessment Tool; ASI – Acne Severity Index; CADI – Cardiff Acne Disability Index; CASS – Comprehensive Acne Severity Scale; CI – Confidence Interval; COCs – Combined Oral Contraceptives; CR – Complete Response; D – Day(s); ECLA – Échelle d'évaluation clinique de l'acné (Clinical Acne Assessment Scale) ; EDF S3-European Dermatology Forum guideline for the treatment of acne (grade) ; E.g. Exempli gratia/For example; EQ-5D – EuroQol 5-Dimension (health-related quality of life scale); FDA – U.S. Food and Drug Administration; Fig. – Figure; GEA – Global Evaluation Acne; Gen – Generation; ID – Identification; IGA – Investigator's Global Assessment; IUD – Intra-uterine device; ITT – Intention-to-Treat; Mg- milligrams; M – Month; mITT – Modified Intention-to-Treat; N – Number; NSS – Not Statistically Significant; OC – Oral Contraceptive; OR – Odds Ratio; P – P-Value; PCOS – Polycystic Ovary Syndrome; PGA - participant's global assessment; PICOs – Population, Intervention, Comparison, Outcome(s); PP – Per Protocol; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL – Quality of Life; QALY – Quality Adjusted Life Years; R – Retinoid; RCT – Randomized Clinical Trial; RoB 2.0 – Risk of Bias 2.0 (Cochrane tool for RCTs); ROBINS-I – Risk Of Bias in Non-randomized Studies of Interventions; SAFA – Spironolactone for Adult Female Acne; SD – Standard Deviation; SL – Spironolactone; SPL – Spironolactone; SS – Statistically Significant; T3R – Time To Treatment Results; W – Week; Y – Years

Introduction

Acne is the eighth most prevalent disease globally, affecting millions across various age groups and contexts (1). This condition significantly impacts quality of life, leading to psychological and emotional consequences, including depression, anxiety, and social isolation (1). Although commonly associated with adolescence, acne can persist or reappear in adulthood, often exacerbated by hormonal changes—particularly in androgens, which stimulate sebaceous glands to produce excess sebum (2). Beyond hormonal factors, acne in adult women is influenced by genetic and environmental factors, creating a complex interaction that often proves resistant to conventional therapies (3).

One promising treatment targeting the hormonal factor is spironolactone, an antagonist of androgen and mineralocorticoid receptors. By inhibiting androgenic action, spironolactone reduces sebum production, helping control inflammation and reduce lesion formation (4). Originally developed for treating hypertension and heart failure, spironolactone has seen extensive off-label use in managing acne in adult women, particularly in cases resistant to conventional treatments like antibiotics and combined oral contraceptives (COCs) (4).

Despite spironolactone's documented efficacy in acne treatment, its dermatological use remains off-label, as it lacks formal regulatory approval—such as from the U.S. Food and Drug Administration (FDA)—for this specific indication (5). The first comprehensive hybrid systematic review of spironolactone for acne in adult women, conducted in 2017 by Layton, provided a detailed analysis of its efficacy in this population (3), though under 200 mg dosages lagged in terms of confirmation.

However, this review underscored the need for more high-quality, randomized clinical trials, particularly in the sub 200mg range, given the limitations in sample size and rigor of available studies prior to Santer (6), acclaimed top 20 study (7). In subsequent years, narrative reviews updated the evidence, confirming spironolactone's therapeutic potential but lacking the methodological rigor required for definitive conclusions. This further emphasized the necessity for more robust studies.

This updated review brings forth results that reinforce spironolactone's potential as a promising therapeutic alternative, even in the sub 200mg range, especially considering the rising bacterial resistance associated with prolonged antibiotic use in acne management.

Given growing concerns regarding antimicrobial resistance and the recommendation to limit prolonged antibiotic use (8), recent clinical guidelines, including those from the American Academy of Dermatology, as recently as 2024, now recommend spironolactone as a safe and effective option for treating acne in adult women (5). Despite these promising study outcomes, guidelines and practice, it remains essential to consolidate and update the scientific evidence on spironolactone's efficacy, and its effective dosage to provide clearer clinical guidance.

This systematic review seeks to synthesize the latest evidence on the efficacy of oral spironolactone in treating acne in adult women. Through a comprehensive analysis of studies published between 2010 and 2024, this review aims to provide a solid foundation for evidence-based practices in managing acne vulgaris within this specific population.

Materials and Methods

To conduct this review, we strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, ensuring a systematic and unbiased process. The methodological approach aimed to include relevant and high-quality studies.

We included randomized clinical trials, observational studies, and case series that investigated the efficacy of oral spironolactone in treating acne vulgaris in adult women aged 18 years or older. Selected studies were required to report clinical data on acne lesion improvement, quality of life enhancement, or other clinical outcomes associated with spironolactone use. Additionally, studies combining oral spironolactone with other topical acne treatments, such as benzoyl peroxide or retinoids, were included if their primary focus was on the efficacy of spironolactone in treating acne vulgaris.

The following studies were excluded:

- a) Studies assessing topical formulations of spironolactone or using it to treat other clinical conditions, such as polycystic ovary syndrome, hirsutism, or alopecia, even if these conditions were associated with acne, as well as those focused on safety or potassium control.
- b) Studies focusing exclusively on adolescents or including participants under 18 years of age. However, studies with a mixed age range (including those under 18) were considered if they included subgroup analyses focusing solely on adult women (≥ 18 years).
- c) Studies involving male participants, animal studies, or in vivo studies.

d) Systematic reviews, narrative reviews, conference reports, congress abstracts and letters to the editor.

e) Publications in languages other than English, as they would not be accessible for analysis in this review.

f) Duplicate studies or studies that did not provide sufficient data on the interaction of spironolactone with acne vulgaris treatment.

This careful approach was adopted to ensure the review focused exclusively on studies that directly addressed the efficacy of spironolactone in treating acne in adult women, allowing for a robust analysis

The search was conducted in the Web of Science, PubMed, and Scopus databases through September 2024, covering the period from 2010 to 2024. This timeframe was selected due to the marked increase in the use of spironolactone for acne treatment since 2010, reflecting shifts in global clinical practice. The chosen databases were prioritized for their comprehensive coverage of biomedical research and high relevance to dermatology studies. Reference lists of included articles were also manually reviewed to identify any additional studies.

The search strategy included the terms: "spironolactone" AND ("acne vulgaris" OR "acne" OR "facial acne") AND ("women" OR "female" OR "adult"). Automatic filters limited studies to those published between 2010 and 2024 and restricted results to articles in English. The search strategy was adjusted for each database according to its specific filters and features.

The study selection was conducted in three phases: initial title screening based on relevance to the topic, abstract evaluation focusing on alignment with inclusion criteria, and full-text review to confirm eligibility and extract detailed data. Two independent

reviewers conducted each phase, and in case of discrepancies, a third reviewer was consulted for resolution. The Rayyan tool was used to manage search results and automatically remove duplicates. Studies not meeting the inclusion criteria were excluded with clear justifications and documented in the PRISMA flowchart (Figure 1).

Data extraction was independently performed by two reviewers using a standardized form. Extracted information included publication title, year, lead author, study design, and participant characteristics (number of participants randomized and completed, age, location, acne severity, and treatment history). Details on the treatment regimen (daily dose of spironolactone, treatment duration, and concomitant therapies) and primary and secondary outcomes were also collected. In case of discrepancies, a third reviewer was consulted to resolve differences.

Risk of bias assessment was conducted according to study type. The Cochrane Risk of Bias 2.0 (RoB 2.0) tool was used for randomized clinical trials, and the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool was used for observational studies. Two independent reviewers assessed the risk of bias, categorizing studies as low, moderate, or high risk. Any discrepancies were resolved by a third reviewer. The bias assessment results were reported in detail.

Due to the heterogeneity of the included studies in terms of methodologies and outcomes, a narrative synthesis of the results was conducted. The heterogeneity primarily stemmed from differences in study designs (e.g., randomized trials vs. observational studies), variability in dosing regimens, treatment durations, and outcome measures used to assess efficacy. Studies were grouped based on shared characteristics, such as outcomes analyzed, and compared in terms of spironolactone's efficacy in treating acne. Meta-analysis was not feasible, but results

were presented in a tabular and descriptive format to ensure a clear and rigorous presentation of the findings.

Results

The initial research conducted across the databases of PubMed, Web of Science, and Scopus yielded a total of 1,223 articles. Subsequently, filters regarding the publication period (2010-2024) and language (English) were applied to narrow down the results. After the automatic filters were implemented and 216 duplicates removed, 474 titles were screened through the analysis of titles and abstracts, adhering to relevance criteria based on the study's objective, which focused on adult female acne treated with spironolactone. Studies involving differing interventions or populations beyond the defined scope were excluded at this stage. Following this preliminary screening, 15 articles were selected for full-text review. Ultimately, 8 studies met the inclusion criteria. Seven studies were excluded for the following reasons: four were discarded for including patients under the age of 18 without a clear sub-analysis for this demographic, limiting the generalizability of results to the adult population; one study was excluded for employing isotretinoin in conjunction with spironolactone, complicating the identification of the isolated impact of spironolactone; another was excluded due to outcomes deemed irrelevant to the review's aim, such as Quality Adjusted Life Years (QALY); and finally, one study was identified as a duplicate, representing a redundant inclusion of the same data. The selection process was meticulously detailed and illustrated in a PRISMA diagram, ensuring methodological transparency (Fig. 1).

[Fig.1.]

The studies encompassed a total of 1,639 adult women aged between 18 and 66 years, diagnosed with moderate to severe acne. The interventions varied, with dosages of spironolactone ranging from 25 to 200 mg/day, administered either in isolation or in conjunction with topical therapies such as retinoids and benzoyl peroxide. Treatment durations fluctuated between 3 to 132 months. Notable differences were observed among the population profiles, including the inclusion of women with prior conditions, such as relapses post-isotretinoin or concurrent use of oral contraceptives, which may have influenced the outcomes. Furthermore, disparities in acne severity and the scales employed for assessment complicated direct comparisons among the studies. The populations varied significantly in terms of acne severity and prior treatment experiences with agents such as isotretinoin or oral antibiotics.

Prior to presenting the results, and as a caveat while reading them, we present the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Fig.2) and Robins-I (Fig3). We further point to some of the elements that justify the grade provided in this review.

[Fig.2]

Santer's SAFA clinical trial (6) (Effectiveness of Spironolactone for Women with Acne Vulgaris), recognized as one of the "Top Studies of 2023" (7) for clinical practice. This multicenter, phase 3, double-blind, randomized trial (6) presents no risk bias and sets the standard for further studies, for the others, some issues presented in the discussion might limit the interpretation of some conclusions.

[Fig.3]

While ROBINS-I emphasizes the importance of assessing the timing of intervention initiation relative to study follow-up, it's crucial to acknowledge that strict adherence to this criterion might unfairly penalize retrospective cohort studies. In this study, we assessed the risk of bias related to this domain considering the specific research question and the feasibility of obtaining precise data on intervention timing in a retrospective setting.

Regarding participant attrition, we observed a “normal” loss to follow-up leaving just shy of 70%, while lower than ideal thresholds of 80% or even 90%, it is comparable to the rates reported in other studies in this field. For instance, Santer (6), a large and influential RCT in this area, reported a similar loss to follow-up at 24 weeks. Based on this context, we judged the risk of bias due to missing data as moderate in cases where that happened.

We acknowledge that the relatively small sample size ($n=50$) of the only study with a low assessed risk of bias under Robins I may limit the generalizability of our findings. However, given the preliminary nature of this study and the challenges of conducting research in this specific area, we believe that the potential insights gained from this analysis warrant its inclusion in the literature. Future studies with larger sample sizes are needed to confirm these findings

First and foremost, general information concerning the reviewed studies can be found in the, condensed Table 1. PICO's. For physicians and alike investigators, it is strongly advised the consultation of the supplementary material, full figures/tables, under Supporting Information, that extend and detail the information regarding each study beyond the media constraints, as Supplementary Table 1. FULL PICO's and presents a tool we found useful Supplementary Table 2. T3R-Time To Treatment Results, that details, additional most of the relevant outcomes in a standardized time grid.

Roberts (9) found 91.4% of patients demonstrated clinical improvement with a median dose of 100 mg (range: 25–200 mg), including 66.1% achieving complete response (CR $\geq 90\%$). Acne responded favorably across all severity grades, with median response times of 3 months for initial and 5 months for maximum response. Notably, 64.6% achieved CR in grade 4 acne. Lessner (10) reported 85.4% of patients achieving results rated as “good,” “excellent,” or “clear” during long-term treatment (starting at 50 mg, adjusted up to 200 mg), with 63.4% eventually reaching “excellent” or “clear.” Isvy-Joubert (11) reliably observed 71% remission with using stringent criteria (≤ 5 comedonal and ≤ 2 inflammatory lesions) in 70 women after six months at 150 mg, alongside significant reductions in seborrhea (72.9%). Sanai (12) reported a 73.07% reduction in Acne Severity Index (ASI) ($p \leq 0.001$) and a significant decrease in serum testosterone (74% to 16%; $p \leq 0.001$) after three months of 100 mg/day treatment and follow-up.

Garg's retrospective study (13) of 403 women found 96% achieved complete acne clearance after up to two years of 100 mg/day treatment, though only 56% remained at 24 months, a mean drug survival of 470 days should also be mentioned. Initial success rates at 3–5.9 months were 75.5% (face), 84% (chest), and 80.2% (back),

with improvements in the Comprehensive Acne Severity Scale (CASS) of 1 point (face), 0.5 (trunk), and 0.8 (back). However, a 23% follow-up loss and concurrent contraceptive/antibiotic use complicate interpretation. Patiyasikunt's RCT (14) reported 75% clinical success in the SPL50 group at week 12 (OR: 7.0; $p = 0.01$), though no significant difference in acne count. Santer (6) found 32% success in the spironolactone group vs. 11% in placebo (OR: 3.76; $p \leq 0.001$) on IGA, with significant Acne-QoL improvements (3.45 points; $p \leq 0.001$). By 24 weeks, 82% in the spironolactone group reported global improvement vs. 63% in placebo (OR: 2.72; $p < 0.001$). Despite robust findings, exclusion of half the planned participants raises generalizability concerns.

Dréno (15) compared spironolactone (150 mg/day for six months) to doxycycline (100 mg/day for three months, then placebo). Spironolactone showed greater efficacy in reducing inflammatory lesions (OR: 2.87; $p = 0.007$) and improved quality of life (CADI), with pronounced trunk lesion reduction. However, the reduced sample size (133 vs. planned 182) and differing treatment durations limit comparability.

Combination therapies were also effective. Lessner (10) found spironolactone (50–100 mg/day) with topical retinoids superior to oral antibiotics in cyclic acne. Roberts (9) and Garg (13) noted fewer adverse events with concurrent COCs (OR: 0.23; 95% CI: 0.11–0.50). Patiyasikunt (14) highlighted challenges in isolating spironolactone's efficacy at lower doses due to confounding factors like benzoyl peroxide, while Isvy-Joubert (11) found 1st and 2nd Generation COC, significantly impacted success compared to 3rd and 4th Generation (OR = 0.27; 95% CI: 0.10–0.77; $p = 0.01$).

Adverse events were generally mild. Menstrual irregularities were most common (30% in Patiyasikunt (14); $p = 0.013$, reduced with COCs (OR: 0.23; Garg (13)). Headaches

(20% vs. 12%; $p = 0.02$) and dizziness (24%; $p = 0.039$) were also reported. Hypotension, cramps, and weakness occurred without significant clinical impact. Isolated cases of abdominal pain, gastric reflux, and breast discomfort were noted in Dréno (15), with no treatment discontinuations. No significant hyperkalemia was observed, though isolated cases of subclinical hyperkalemia and polyuria occurred (Isvy-Joubert (11); Sanai (12)).

Retention rates varied. Santer (6) maintained >80% retention at 12 weeks, while Garg (13) and Lessner (10) faced up to 29% dropout, potentially due to adverse effects or lack of initial response. Patiyasikunt achieved adherence levels of 95% (14) and Sanai 100% (12) with frequent evaluations, suggesting intensive follow-up improves retention.

Discussion

Spironolactone has emerged as a promising therapeutic option for adult female acne. Despite its widespread, and growing (8), use, the literature presents a mix of robust studies and others with significant limitations, with the latest systematic review dating back to 2017 (3). Our systematic review updates that assessment with last decade's studies within scope.

Unlike the previous systematic review (3), that could find no robust evidence for under 200mg dose, current studies provide robust results. One of 2023's best studies (7), marked a pivotal advance, delivering statistically robust evidence for spironolactone's efficacy at ≤ 100 mg/day in moderate-to-severe acne, with a sample size justified by power calculations and improved side-effect documentation (6). This aligns with the call (3) for rigorous RCTs. Similarly, another RTC focused on the efficacy of low-dose spironolactone (14) reinforced effectiveness of 50mg/day in moderate acne. Also supporting this, the prospective study (12), lowest bias risk in cohort studies, where the strictest spironolactone monotherapy, showed significant improvements of a single intervention of 3 months, 100 mg/day, and an adequate follow up of 3 months that by itself confirms the effectiveness without concomitant use topical agent that inhibit comedogenesis. Other studies also present typical median doses close to 100 mg (9,13), and 150mg as a typical upper limit for reasonably certain efficiency in a vast majority of cases (11,15), well below the previous 200 mg threshold.

In terms of subgroups, we now have evidence that spironolactone is equally effective in body acne (13), also there is now evidence that testosterone level normalization continues even 3 months beyond treatment stop (12) even without COC, evidence also available for seborrhea treatment success (11) as in Papulopustular and nodulocystic

acne (9), Spironolactone seems particularly well suited for older, over 25 years, women (6), retinoid resistant acne (10,11) and presenting more inflammation (11), although all groups strongly benefit from treatment.

This provides an update to the evidence-based knowledge well within current off-label usage of spironolactone for acne, at 50-100mg/day. A final consideration regarding the initial dosing approach: in the largest RCT (6), starting with a lower dose (50 mg) did not reduce the high attrition rate observed at 24 weeks—an issue commonly seen in this field. Moreover, as the author herself noted, this lower starting dose likely compromised the 12-week results. A more effective approach would be to initiate treatment at 100 mg/day, with adjustments downwards if needed, or upwards depending on clinical response, as was frequently the case in all cohort studies (9,10,11,13).

Concerning duration of treatment, the previous review (3) noted that a 3-month treatment period may not be sufficient to achieve an optimal response to spironolactone in acne. The current review confirms that initial improvements typically occur around 3–4 months (6,9,11,15), while full results are usually seen after 5–6 months (5,9,11,15). A significant variability exists and patient expectation management is critical to assure correct duration and treatment adherence. A minimum treatment period of 12 weeks is confirmed. Although continued improvement 3 months beyond intervention was observed in a solid RTC study with concomitant benzoyl peroxide (15), the same did not occur in a prospective study (12) without any concomitant treatments; but both showed sustained results 3 months beyond intervention. This raises the possibility of implementing scheduled treatment pauses of up to 3 months, starting from week 12 onwards, or pauses triggered by adverse effects, potentially

without increasing the risk of acne recurrence. Confirmation of long-term tolerability, with new studies (9,11) confirming old (19), mean drug survival beyond a year also attest to that (13).

Regarding comparators, other than placebo, one might start by mentioning an RTC which asserts significant advantage, when used with benzoyl peroxide, to that topical treatment with a matched placebo (12) presenting significant superiority at 50mg and a non-significant signal that is worth exploring further at 25mg. But mainly a major, prestigious, double-blind clinical study (15) as another outstanding contribution. It compares the effectiveness of spironolactone (150 mg/day for six months) with doxycycline (100 mg/day for three months, followed by placebo for three months), allowing for a non-inferiority assessment. Oral antibiotics, particularly doxycycline, have long played a pivotal role in acne management, making it especially relevant that spironolactone was shown to be non-inferior in a good quality study, the previous review (3) had identified a study that pointed to equivalence to tetracycline but it was too small, too short and groups were significantly unbalanced. Furthermore, if non-inferiority is already achieved at 150 mg/day, one might reasonably expect even greater efficacy at doses closer to 200 mg/day, which are often required in severe cases, or still significant equivalence at 100mg for milder cases. It (15) also addresses the issue (3) of combined oral contraceptives (COCs), demonstrating spironolactone's superiority over doxycycline in all cases, regardless of the contraceptive method used (whether 1st- to 4th-generation oral contraceptives, intrauterine devices, or any other hormonal method).

However, a long-term retrospective study (11) provides the best available evidence on the role of COC generation and androgenicity in spironolactone efficacy with significant

results that low androgenicity, 3rd and 4th generation, COCs are superior to 1st and 2nd generation containing progestin that hinder spironolactone efficiency (11), these enhanced improvements, by adding spironolactone, also settle the question (3) of superiority of added spironolactone to COCs with antiandrogenic activity alone. Conversely, a bias free prospective study (12) offers a baseline for low-dose spironolactone treatment without COCs, reporting a very significant resolution of abnormal levels in serum testosterone ($p \leq 0.001$), particularly relevant as testosterone drives sebaceous gland activity in acne, with improvements that persisted even three months after treatment cessation.

There are still few studies directly comparing spironolactone with other key acne treatments. In particular, no further high-quality RCTs have been identified comparing spironolactone with isotretinoin (10,13) or antiandrogenic COCs (11), and the available evidence for these comparisons remains of lower quality.

Regarding long-term safety, while this review does not focus on spironolactone's safety profile, no significant changes to the current consensus have emerged. retrospective studies provide valuable insights, often with dosages above 100mg, in one such study of 814 female patients (9), with a mean treatment duration of 21.7 months (SD 22.4; median 13 months, range 3–132), only 25 patients (6.3%) discontinued spironolactone due to adverse effects, reinforcing the findings of a previously assessed one (10). Hyperkalemia remains rare and subclinical, unlikely to warrant routine monitoring in healthy young women without additional risk factors or reported side effects, such as muscle pain, weakness, and polyuria. As mentioned in the efficiency section, pauses without acne relapse (14,15) can be used to manage, often transient, adverse effects and improve tolerability and treatment adherence, although the most frequent side

effect, menstrual irregularities is most often solved by COCs (13). A final note on the importance of applying and clearly communicating the methodologies used for adverse effects collection and treatment evaluation (6,11,14).

In terms of study limitations and methodological issues, synthesizing these findings remains difficult, as noted in the methodology section, because heterogeneity is still common and complicates any attempt at synthesis. In a more specific comment to the studies presented we can say certain points should be mentioned, Double blind RCT represent a significant qualitative leap in methodological soundness. The way forward is through solid, well-balanced, and properly analyzed studies like the award-winning RCT (6). Another large RCT (15) received only a moderate assessment because, although it correctly determined the required group size based on expected power, it ultimately used smaller groups without acknowledging this deviation. Another way forward are smaller homogenous groups with adequate power, and the smaller RCT (14) only failed to attain results on the primary outcome, although luckily, not on the secondary one, due to a problem with its assumptions on control results, which can be a particular risk for these smaller studies.

Prospective studies were few, with only one available (12), and the ITT presented a small sample size. However, the choice of a single intervention, the absence of any concomitant treatments, and the ability to ensure long and complete follow-up made it a good initial baseline for evaluating spironolactone as a standalone treatment.

One final comment on the therapeutic efficiency signals, although the largest RCT (6) presents statistically significant results, it happens later on Acne-QoL/PGA (quality of life/disability score families) than IGA (objective grading by professionals), and the choice of primary indicator was the quality/disability score and the differences seen,

seems to confirm low correlation between the two approaches (16). Another study's attempt (15) to use EQ-5D, a nonspecific QoL score, points to their inadequacy when assessing acne treatment compared to QoL or CADI.

If more detailed information on selected subgroups from some of these studies becomes available a metanalysis would be possible; however, this is not feasible with the currently available data.

Retrospective cohorts always pose a bigger challenge, and if some present a moderate bias risk. These have produced robust and occasionally original evidence (13), even in smaller cohorts (11). However, in some cases, newer studies (9) contribute little beyond confirming the more robust evidence from previous research. These newer studies also replicate methodological flaws that had already been criticized (3) in older studies (10).

The recent meta-analysis by Aleid (17) aims to consolidate research on spironolactone for acne but presents certain methodological challenges that may impact its reliability and applicability.

The inclusion of both adults and non-adult females raises concerns, as adult acne is increasingly recognized as a distinct clinical entity. These factors explain the non-overlapping studies between their review and ours.

In conclusion, spironolactone has emerged as a highly effective and well-tolerated therapy for adult female acne across all severity grades, particularly in cases resistant to first-line topical treatments or requiring prolonged systemic intervention. Its role as a safe alternative to antibiotics and isotretinoin is critical in addressing the global antimicrobial resistance crisis, offering a viable strategy to reduce reliance on antibiotics—frequently overused in clinical practice despite guideline recommendations (3,6,7,15).

Dosing and Efficacy: Robust evidence supports spironolactone's efficacy at 50–150 mg/day, with doses of 50–100 mg/day, within clinical practice, achieving significant improvements in moderate acne (Evidence High) and 150–200 mg/day reserved for severe cases (Evidence Moderate) (6,14,15). Doses below 50 mg/day show limited efficacy but may serve as adjuncts in mild acne to enhance adherence to topical regimens (3,14), possibly by creating patient perception of taking an active systemic treatment. Notably, spironolactone's anti-androgenic mechanism—evidenced by testosterone normalization ($p \leq 0.001$) and reduced sebum production (Evidence Moderate)—underpins its utility even in isotretinoin-resistant cases (12,15). Also, it presents non inferiority to current antibiotics (15) (Evidence Moderate).

Safety and Tolerability: Long-term use (up to 12 months) is associated with mild, transient adverse effects (e.g., menstrual irregularities), with hyperkalemia remaining rare and subclinical in healthy patients (Evidence High) (9,10). However, data beyond two years are limited (Evidence Low), warranting further investigation into its safety as maintenance therapy. Scheduled treatment pauses or pulsed regimens may optimize tolerability without compromising efficacy, as suggested by sustained post-cessation effects (Evidence Moderate) (12).

Combination Strategies: Synergy with non-comedogenic topicals (e.g., benzoyl peroxide) enhances clinical outcomes by targeting both inflammatory and infectious pathways (6,14). Concurrent use of third- or fourth-generation COCs (low androgenicity) mitigates menstrual side effects and potentiates efficacy, whereas older COC generations may diminish therapeutic success (Evidence Moderate) (11).

Patient Management: Clinicians should emphasize a minimum 12-week treatment period, with peak improvements typically observed at 24 weeks (Evidence High). Structured follow-up protocols—adapting studies like (12,14), which minimized attrition through scheduled pauses and rigorous monitoring—are essential to manage expectations, ensure adherence, and detect delayed adverse effects.

Research Priorities: Future studies must prioritize; Long-term safety and maintenance data (>2 years). Standardized outcome measures (e.g., lesion counts, IGA, QoL tools) to enable meta-analyses. Subgroup analyses in PCOS, cyclical acne, and severity-stratified cohorts. Validation of low-dose regimens (<75 mg/day) in homogeneous populations, Optimization of therapeutic combinations (e.g., topical retinoids + spironolactone) (6,14).

Policy and Clinical Practice Formal on-label approval of spironolactone (50–150 mg/day) for adult female acne is strongly justified, aligning with antibiotic stewardship imperatives. Integration into clinical guidelines as a first-line systemic therapy will curb antibiotic, overuse while addressing unmet needs in long-term acne management (7,15).

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Tables

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

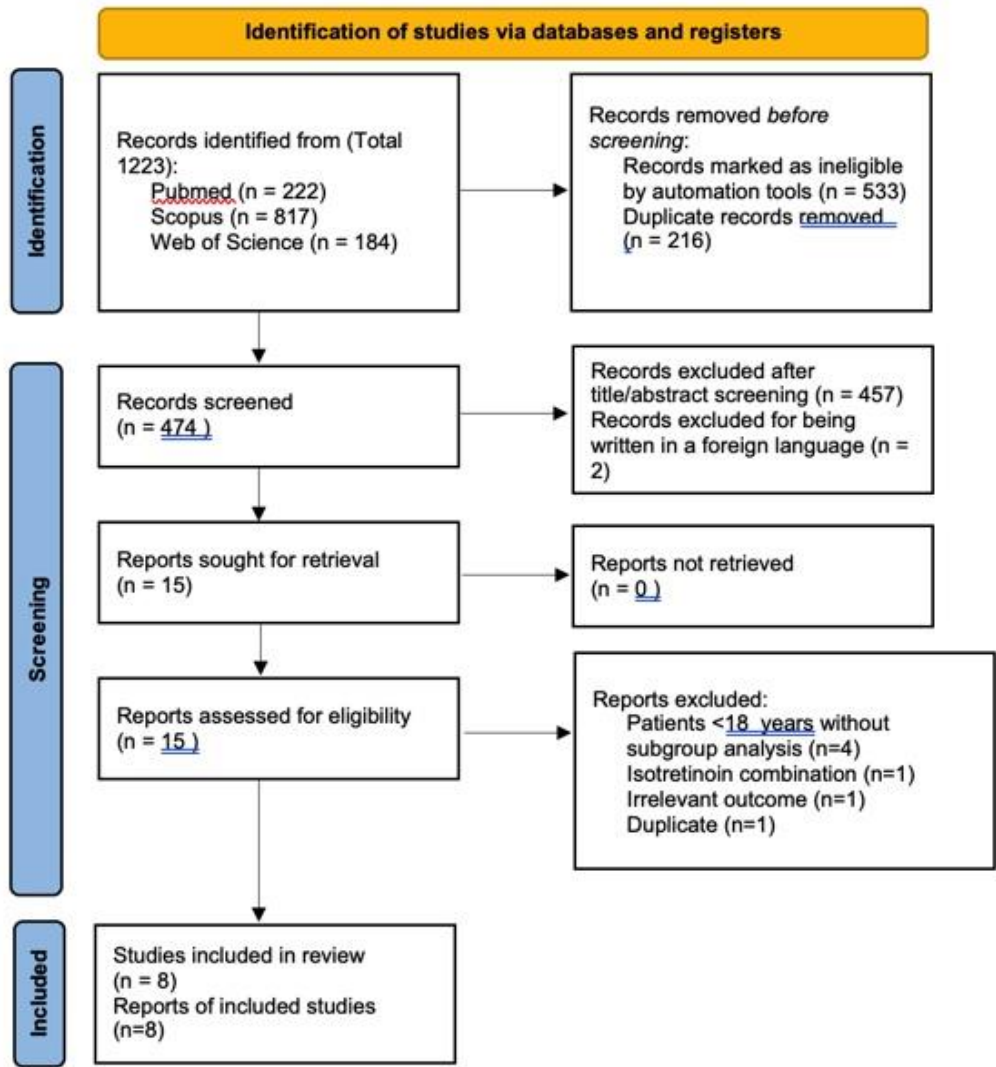


Figure 1.

Study ID	D1	D2	D3	D4	D5	Overall	
Santer et al 2023	+	+	+	+	+	+	
Dréno et al 2024	+	!	+	+	!	!	
Patiyasikunt et al 2020	+	+	+	+	!	!	
	D1	D2	D3	D4	D5		
	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result		
							Low risk
							Some concerns
							High risk

Figure 2.

	D1	D2	D3	D4	D5	D6	D7	Overall
Roberts et al. (2020)	Serious	Serious	Low	Low	Serious	Low	Moderate	Serious
Madiha Sanai et al. (2019)	Low	Low	Low	Low	Low	Low	Low	Low
Lessner et al. (2014)	Low	Serious	Low	Serious	Moderate	Serious	Moderate	Serious
Garg et al. (2020)	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Isvy-Joubert et al. (2017)	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate

D1-Confounding: How well were potential confounders measured and controlled for?
D2-Selection of participants: Was there any systematic difference between the exposed and unexposed groups at baseline?

D3-Classification of interventions: Were the exposures accurately defined and measured?
D4-Deviations from intended interventions: Were there any significant deviations from the planned exposure protocols?

D5-Missing data: How were missing data handled, and could this have introduced bias?

D6-Measurement of outcomes: Were the outcomes accurately and reliably measured?

D7-Selection of the reported result: Was the chosen analysis appropriate and free from bias?

Figure 3.

Study	P-Population	I-Intervention	C-Control	O-Outcome	S-Subgroup
Santer 2023 (6) PP RCT	ITT201+209 PP176+166 W12 29.2Y IGA $\geq$ 2	50 mg W6 (one tablet) 100 mg W12	Matched Placebo	QoL improved W 24 (OR 5.18 CI:2.18-12.28). All SS W24. Some NSS W12. > previous RCT	Better outcome $\geq$ 25 Year old
Roberts 2020 (9) PP Cohort retrospective	ITT 814/PP395 M3 32Y Clinically diagnosed	25-200 mg Med.100 Monotherapy 327(82.8%)	N/A	91.4% improved 66.1% CR. Median Response: initial 3M Full 6M	Papulopustular and nodulocystic: Effective.
Lessner 2014 (10) PP Cohort retrospective	ITT58/PP41 19-57Y Resist Antibiotics and retinoids	50-200 mg (start 50) +3M topical retinoid	N/A	Improved 85.4% 63.4% CR/excellent	100 mg improved up to CR superior to retinoid with tolerance
Isvy-Joubert 2017(11) PP Cohort retrospective	ITT 70/ PP52 M6 47 31.3Y Mild acne face & trunk	$\leq$ 150 mg + Previous COC	N/A	71% (47/70) CR M6 (median response time)	Prior retinoid 2.46 Inflammatory 1.08 Gen.1-2COC 0.27 (p0.03/0.001/0.01)
Sanai 2019 (12) ITT=PP Cohort Prospective	ITT=PP 50 M6 20.90Y Moderate or severe	100mg to M3 Monotherapy Strictly	N/A	73% improved p $\leq$ 0.001 48% excellent ASI.	84% Testosterone Normalization 6M (p $\leq$ 0.001)
Garg 2020 (13) PP Cohort retrospective	ITT403/ PP269 217-52 M6 26Y Resistant to treatment	25-200mg (start 104.2 $\pm$ 25.2mg) 68.0% topic R 40.7% COC	N/A	96% CR Y2 Median to full 4-6M CR75.5%face, 84%chest, 80.2%back M6 Survival 470.7D	COC use reduces menstrual effects (0.23,CI0.11-0.50)
Patiyasikunt 2020 (14) RCT PP	ITT 3X21 PP 3X20, W12 25-45Y Moderate	25/ 50 mg W12 + Benzoyl gel Blinded 12+4W	Matched Placebo + Benzoyl gel	Lesion Count (NSS). AFAST CR: SPL50 75% vs Placebo 30%(p=0.01)	SPL50 Better outcomes than SPL25 (NSS)
Dréno 2024 (15) RCT mITT+PP	ITT 71+76/ mITT 65+68/ PP63+66 M6 27.52 $\pm$.6Y	150 mg M6 +Benzoyl gel	Doxycycli ne100 M3 + Placebo M6 + gel	SL efficacy: 1.37 (0.60– 3.12 p = 0.579) M4 NSS, 2.87(1.38–5.99 p=0.007) M6. QoL/CADI SS M6.	SL better across COC (3.40 p=0.001). Slower onset

Table 1.

Study	P-Population	Intervention	C-Control	O-Outcome	s-sundry/subgroup findings/variance
Santer et al., 2023 (6) RCT PP	R413 ITT201+209 PP 181(-5 data)+176(-10 data) at 12 weeks endpoint	50 mg/day until week 6 (one tablet daily)	matched placebo	Main: Acne-QoL symptom scores improved significantly with spironolactone; mean difference at week 12 1.27 (95%CI 0.07 to 2.46) week 24: 5.18 (95%CI 2.18 to 12.28) not all outcomes were significant at 12 weeks, but all were significant at 24 weeks By week 24, 82% of participants in the spironolactone group reported improvement, compared to 63% in the placebo group (OR: 2.72, 95% CI: 1.50-4.93)	Spironolactone improved outcomes compared with placebo, with greater differences at week 24 than week 12. Spironolactone is a useful alternative to oral antibiotics for women with acne.
	Mean 29.2 years IGA≥2	100 mg/day until week 24 (Two tablets daily)	matched placebo	By week 24, 82% of participants in the spironolactone group reported improvement, compared to 63% in the placebo group (OR: 2.72, 95% CI: 1.50-4.93)	Benefits were more pronounced at 24 weeks compared to earlier evaluations
	Facial acne for at least six months warranting oral antibiotics	Unpromoted Topical to week 12 Continued COC allowed Beyond 12 weeks: oral antibiotics, hormonal treatments, or isotretinoin if advised	Until week 12: Unpromoted Topical Continued COC allowed Spironolactone beyond week 24 if chosen	IGA scores improved significantly with spironolactone; mean difference at week 12 unadjusted 3.78 (95%CI 1.73 to 8.27) adjusted 3.45 (95% CI: 2.16 to 4.75) Mild adverse reactions were more frequent with spironolactone (64% vs. 51% placebo), mainly headaches and dizziness; no severe events reported Greater efficacy at 24 weeks vs. placebo, with sustained QoL improvements	Subgroup analysis showed greater efficacy in women aged ≥25 years; consistent across acne severities Findings suggest spironolactone as a viable alternative to oral antibiotics for women with persistent acne.
Roberts et al., 2020 (9) Cohort retrospective PP	ITT 814, PP 395 dermatologic follow-up at least 3 month	25-200 mg/day (median 100mg/day) Spironolactone Monotherapy 327(82.8%) Spironolactone+Oral Antibiotic 29(7.8%) Spironolactone+O.Contracep.Pill 29(7.3%) Spironolactone+COC+O.Antibiot c 8(2.0%)	N/A	Main: 91.4% improvement with spironolactone; 66.1% had complete response (≥50%) Median time: to initial response: 3 months; to maximum response: 5 months 10.4% experienced mild adverse effects mainly dizziness, menstrual irregularities, bleeding and fatigue; 6.3% Discontinued due to side effects	Improvement observed regardless of acne severity, including moderate-to-severe papulopustular or nodulocystic acne. Highest CR in patients with grade 1 acne (100%) compared to grade 4 (64.6%) Grade Response ≥90% >50% ≤50% None (G1) 100% (n=2) (G2) 63.7% (n=100) 21.0% (n=33) 6.4% (n=10) 8.9% (n=14) (G3) 68.8% (n=106) 17.5% (n=27) 6.5% (n=10) 7.1% (n=11) (G4) 4 64.6% (n=53)18.3% (n=15) 6.1% (n=5) 11.0% (n= 9)
	Median age of 32 years, diagnosis of acne by a dermatologist, treatment with spironolactone >=21 yo 85.8% presented with acne limited to the jawline, and 46.6% reported acne exacerbation with their menstrual cycle.				Supports, with limitations, previous findings, and the current clinical practice that spironolactone is a safe and effective treatment of acne for women. Per protocol results ignore >50% discontinuation (express 75 implicit 344)
Lessner et al., 2014 (10) Cohort retrospective PP	ITT58 PP41 19-57 years old Lower face and neck Mostly retinoid and chronic antibiotic resistant acne	50-200 mg/day 50mg/day until 3 months+ 25mg increments per 3 month as needed topical tretinoin 0.025% cream or adapalene 0.1% cream	N/A	Main: 85.4% of patients achieved good, excellent or clear outcome 63.4% of patients showed excellent or clear outcome Minimal side effects: 4.9% reported irregular periods (dosages of 200 mg and 50 mg); 2.4% experienced lightheadedness or orthostatic hypotension (50 mg). Patients on spironolactone + retinoids showed superior outcomes to retinoids alone	Significant improvement with dose increases over time. 50-100 mg/day showed marked improvement to complete resolution of acne lesions when compared to the previous studies of higher doses There were no severe adverse events. No change in tolerance to topical retinoids in any of the patients as a result of spironolactone treatment Combination therapy yielded better results compared to previous monotherapy with retinoids
Issy-Joubert et al., 2017 (11) Cohort retrospective PP	ITT 70 PP52 PP 47 at 6 months Mean age 31.3 (20-34) years Face, neck, chest, and back lesions. 76% mild acne Long-standing history of acne with 76% having had acne since adolescence. (hydradenitis suppurativa, rosacea and using other anti-androgens excluded) Oral Contraception 53 (76%) 1st/2nd Generation 17 (32%) 3rd-4th Generation 15 (28%) Hormonal Intra-Uterine Device 4 (8%) non Hormonal IUD (30%) mild acne <10 superficial inflammatory lesions) 53 (76%) moderate acne (10-20 superficial inflammatory lesions) 12 (17%) severe acne (>20 superficial inflammatory lesions) 5 (7%)	≤150 mg/day COC	N/A	Main: 71% remission after median 6 months (47/70 patients) Specific: increased success with high inflammatory lesions and prior isotretinoin use Specific: Lower success with 1st/2nd-gen progestin COC (OR=0.27, 95% CI: 0.10-0.77; p = 0.011) 24% (17) experienced mild/moderate side effects (CTCAE Grade 1 or 2); no severe adverse events Assessing acne lesions on the back, confirmed efficacy of spironolactone on extra-facial lesions	Variance in response based on lesion type and severity OR=1.08 (95% CI: 1.03-1.13; p = 0.001) for inflammatory lesions, OR=2.46 (95% CI: 1.09-5.54; p = 0.03) for relapse with prior isotretinoin Significant impact of 1st/2nd generation oral contraceptives with androgenic activity on success (p=0.01<0.05)(unlike 3rd/4th gen with low or anti-androgenic activity, particularly 4th generation drospirenone). Side effects: cramp/pain (4.2%), low blood pressure (2.9%), anorexia/loss of weight (2.9%), giddiness (2.9%). Maculo-papular rash, generalised eczema, sadness, nausea, dysphagia, diarrhoea, polyuria, hot flush, and breast tenderness were each reported in one patient (1.4%), also a clinical, but non-significant, increase in serum potassium level reported in one patient (1.4%). Confirms low doses valuable alternative where oral isotretinoin has failed, both for face and trunk, and 1st or 2nd generation COC should be avoided.
Sanai et al., 2019 (12) Cohort prospective PP+ITT	ITT 50, PP 50 fm Mean age of 20.90 ASB±4 No topical medications <= 1 month prior No systemic antibiotics nor retinoids <=3 Neither (PCOS),(CAH), adrenal/ ovarian tumor, medications affecting androgen action (including COC) or metabolism, nor potassium rich diet or supplements.	100mg/ day until 3 months, (strictest monotherapy) No further treatment 3-6 months	N/A	Main: 73% reduction in ASI score at the end of the study (p<0.001). 94% achieved ≥50% improvement in ASI score; 48% showed excellent response, 42% good response. Specific: Testosterone level normalized for high values beyond the 3 month treatment period, no less than 6 month at follow up and point. Transient side effects during 3 months of therapy. Menstrual irregularities: 12% (1st month), 24% (2nd), 12% (3rd), none after 4th month. Postural hypotension: 4% (1st), 8% (3rd). Sub-clinical Hyperkalaemia & polyuria: 4% (3rd). All resolved post-treatment (p < 0.001).	Initial Response at the second month of treatment: 46% of patients had mild acne and 54% had moderate acne, compared to baseline values of 80% with moderate acne and 20% with severe acne. Testosterone level normalization for high values beyond the 3 month treatment period, no less than 6 month at follow up and point. Strictly monotherapy Spironolactone is effective and safe for the treatment of moderate to severe acne in females, well tolerated even in the absence of COC and normalizes testosterone levels without other hormonal treatments
Garg et al., 2020 (13) Cohort retrospective PP	403 ITT 269 PP 217-52 at 6 months Median age 26 years, PCOS 32 (7.9%) 371 (92.1%) previous treatment with topical retinoid, 254 (63.0%) oral antibiotic, and 68 (16.9%) isotretinoin Face, chest, back (truncal acne)	25-200 mg/day Initial dose 104.2 ±25.2 Adjustments common; 50.6% increased to 150-200 mg/day 37.3% stayed at 100 mg/day, 9.2% reduced to 25-75 mg/day, 274 (68.0%) Topical retinoid 9 (2.2%) Oral antibiotic 154 (40.7%) COC	N/A	Main: 96% clearance achieved by 2 years of treatment At follow-up, acne reduction or clearance was achieved in 75.5% (SPL), 84% (chest), and 80.2% (back) of patients 23% discontinuations due to adverse effects (15 nonmenstrual, 6 menstrual) Optimal starting dose: 100 mg/day; Mean drug survival: 470.7 days	Gradual improvement observed over time, requiring 4-6 months for peak efficacy Chest and back display higher CR but lower CASS improvement, 0.5 (0.4-0.7) 0.6 (0.6-1) vs 1.0 (0.9-1.1) Menstrual adverse effects decreased with COC use (OR 0.23, 95% CI 0.11-0.50). Spironolactone improves clinical outcomes and is well tolerated for an extended duration.
Patiyasilkunt et al., 2020 (14) RCT PP	ITT 63, 3X21 PP 60, 3X20, w12 25-45 years moderate AFASIT-F only (no mild nor severe) Excluded: rashes antiandrogens and drug induced acne <4 weeks, isotretinoin <6 months.	25 mg/day or 50 mg/day to w12 Mandatory benzoyl peroxide gel Blinded weeks 12 + 4 followup	matched placebo Mandatory benzoyl peroxide gel Blinded weeks 12 + 4 followup	(SS) At week 12, 75% in the SPL50 group achieved success and target improvement in acne status, compared to 30% in the placebo group (p=0.01) Main: Lesion Count (NSS OR). Significant acne reduction in all groups (placebo, SPL25, SPL50) compared to baseline, but no statistical difference between them at 12 weeks. Mild, transient side effects: 30% SPL50 vs 0% SPL25 menstrual irregularities; 24% SPL50 vs 5% SPL25 dizziness. No severe events or significant changes in potassium/creatinine levels. Combination of SPL50 + benzoyl peroxide gel proved more effective than placebo with acceptable tolerability	Dose-response trend observed with SPL50 showing better outcomes than SPL25 Efficacy persisted for at least one month post-treatment with continued topical maintenance. Using a low-dose (25-50 mg/ day) of SPL in moderate adult female acne resulted in a high rate of success with minimal side-effects. SPL50 showed significantly higher success rates vs. placebo (75% vs. 30%, p = 0.01), with a dose-response trend compared to SPL25. Adherence to benzoyl peroxide probably improved.
Dréno et al., 2024 (15) RCT PP+MTT	ITT 71+76, mITT 65+68, PP63+66 Spironolactone 27.52±6 years Doxycycline 29.75±7.90 years Facial and Trunk acne	150 mg/day 6 months benzoyl peroxide 5% 6 months 150 mg/day) beyond 6 months Blinded months 6 +) 6 unblinded open label	doxycycline 100 mg/day 3 months Placebo 3 months benzoyl peroxide 5% 6 months benzoyl peroxide 5% beyond 6 months Blinded months 6 + 6 unblinded open label	Main: Spironolactone showed better efficacy than doxycycline with OR of 1.37 and a 95% confidence interval (95% CI) of 0.60-3.12 (p = 0.57%) at month 4, and an OR of 2.87 and a 95% CI of 1.38-5.99 (p = 0.007) at month 6. Significant lesion reduction: non-inflammatory lesions decreased by 9.2 (spironolactone) vs. 5.6 (doxycycline) at 4 months; 12.2 vs. 6.2 at 6 months. Mild/moderate side effects in spironolactone group; no severe treatment-related events Quality of life improved significantly with spironolactone by month 6 (CADi: 2.56 ± 2.38 vs. 3.44 ± 2.44). CADi scores were similar in both groups at baseline and remained so until month 4. Puzzling unchanged EQ-SD baseline: spironolactone: 5.8 ± 0.8 points; doxycycline: 5.7 ± 0.9 points), no relevant change during the study (month 6: spironolactone: 5.5 ± 0.8 points; doxycycline: 5.8 ± 0.7 points month 12: spironolactone: 5.6 ± 0.8 points; doxycycline: 5.5 ± 1.0 points)	Higher success rates with spironolactone, versus doxycycline, observed across all contraceptive methods (p=0.001, OR=3.40, 95% CI 1.66-6.98) Slower onset for spironolactone but better long-term outcomes compared to doxycycline 23 mild/moderate AEs related to spironolactone resolved during the study; AE incidence was higher with spironolactone (61.2%) than doxycycline (38.8%). Treatment with spironolactone is superior to doxycycline, on, and very well tolerated. Objective and, acne specific, quality of life (CADi) confirms but acne seems to not reflect on EQ-SD, said EQ-SD meriting caution for clinical or trial usage.

ITT = Intention To Treat(RCT) / Eligible Cohort (Cohort studies) PP= Per Protocol (RCT) / Complete-Case analysis (Cohort studies) SS = Statistically Significant NSS= non Statistically Significant OR=Odds Ratio CI=Confidence Interval p=P-Value
COC/COO = Combined Oral Contraceptives

Supplementary Table 1.

Study	Scale	Baseline / Month 0	Sub 2.5 Months Value <2,5	3 Months Value [2,5-5]	6 Months Value [5-8]	9 Months Value [8-11]	1 Year Value [11-23]	>=2 Year Value >23	Size
Santer et al., 2023 (6)	Acne-QoL Symptom Subscale Score	Spirolactone 13.2 (SD4.9) Placebo 12.9 (SD4.5)		19.2 Spirolactone; 17.8 Placebo group; OR 1.27 (95%CI 0.07 to 2.46)	21.2 Spirolactone.; 17.4 Placebo; Mean Difference 3.45 (2.16 to 4.75)				176 & 166 w12; 163 & 136 w24
	Self-assessed overall improvement score			72% (spironolactone) vs. 68% (placebo); OR: 1.16 (95%CI: 0.70–1.91) Not statistically significant	82% (spironolactone) vs. 63% (placebo); OR: 2.72 (95% CI: 1.50–4.93)				122 & 108 w12; 131 & 81 w24
	Participant's global assessment (PGA)			21% (spironolactone) vs. 12% (placebo); Not statistically significant OR 1.69 (95% CI 0.89 - 3.19)	32% (spironolactone) vs. 11% (placebo) OR 3.76 (95% CI 1.95-7.28)				36 & 20 w12 ; 53 & 15 w24
	Investigator Global Assessment (IGA)	Treatment/Placebo Clear/almost clear 0 (0%) Mild 92 (46%) 98 (47%) Moderate (42%) 82 (39%) Severe 25 (12%) 29 (14%)		19% (spironolactone) vs. 6% (placebo); OR: 5.18 (95% CI: 2.18–12.28)	No face-to-face assessments ()				31 & 9 w12
Roberts et al., 2020 (9) PP	4-grade European EDF S3 guidelines Per Protocol Results, Attrition>50%			Time to initial improvement, months Mean 4.6 (SD3.2) Median 3 (1–21)	Time to maximal improvement, months Mean 5.7 (SD3.5) Median 5 (1–21)		CR (≥90%) 261 (66.1%) PR (>50%) 75 (19.0%) PR (≤50%) 25 (6.3%) NR 34 (8.6%)		814 ITT, 395 PP Follow-up months Mean 35.0 (SD32.6) Median 24 (3–191)
Lessner et al., 2014 (10) PP	Unspecified 0-4 scale (response rating, 0=no response and 4=clear skin) Per Protocol							CR 14 (34.1%) excellent 12 (29.3%) good 9 (22.0%) minimal 5 (12.2%) no response 1 (2.4%)	58 ITT & 41 PP at end of treatment
Issy-Joubert et al., 2017 (11)	ECLA scale Mild <10 inflammatory Moderate [10;20] infl. Severe>20 inflammat.	Mild 53 (76%) Moderate 12 (17%) Severe 5 (7%)		Lower 95% CI: 4 months	median duration to remission 6 months	Higher 95% CI: 9	71% (47) Remission F1 R0 or R1, Is0 or 1 IP0, and F2 0 or 1		ITT70
	Seborrhea ECLA (Grade 0 to 4)	<2 19 (27.1%) =2 35 (50%) >=3 16 (22.9%)			<2 60 (85.7%) =2 10 (14.3%) >=3 0 (0%)				ITT 70 PP 70 M6
Sanai et al., 2019 (12)	Acne Severity Index (ASI)	Mean: 41.03±9.73	21.68±9.25	12.21±5.01 M3 10.91±3.75 M4	10.47±3.63 M5 9.85 (±3.20) M6				50
	Acne Severity Index (ASI) Response % reduction				Excellent response 48% good response in 42% Fair Response 10% 73.07±18.17% p-value < 0.001				
	acne grading scale	Mild 0 0% Moderate 40 80% Severe 10 20%	Mild 23 46% Moderate 27 52% Severe 0 0% M2	Mild 44 88% Moderate 6 12% Severe 0 0%	Mild 44 88% Moderate 6 12% Severe 0 0%				
	Serum Testosterone (High/Normal)	37 74% high		12 24% High	8 16% high				
	Serum Potassium (Mean)(SD)(Range)	Mean: 4.005 (±0.76) (3.30 9.10) mmol/L		Mean: 4.07 (±0.24) (3.50 4.41) mmol/L	Mean: 4.23 (±0.21) (3.70 4.61) mmol/L				
Garg et al., 2020 (13)	Comprehensive Acne Severity Scale (CASS) CR			20% (73) clear	40% (125) clear	53% (152) clear (9-12 months)	96% (217) clear (> 24 months)		ITT403 PP 365 M6 287 M12 226 M24
	CASS FACE n=269 Cleared Improved Unchanged Worsened	mean 1.8 (1.7-1.9)		mean 0.8 (0.7-0.9) 95 (35.3%) 108 (40.2%) 59 (21.9%) 7 (2.6%)					ITT269 PP 269
	CASS Chest n=106 Cleared Improved Unchanged Worsened	mean 0.8 (0.6-0.9)		mean 0.3 (0.2-0.4) 82 (77.4) 7 (6.6) 13 (12.3) 4 (3.8)					ITT 106 PP 106
	CASS Back n=106 Cleared Improved Unchanged Worsened	mean 1.2 (1-1.3)		Mean 0.4 (0.3-0.5) 72 (67.9) 13 (12.3) 16(15.1) 5 (4.7)					ITT 106 PP 106
Patiyasilunt et al., 2020 (14)	Total Acne Lesions	Placebo: 53.2; SPL 25 mg: 45.4; SPL 50 mg: 39.1		Reduction: Placebo: 11.4, SPL25: 11.3, SPL50: 9.9 (P < 0.001 for all) (NSD OR)					R 63 ITT 63 PP 60 w12
	Inflammatory Lesion Reduction	Placebo: 9.4; SPL25: 10.0; SPL50: 5.3		Reduction:Placebo: 2.9 (P < 0.001); SPL25: 3.0 (P < 0.001); SPL50: 1.2 (P = 0.02) (NSD OR)					
	Comedonal Lesion Reduction	Placebo: 43.7; SPL25 35.4; SPL50: 33.8		Reduction: Placebo: 8.6; SPL25: 8.3, SPL50: 8.7 (P < 0.001 for all) (NSD OR)					
	AFAST Improved two grades lower (clear/most clear)	Moderate grade 3		Placebo: 30%; SPL25 40% : SPL50: 75% OR 7.0; (95%CI 5.6–8.3) P = 0.01					
Dréno et al., 2024 (15) m(odified)ITT +PP	Global AFAST score	Spirolactone / Doxycycline Mean 2.71 ± 0.50 2.70 ± 0.50 Median 3 (2–4) 3 (2–4)	Fig 4	1.37 (95%CI 0.60–3.12) p = 0.579 Not Signif.	2.87 (95%CI 1.37–5.99) p = 0.007 Significant	Fig 4	Fig 4		147 ITT 65&68 PP 63&66 m6
	AFAST 1 Score (GEA)	Spirolactone / Doxycycline: 2.7 ± 0.5	Fig 4	Spirolactone: -1.3; Doxycycline: -1.1	Spirolactone: -1.7; Doxycycline: -1.1	Fig 4	Fig 4		
	AFAST 2 Score (submandibular)	Spirolactone 2.0 ± 0.7 ; Doxycycline: 1.9 ± 0.8	Fig 4	Spirolactone: -1.2; Doxycycline: -1.1	Spirolactone: -1.6; Doxycycline: -1.2	Fig 4	Fig 4		
	Spirolactone group Mean 3.2 SD 2.3 Median 3 (0–11)		Fig 6	Fig 6	Fig 6	Fig 6			
	ECLA Global Score	Spirolactone group Mean 2.9 SD 2.4 Median 2 (0–11)							
	ECLA trunk reduction Inflammatory Lesions	Spirolactone Mean 17.6 ± 5.6 Median 17 (10–33) Doxycycline 20.3 ± 15.3 Median 16 (10–109)	Fig 5b	Mean Delta 12.7 (spironolactone), 13.0 (doxycycline)	Mean Delta: 14.4 (spironolactone), 12.9 (doxycycline)	Fig 5b	Fig 5b		
	ECLA trunk reduction Non-inflammatory Lesions	Spirolactone Mean 19.8 ± 14.5 Median 17 (1–100) Doxycycline 17.4 ± 9.3 Median 16 17 (0–47)	Fig 5a	Mean Delta: 9.2 (spironolactone), 5.6 (doxycycline)	Mean Delta: 12.2 (spironolactone), 6.2 (doxycycline)	Fig 5a	Fig 5a		
	Quality of Life (CADI)	spironolactone: 6.24 ± 2.64 points; doxycycline: 6.32 ± 2.65 points	Fig 7	spironolactone 2.56 ± 2.38 doxycycline 3.44 ± 2.44	Spirolactone: 2.56 ± 2.38; Doxycycline: 3.44 ± 2.44 M6	Fig 7	Fig 7		
	EQ-5D patient's self-rated health on 5 dimensions	spironolactone: 5.8 ± 0.8 points doxycycline: 5.7 ± 0.9 points		spironolactone: 5.5 ± 0.8 doxycycline: 5.8 ± 0.7 (unchanged)	spironolactone: 5.6 ± 0.8 doxycycline: 5.5 ± 1.0 (unchanged)				

ITT = Intention To Treat(RCT) / Eligible Cohort (Cohort studies) PP= Per Protocol (RCT) / Complete-Case analysis (Cohort studies) SS = Statistically Significant NSS= non Statistically Significant OR=Odds Ratio CI=Confidence Interval p=P-Value COCCCO = Combined Oral Contraceptives

Supplementary Table 2.

Tables and Figures legends:

(Including Supplementary materials)

Figure 1: PRISMA Flowchart Diagram

Figure 2: Quality assessment and risk of bias of clinical trials according to Cochrane risk-of-bias tool for randomized trials (RoB 2)

Figure 3: Quality assessment and risk of bias of clinical trials according to ROBINS-I tool (Risk Of Bias in Non-randomized Studies of Interventions)

Table 1: Compact PICO(s) Population, Intervention, Control, Outcome, subgroups

Supplementary Table 1: FULL PICO(s) Population, Intervention, Control, Outcome, sundry/subgroups

Supplementary Table 2: T3R - Treatment Timeline To Results

Appendices

Author Guidelines – International Journal of Dermatology (IJD)

1. ABOUT IJD

Published monthly, the International Journal of Dermatology (IJD) is specifically designed to provide dermatologists around the world with a regular, up-to-date source of information on all aspects of the diagnosis and management of skin diseases.

IJD's longstanding interest in global dermatology and tropical skin diseases began upon its first issue release in the early 1960s. Today a well-established global presence, IJD showcases a comprehensive exploration into all aspects of dermatology as basic sciences, venereology and public health, and in teaching dermatology in developing countries.

IJD is guided by a distinguished, international editorial board and emphasizes a global approach to continuing medical education for physicians and other providers of health care with a specific interest in problems relating to the skin.

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IJD welcomes the submission of both narrative reviews and systematic reviews with meta-analysis. Topics may include updates in clinically relevant basic science and cutaneous biology.

The length of the body text should not exceed 5000 words (excluding the abstract, reference list, and figures), with a maximum of 5 figures and tables allowed. These submissions must include an unstructured abstract of a maximum of 250 words. Graphical abstracts, visually summarizing the key message and main results of the submission, are highly encouraged, though optional.

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Narrative Review Articles summarize existing knowledge in a particular field without appearing as exhaustive reviews of literature.

Systematic Review Articles with Meta-analysis function as synthesized summaries and critical appraisals that account for explicit questions through detailed and comprehensive literature searches in medicine.

A maximum of 5 supplementary figures/ tables restriction applies to this article type. These will be published under the Supporting Information tab once the article goes live. Tables must be 35 lines or less in portrait layout, with 2.5cm/1-inch margins and 12-point font, to fit on one journal page.

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Abbreviations must be defined when first used, both in the abstract and in the main text.

Manuscripts must be as succinct as possible. Text must comply with the word and figure limits defined in Section 2. If authors consider that a manuscript should not conform to the limits specified, exceptionally good reasons must be clearly provided in a cover letter accompanying the submission. Repetition of information or data in different sections of the manuscript must be carefully avoided.

Manuscripts should, where appropriate, include:

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The first page of all manuscripts should contain the following information:

- 1) the title of the paper
- 2) the full names of each author
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- 4) name of the institution(s) at which the research was conducted
- 5) name, address, telephone number and email address of corresponding author
- 6) manuscript word count (excluding abstract and references), table and figure count
- 7) any conflict of interest disclosures (see Section 5)
- 8) a running head not exceeding 50 characters
- 9) a list of keywords

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Keywords

The selection of keywords is a crucial step in the submission process, as it is with the help of these phrases that a broad audience will discover the work. Therefore,

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MeSH Tools provide adept assistance to authors seeking to elect the best possible keywords for their articles.

Text

This should in general, but not necessarily, be divided into sections with the headings: Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Table and figure legends. Figures should be submitted as separate files. The acknowledgements should include a statement of all funding sources that supported the work.

Please submit the full text of the manuscript, including the abstract, references, tables and legends as a single document. The title page may be included as page 1 of the main manuscript document or can be uploaded as a separate file but must be included.

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Please consider our checklist before submitting tables and figures for your article.

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- Figure legends must be included as a separate section in your main text file.
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Tables and figures should be referred to in text as follows: Fig. 1, Figs. 2–4; Table 1, Tables 2 and 3. The place at which a table or figure is to be inserted in the printed text should be indicated clearly on a manuscript. Each table and/or figure must have a legend that explains its purpose without reference to the text. Where a figure has more than one panel, each panel should be labelled in the top left-hand corner using lower case letters in parentheses i.e. '(a)', '(b)' etc., and a brief description of each panel given in the figure legend. When using histology figures, the stain type and magnification level must be included in the legend. Tables must be 35 lines or less in portrait layout, with 2.5cm/1-inch margins and 12-point font, to fit on one journal page.

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References

References should be in Vancouver format and appear as consecutive, unbracketed superscript numbers in the text, e.g. 'in our previous reports^{1,2} and those of Smith et al.^{3–5}' and should be listed numerically in the reference list at the end of the article.

Format references as below, using standard (Medline) abbreviations for journal titles. When there are more than six authors, include the first six authors followed by et al.

1. de Berker DAR, Baran R, Dawber RPR. The Nail in Dermatological Diseases. In: Baran and Dawber's Diseases of the Nails and their Management (Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds), 3rd edn. Oxford: Blackwell Science Ltd., 2001: 172–92.
2. Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. Clin Exp Dermatol 2007; 32: 23–7.
3. Graham-Brown R, Burns T. Lecture Notes: Dermatology. Oxford: Wiley-Blackwell, 2006.
4. Smith A. (1999) Select committee report into social care in the community [WWW document]. URL <http://www.dhss.gov.uk/reports/report015285.html> [accessed on 7 November 2003].

5.DECLARATIONS

Conflicts of Interest

Authors are responsible for disclosing all financial and personal relationships between themselves and others that might be perceived by others as biasing their

work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist.

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Prisma



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Spironolactone in the treatment of acne in adult women: Systematic review	Page 1
ABSTRACT			
Structured summary	2	Acne, the eighth most prevalent disease globally, significantly impacts quality of life, particularly in adult women, where hormonal factors play a key role. Spironolactone, an androgen receptor antagonist, has emerged as a promising treatment for acne by reducing sebum production and inflammation. Despite its off-label use, spironolactone is increasingly recommended as an alternative to antibiotics, especially amid rising antimicrobial resistance. This systematic review synthesizes evidence from studies published between 2010 and 2024 to evaluate spironolactone's efficacy and safety in treating adult female acne. High-quality, studies, such as the 2023 Santer/SAFA trial have provided robust evidence for spironolactone's efficacy at doses below 200 mg/day, resolving prior uncertainties identified in the 2017 review by Layton. Current findings indicate significant improvements in acne severity, particularly in moderate to severe cases, with doses near 100 mg/day. Combined oral contraceptives (COCs) of different generations enhance, or reduce, spironolactone's efficacy, through the associated androgenicity. Despite these advancements, methodological limitations, including varied assessment tools and high follow-up loss, hinder definitive conclusions. Future research should prioritize standardized methodologies, long-term maintenance studies, and subgroup analyses, particularly in populations with polycystic ovary syndrome (PCOS) or cyclical acne. Spironolactone's unique profile as a	Page 8

		hormonal and anti-inflammatory agent positions it as a first-line option for antibiotic-resistant or recurrent acne. This review underscores its potential for on-label approval and highlights the need for further research to optimize its use in clinical practice.	
INTRODUCTION			
Rationale	3	Given growing concerns regarding antimicrobial resistance and the recommendation to limit prolonged antibiotic use, recent clinical guidelines now recommend spironolactone as a safe and effective option for treating acne in adult women. At time of latest systematic review, data for sub 200 mg doses was found non robust neither did a robust comparison to antibiotics exist, finally evidence for long term tolerability of spironolactone, as well as other still open questions, was also needed.	Page 11
Objectives	4	This systematic review seeks to synthesize the latest evidence on the efficacy of oral spironolactone in treating acne in adult women. Confirmation of spironolactone's effectiveness and evidence for lower, typical for acne, doses, non-inferiority to currently prescribed treatments. and long-term usage guidelines and safety were also assessed, as were contributions to better understand best therapies found or to be further studied.	Page 11
METHODS			
Protocol and registration	5	A review protocol has been submitted to PROSPERO and is currently awaiting registration. The submission ID is 645419.	
Eligibility criteria	6	We included randomized clinical trials, observational studies, and case series that investigated the efficacy of oral spironolactone, within the last 10 years, in treating acne vulgaris in adult women aged 18 years or older. Studies focusing exclusively on adolescents or including participants under 18 years of age were excluded. Publications in languages other than English were excluded.	Page 13
Information sources	7	The search was conducted in the Web of Science, PubMed, and Scopus databases through September 2024. Reference lists of included articles were also manually reviewed.	Page 14
Search	8	Spironolactone' AND ('acne vulgaris' OR 'acne' OR 'facial acne') AND ('women' OR 'female' OR 'adult') AND [Date >= 2010 AND Lang=ENG as filters]	Page 14

Study selection	9	The study selection was conducted in three phases: initial title screening, abstract evaluation, and full-text review. Two independent reviewers conducted each phase, and in case of discrepancies, a third reviewer was consulted. The PRISMA flowchart was used to illustrate the selection process.	Pages 14/15 Figure 1
Data collection process	10	Data extraction was independently performed by two reviewers using a standardized form. Extracted information included publication title, year, lead author, study design, and participant characteristics.	Pages 14/15
Data items	11	Details on the treatment regimen (daily dose of spironolactone, treatment duration, and concomitant therapies) and primary and secondary outcomes and durations were collected.	Table 1, Supplementary Table 1 and 2
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Risk of bias assessment was conducted according to study type. The Cochrane Risk of Bias 2.0 (RoB 2.0) tool was used for randomized clinical trials, and the ROBINS-I tool was used for observational studies Two independent reviewers assessed the risk of bias, categorizing studies as low, moderate, or high risk.	Page 15
Summary measures	13	Not applicable. This review is narrative in nature, and no principal summary measures (e.g., risk ratio, difference in means) were calculated.	Not applicable
Synthesis of results	14	Not applicable. Data synthesis was performed narratively due to the heterogeneity of the included studies in terms of methodologies, outcome measures, and treatment regimens. No statistical combination of results or assessment of consistency (e.g., I^2) was conducted.	Not applicable
Additional analyses	16	Not applicable. No additional analyses (e.g., sensitivity analysis, subgroup analysis, meta-regression) were performed, as this was a narrative synthesis.	Not applicable
RESULTS			
Study selection	17	The initial search yielded 1,223 articles, narrowed down to 474 after applying filters, and 15 articles were selected for full-text review. Ultimately, 8 studies met the inclusion criteria.	Page 17, Figure 1
Study characteristics	18	The studies encompassed 1,639 adult women aged between 18 and 66 years, diagnosed with moderate to severe acne. Treatment durations ranged from 3 to 132 months. PICO, variance/sub-	Page 18, Table 1, Supplementary

		groups and Treatment Time To Outcome as described in aforementioned tables.	Table 1 and 2
Risk of bias within and across studies	19/22	Risk generally still significant in Cohort studies, with some exceptions, RCT no longer present serious Risk but room for improvement remains. Figures 1 and 2 detail risk assessment and subsequent discussion clarifies points found to need explanation.	Figure 2 and 3
Results of individual studies	20	Not applicable. Outcomes and key results for each individual study were presented narratively and summarized in tabular format (Table 1 and Supplementary Tables 1 and 2). No effect estimates or confidence intervals were pooled, and no forest plot was generated due to the heterogeneity of study designs and outcome measures.	Not applicable
Synthesis of results	21	Not applicable. A meta-analysis was not conducted due to heterogeneity across the included studies	Not applicable
Additional analysis	23	Not applicable. A meta-analysis was not conducted due to heterogeneity across the included studies	Not applicable
DISCUSSION			
Summary of evidence	24	Spironolactone's efficacy in moderate to severe cases is well-supported, particularly at doses near 100 mg/day. Evidence High Spironolactone's efficacy, with concomitant benzoyl peroxide, in mild to moderate cases at doses under 100 mg/day, but no smaller than 50 mg. Evidence Low Spironolactone's efficacy in normalizing testosterone without concomitant treatments. Evidence Moderate Spironolactone's efficacy in reducing Sebum. Evidence Moderate Long term usage of spironolactone found generally well tolerated and safe up to a year. Evidence High Long term usage of spironolactone found generally well tolerated and safe up to two years. Evidence Low Spironolactone's continued effect beyond treatment cessation, and side effects and attrition beyond three months, might warrant a prescribed pause / Pulsed therapy. Evidence Moderate Spironolactone effectiveness, in Isotretinoin resistant acne, confirmed. Evidence Moderate	Page 23-28

		Spironolactone's non inferiority to current antibiotics, namely doxycycline on typical acne treatment, confirmed. Evidence Moderate Concomitant oral contraceptives' generation/androgenicity, have statistically significant effect on treatment success." Evidence Moderate For users, spironolactone's initial results should be expected no sooner than 12 weeks and maximum results no sooner than 24 weeks, even without active treatment between 12- and 24-weeks endpoints. Patient's expectations must be managed and significant variability may apply. Evidence High For Policy makers, On-Label use of spironolactone 50-150mg for severe (and up to 200mg on extreme cases), or first line treatments resistant acne, should be considered. Evidence Strong On-Label use of spironolactone 50-100mg for moderate (and even mild), on first line treatments resistant acne, should be considered. Evidence Strong For investigators, correct study sizes, methods and duration, standard outcome scores, clear concomitant treatments and adverse side effects methodology, are still a work in progress but good examples exist. Evidence High	
Limitations	25	Methodological limitations, including varied assessment tools and high follow-up loss, as well as widespread risk of bias, still hinder definitive conclusions.	Page 27-28
Conclusions	26	Spironolactone, 50-150 mg, should be considered a preferred, systemic alternative to, Isotretinoin or antibiotics, for cases resistant to first line treatments in adult women." Long term tolerability seems clear, but may be improved, without loss of effectiveness, by scheduled pauses. Topical treatments and judicious choice of oral contraceptive type can improve efficiency and mitigate adverse effects Future studies should prioritize standardized methodologies, including for adverse effects collection, and large, long-term maintenance studies. Exhaustive description of population, concomitant treatments and adequate analysis, including. Smaller studies should focus on strict sub-sets Sub 75 mg doses should be studied in severity homogenous cases on a longer timeline and/or larger	Page 29

		populations, to achieve robust results on its effectiveness. On label approval, in line with changing guidelines, should be granted to spironolactone for adult female acne.	
FUNDING			
Funding	27	This study was not supported by any grants or funding.	