Long-term use of spironolactone for acne in women: A case series of 403 patients

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Background: There are limited data regarding the long-term outcomes of spironolactone use for women with acne and its effect on truncal acne.

Objective: To comprehensively describe outcomes of patients treated with spironolactone in routine clinical practice, including long-term outcomes.

Methods: We performed a retrospective case series of 403 adult women treated for acne with spironolactone at an academic medical center between 2008 and 2019. Rates of objective, as assessed by Comprehensive Acne Severity Scale scores, and subjective acne clearance were evaluated, as well as rates of treatment discontinuation, dosage changes, and drug survival. Logistic regression was used to assess for association between incidence of menstrual adverse effects and combined oral contraceptive use.

Results: As evaluated by Comprehensive Acne Severity Scale scores, at the first follow-up, 75.5%, 84.0%, and 80.2% of patients with available data had reduction or complete clearance of acne on the face, chest, and back, respectively. The mean drug survival was 470.7 days. Menstrual adverse effects were less common among those using combined oral contraception (odds ratio, 0.23; 95% confidence interval, 0.11-0.50).

Limitations: This study was conducted at a single academic medical center.

Conclusions: Spironolactone improves clinical outcomes and is well tolerated for many adult women with acne using it for an extended duration. (J Am Acad Dermatol 2021;84:1348-55.)

Key words: acne; acne vulgaris; birth control pill; combined oral contraceptive; comprehensive acne severity scale; oral antibiotics; outcomes; spironolactone.

One of the most common dermatologic issues, acne affects 85% of adolescents and frequently persists into adulthood.[1] Although topical therapies are often effective for mild acne, systemic medications may be required for patients with moderate to severe acne.

While oral antibiotics are the most commonly prescribed systemic treatment for acne, use of antibiotics can result in antibiotic-associated adverse events and the development of antibiotic resistance.[2-4] In addition, antibiotics are often prescribed for longer than is recommended in the guidelines.[3-7] Although isotretinoin is a potential alternative to oral antibiotics, some patients are not comfortable taking isotretinoin, do not tolerate it, or relapse after discontinuation.[2] Notably, a recent survey of patients

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with acne and their parents found that nearly 75% responded that they would prefer an effective, antibiotic-free prescription rather than an oral antibiotic for acne.[8]

Because hormones play an important role in the development of acne, medications that target this pathogenic factor can be effective for patients with acne. Spironolactone may be an effective alternative for women with acne because of its antiandrogenic effects. However, compared to oral antibiotics, spironolactone is relatively underused; oral antibiotics are prescribed 3 to 7 times more often than spironolactone.[7] In addition, in the aforementioned survey, only 32% of antibiotic users responded that they were aware of nonantibiotic alternatives, such as spironolactone.[8]

CAPSULE SUMMARY

- Spironolactone is becoming a more common acne therapy for women, but long-term follow-up data are limited. This study shows that spironolactone continues to improve acne and is well tolerated with long-term use.
- Increasing the use of spironolactone for women with acne may improve outcomes and reduce reliance on oral antibiotics.

Although randomized trial data evaluating the effectiveness of spironolactone for acne are limited, there have been several large retrospective chart reviews supporting its effectiveness.[9-17] The majority of patients have been shown to improve with spironolactone, and complete clearance has been shown in up to two thirds of patients.[9-17] Low rates of adverse effects, relapse, and discontinuation have been reported, with the most common adverse effects being menstrual irregularities.[9-12] In addition, studies using commercial claims data have found that treatment with spironolactone may have both superior long-term drug use survival and similar rates of treatment switching (as a proxy for effectiveness) when compared with oral tetracycline–class antibiotics.[18,19]

However, prior studies have been limited by incomplete evaluation of the influence of dosing, incomplete evaluation of adverse effects, and inconsistent evaluation of clinical outcomes without use of objective outcome measures. In addition, many of these studies do not consider long-term outcomes or evaluate outcomes with respect to truncal acne. The purpose of this study was to comprehensively describe the outcomes of patients treated with spironolactone in routine clinical practice, including the long-term clinical outcomes of this treatment.

METHODS

This study was a retrospective case series study of female patients who were at least 18 years old and were treated for acne with oral spironolactone by 2 physicians (JKC and WDJ) at the University of Pennsylvania between January 1, 2008, and June 31, 2019. These providers were chosen because they usually document acne severity at clinical encounters using the Comprehensive Acne Severity Scale (CASS). A CASS score ranges from 0 (no or barely visible lesions) to 5 (highly inflammatory lesions with nodules and cysts).[20] Of note, this cohort has overlap with a prior retrospective study of 110 patients treated for acne with spironolactone, which has been previously described.[11]

Each patient's medical record was reviewed, and standardized data were extracted from the chart, including age at start of treatment, blood pressure, allergies, medical history (ie, polycystic ovary syndrome [PCOS], breast cancer, migraines with aura, Crohn's disease, hypercoagulability), and prior acne treatments. At each visit, blood pressure (when available), spironolactone dose, and concomitant therapies, including combined oral contraceptive (COC) use, were recorded. CASS score, patient-reported subjective acne improvement, and adverse effects were also abstracted from the medical record. For patients who discontinued treatment, the reason for discontinuation was abstracted from the medical record when available.

The primary outcome of interest was the long-term clinical outcomes of spironolactone, as assessed by rates of acne clearance, treatment discontinuation, and drug survival. In addition, changes to dosage over time were summarized by using a Sankey diagram with SankeyMATIC (beta version, @SankeyMATIC). Subjective clearance outcomes were assessed at 3 to 5.9, 6 to 8.9, 9 to 11.9, 12 to 17.9, 18 to 23.9, and 24+ months. Changes in CASS scores were assessed between the baseline visit and the first follow-up encounter. Logistic regression was used to assess for an association between the incidence of menstrual adverse effects and COC use, controlling for age at treatment initiation and spironolactone dose. The paired Student *t* test was used to compare for differences in blood pressure between the first follow-up visit with available blood pressure data compared to the baseline visit before starting spironolactone. Statistical analyses were performed With Stata 15 (StataCorp) and Excel (Microsoft). This study was approved by the institutional review board of the University of Pennsylvania

Abbreviations used:

CASS: Comprehensive Acne Severity Scale
CI: confidence interval
COC: combined oral contraceptive
PCOS: polycystic ovary syndrome

and conducted in adherence with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[21]

RESULTS

Among 403 patients meeting the inclusion criteria, the median age was 26 years (interquartile range, 22.0-29.5), and 32 (7.9%) had a history of PCOS. Of these patients, 371 (92.1%) previously had been treated with a topical retinoid, 254 (63.0%) previously had been treated with an oral antibiotic, and 68 (16.9%) previously had been treated with isotretinoin (Table I).

The majority of patients were initially prescribed spironolactone as part of a combination therapy, including 274 (68.0%) patients who were concurrently prescribed a topical retinoid with spironolactone. Nine (2.2%) were concurrently treated with an oral antibiotic, and 154 (40.7%) were concurrently taking a COC (Table I).

Of the 403 patients, CASS scores at baseline and the first follow-up visit were available in the medical record for 269 patients for the face, 106 patients for the chest, and 106 patients for the back (Table II). For patients with available CASS scores, 75.5%, 84.0%, and 80.2% of these patients had a reduction or complete clearance (CASS score of 0) of their acne on the face, chest, and back, respectively. CASS scores decreased by a mean of 0.8 (95% confidence interval [CI], 0.7-0.9), 0.3 (95% CI, 0.2-0.4), and 0.4 (95% CI, 0.3-0.5) for the face, chest, and back, respectively. Among patients available for follow-up, 73 (20%) were clear after 3 to 5.9 months of follow-up, 125 (40%) were clear after 6 to 8.9 months of follow-up, and 152 (53%) were clear after 9 to 11.9 months of follow-up. By the end of the follow-up period (>2 years), a total of 217 (96%) were clear (Fig 1).

The most common initial dosage of spironolactone prescribed was 100 mg/day, which was the case for 346 patients (85.9%) (Fig 2). Among these patients, after the first follow-up visit, 129 (37.3%) remained at 100 mg/day, 175 (50.6%) increased to 150 to 200 mg/day, and 32 (9.2%) decreased to 25 to 75 mg/day. Among those who started at 25 to 75 mg/day, 11 (55.0%) remained at 25 to 75 mg/day, 6 (30.0%) increased to 100 mg/day, and 2 (10.0%) increased to 150 to 200 mg/day. Among those who started at 150 to 200 mg/day, 33 (89.2%) remained at 150 to 200 mg/day, 3 (8.1%) decreased to 100 mg/day, and no patients decreased to 25 to 75 mg/day.

Table I. Characteristics of the study population

Characteristics	Value
Total number of patients	403
Age spironolactone began, years, median (IQR)	26 (22-29.5)
History of PCOS, n (%)	32 (7.9)
History of breast cancer, n (%)	1 (0.2)
History of migraines with aura, n (%)	6 (1.5)
History of Crohn's disease, n (%)	2 (0.5)
Hypercoagulable, n (%)	5 (1.2)
Prior treatment with topical retinoid, n (%)	371 (92.1)
Prior treatment with oral antibiotic, n (%)	254 (63)
Prior treatment with isotretinoin, n (%)	68 (16.9)
Prior COC use, n (%)	258 (64)
Initial dosage, mg, mean (SD)	104.2 (25.2)
Initial concurrent therapy, n (%)	
Spironolactone monotherapy	87 (21.6)
Topical retinoid + spironolactone	274 (68)
Oral antibiotic + spironolactone	9 (2.2)
Topical retinoid + oral antibiotic + spironolactone	33 (8.2)
Initial concurrent COC use, n (%)	164 (40.7)
Drug survival in days, mean (SD)	470.7 (471.6)
Drug survival in days, median (IQR)	327 (147-630)

COC, Combined oral contraceptive; *IQR*, interquartile range; *PCOS*, polycystic ovary syndrome; *SD*, standard deviation.

The mean drug survival until first discontinuation was 470.7 (471.6) days. Among those who were not lost to follow-up (n = 227), 93 patients had discontinued spironolactone by the end of the study period (Fig 3). The most common reason for spironolactone discontinuation was acne clearance (n = 41, 44%). Only 21 (23%) of discontinuations were due to adverse effects (15 nonmenstrual, 6 menstrual). Nonmenstrual adverse effects included dizziness, headache, frequent urination, fatigue, dry skin, anxiety, and abdominal pain. After adjustment for age and initial dosage, menstrual adverse effects were significantly less common among those using combined oral contraception (odds ratio, 0.23; 95% CI, 0.11-0.50). Additionally, among 267 patients with baseline and follow-up data on blood pressure monitoring while on spironolactone therapy, the mean decrease in systolic blood pressure was 3.5 mm Hg (95% CI, 2.0 to 4.9) and the mean decrease in diastolic blood pressure was 0.9 mm Hg (95% CI, -0.2 to 2.1).

Table II. Changes in CASS scores*

	Face (n = 269)	Chest (n = 106)	Back (n = 106)
Baseline CASS (95% CI)	1.8 (1.7-1.9)	0.8 (0.6-0.9)	1.2 (1-1.3)
CASS at first follow-up (95% CI)	0.8 (0.7-0.9)	0.3 (0.2-0.4)	0.4 (0.3-0.5)
Difference (95% CI)	1.0 (0.9-1.1)	0.5 (0.4-0.7)	0.8 (0.6-1)
Cleared, n (%)	95 (35.3)	82 (77.4)	72 (67.9)
Improved, n (%)	108 (40.2)	7 (6.6)	13 (12.3)
Unchanged, n (%)	59 (21.9)	13 (12.3)	16 (15.1)
Worsened, n (%)	7 (2.6)	4 (3.8)	5 (4.7)

CASS, Comprehensive Acne Severity Scale.

*Acne was considered cleared if the CASS score was 0 (clear) at the first follow-up. Acne was considered improved if there was any improvement of CASS score (ie, a 1-point or greater decrease) between baseline and the first follow-up. Acne was considered worsened if there was any worsening of CASS score (ie, a 1-point or greater increase) between baseline and the first follow-up. CASS scores are defined as follows:

- CASS score 0: Clear, no lesions to barely noticeable ones. Very few scattered comedones and papules.
- CASS score 1: Almost clear, hardly visible from 2.5 m away. A few scattered comedones, a few small papules, and very few pustules.
- CASS score 2: Mild, easily recognizable. Less than half of the affected area is involved. Many comedones, papules, and pustules.
- CASS score 3: Moderate. More than half of the affected area is involved. Numerous comedones and papules.
- CASS score 4: Severe. Entire area is involved. Covered with comedones, numerous papules and pustules, and a few nodules and cysts.
- CASS score 5: Very severe. Highly inflammatory acne covering the affected area, with nodules and cysts present.

Fig 1. Clearance rates at follow-up visits among those available for follow-up.

DISCUSSION

This study adds to the growing body of literature supporting the usefulness and tolerability of spironolactone for women with acne.[9-17] As assessed by CASS scores, more than 75% of patients treated with spironolactone had improvement in their acne, with many patients achieving clearance by the first follow-up visit. In addition, estimates of qualitative rates of complete clearance gradually increased over time, with approximately 20% being clear within 6 months, 40% being clear within 9 months, and more than 50% being clear within a year of starting spironolactone. These findings are consistent with spironolactone taking 4 to 6 months to achieve peak effect.[12] Furthermore, some additional patients continued to clear even into the second year of treatment.

Spironolactone use greatly improved both facial and truncal acne. Truncal acne is often overlooked in acne studies, and it can be particularly difficult to manage because of difficulty applying topical products, increased costs, and additional adverse effects of treatment such as bleaching of clothing by

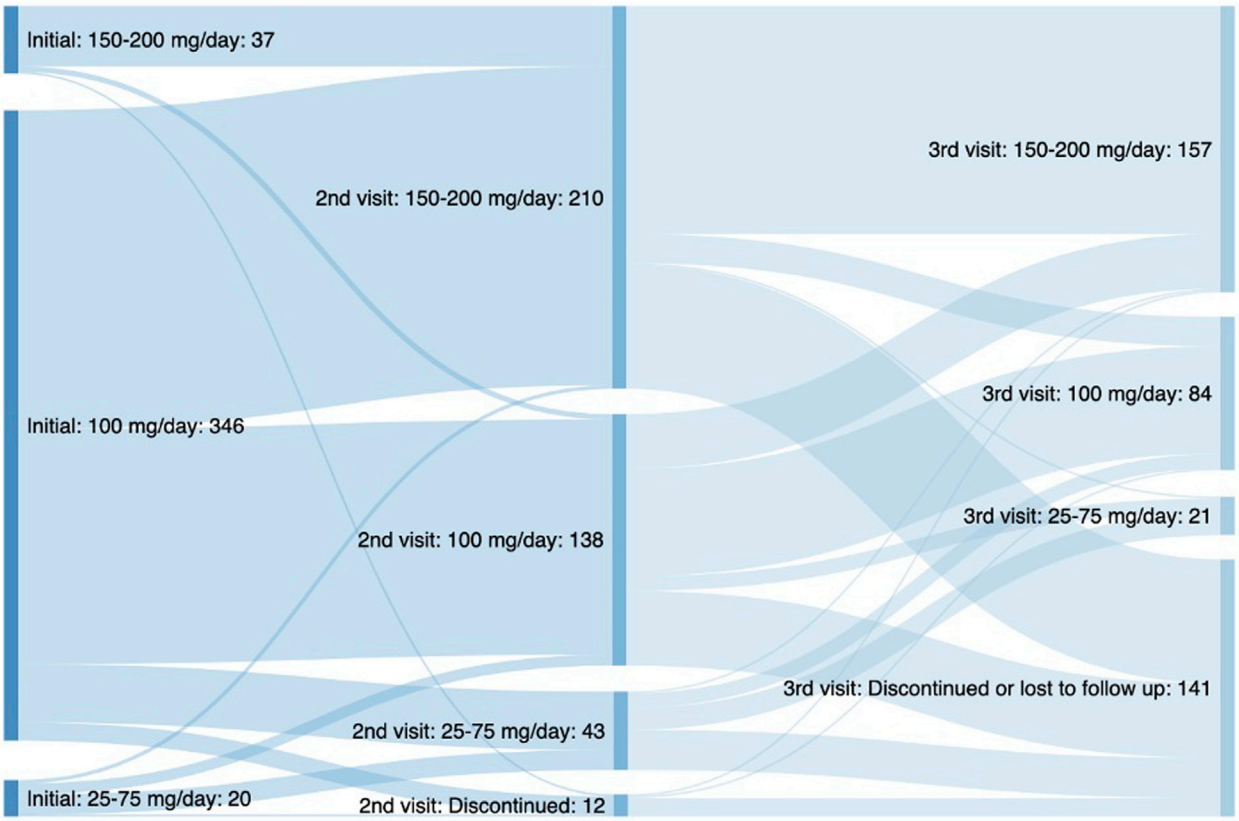

Fig 2. Changes to dosage over time. Among the *2nd visit: Discontinued* patients, the most common reasons for discontinuations were adverse effects (n = 6), other causes (n = 4), and clearance (n = 2). Among the *3rd visit: Discontinued or lost to follow-up* patients, most were lost to follow-up (n = 123). Among the 18 who discontinued, the most common reasons for discontinuations were other causes (n = 8), clearance (n = 6), and adverse effects (n = 4).

products containing benzoyl peroxide.[22] Current treatment guidelines for acne also do not specifically address treatment of truncal acne, and there are limited data on the optimal management strategies for truncal acne.[22] As a result, it is encouraging that more than two thirds of women treated with spironolactone achieved complete clearance of their truncal acne as assessed by CASS scores.

Spironolactone therapy was also well tolerated in the present study, with only 23% (n = 21) of discontinuations occurring due to adverse effects. Other studies have also found low rates of discontinuation due to adverse effects.[9,11,12] In addition, the prolonged drug survival also supports that patients found spironolactone to be helpful and the adverse effects to be acceptable. Among discontinuations due to adverse effects, only a minority were due to menstrual irregularities. In our study, menstrual irregularities were not necessarily higher with increasing dosages of spironolactone, although we are limited in our analysis by the fact that most patients started at a dosage of 100 mg/day. Similar to prior studies, menstrual adverse effects were significantly less common among patients concurrently taking a CO.[23,24]

In this cohort, the most successful dosage of spironolactone was generally 100 mg/day or greater. The most common initial dosage was 100 mg/day, and most patients either remained at this dosage or escalated. In contrast, patients started at lower dosages of 25 to 75 mg/day frequently increased their dosage over time. Given that spironolactone and other hormonal therapies can have a relatively delayed onset of action, taking 4 to 6 months to reach peak efficacy, it may be optimal to start with an initial total dosage of 100 to 150 mg/day, with subsequent dosage tapering if there are adverse effects or once clear.[12,25] In support of this approach, several other studies also report that initiation of a 100 mg/day dosage of spironolactone is effective.[10-12] In addition, Basu et al[10] showed that among a population of patients with PCOS and acne, dosages even higher than 100 mg/day (mean dosage, 143.0 mg/day) were often required to obtain improvement in acne and

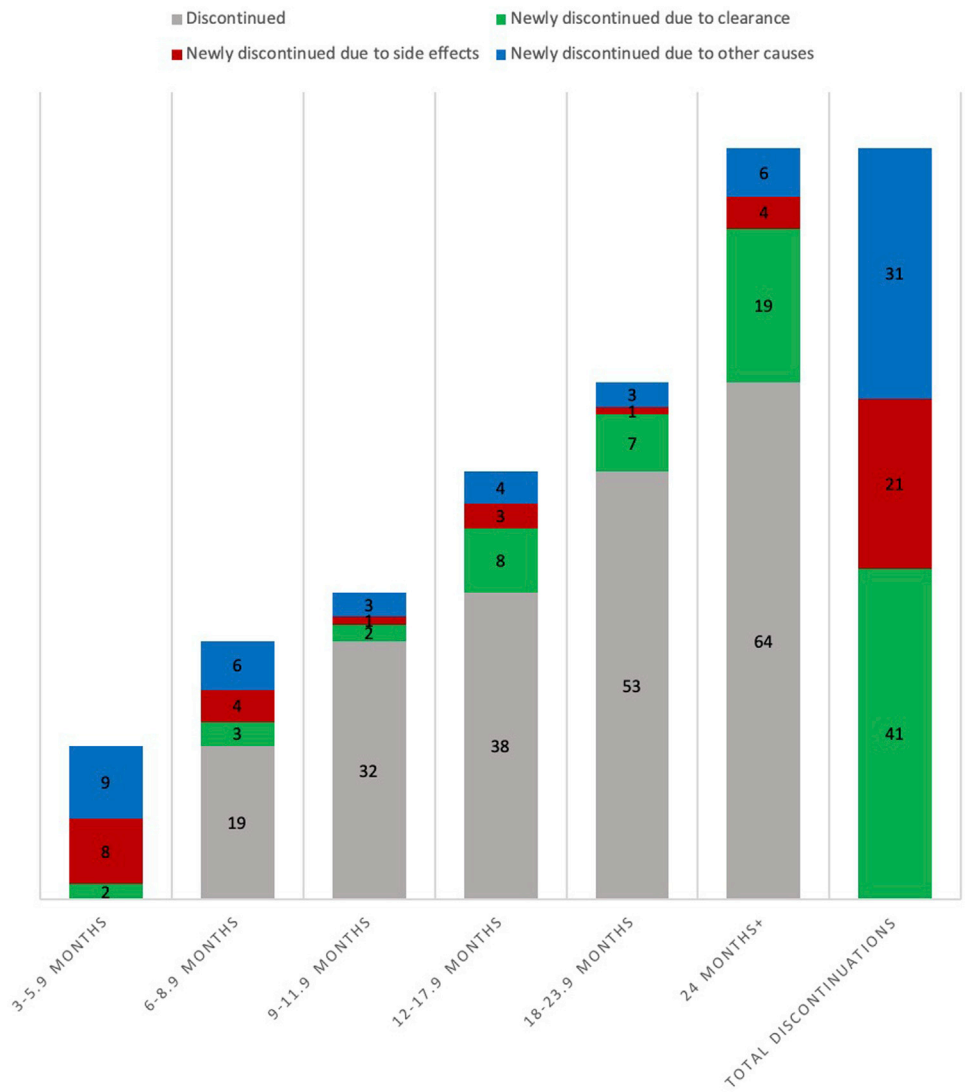

Fig 3. Discontinuation rates at follow-up visits. *Other causes* included the following: desires pregnancy, problems with insurance, told to discontinue by another provider because of another medical problem, felt no change or preferred another treatment, and not specified.

that those with physician-assessed acne improvement had taken a significantly higher dose than those without improvement.[10] A 10-year retrospective review of 395 adult patients at the Mayo Clinic found that one of the primary reasons for nonadherence among those who did not respond was lack of dose escalation.[12] Therefore, starting at a dosage of 100 mg/day or greater and tapering when adverse effects present may be a more effective approach than starting at a lower dosage of 25 to 50 mg/day and later having to escalate the dosage.

Although orthostatic hypotension and blood pressure variations have been described as adverse effects with spironolactone therapy, prior studies have generally not measured the influence of spironolactone use for acne on systolic and diastolic blood pressure. Our findings highlight that spironolactone is associated with a small but statistically significant decrease in systolic blood pressure of approximately 3.5 mm Hg. However, this adverse effect was not clinically significant in our study since no patients discontinued spironolactone because of this issue.

This study has several strengths, including its large sample size of more than 400 patients and long duration of follow-up. The use of a prospectively collected objective outcome with CASS scores to assess improvement and clearance expands on the largely qualitative outcomes used in prior retrospective studies. This study is also one of the first to evaluate clinical outcomes of spironolactone use for truncal acne. In addition, this study is one of the first

to evaluate dosage changes over time and the influence of spironolactone treatment for acne on blood pressure. The findings of this study should be interpreted in the context of its design. This study was conducted at a single academic medical center, and future studies are needed to examine whether these findings generalize to other settings. Although a strength of this study is the use of objective CASS data, these data were not available for all patients. In addition, we are unable to determine outcomes for patients who are lost to follow-up. Although some patients may be lost to follow-up because of acne resolution, moving to a new geographic region, or loss of insurance, others may be lost to follow-up because they changed clinicians in the setting of inadequate response. As a result, it is possible that our findings many overestimate the clinical effectiveness of spironolactone for women with acne. Additionally, concurrent treatments, such as oral antibiotics and topical retinoids, may have affected the observed effect of spironolactone therapy. However, for many patients, previous treatment with topical retinoids (>90%) and oral antibiotics (>60%) had failed, suggesting that at least part of the clinical improvement observed in this study was due to spironolactone rather than other medications.

CONCLUSIONS

Our findings highlight that long-term use of spironolactone improves clinical outcomes and is well tolerated for many adult women with acne. Given that spironolactone is prescribed 3 to 7 times less frequently than oral antibiotics for women with acne, increasing the use of spironolactone for women with acne may represent an opportunity to improve outcomes and reduce our reliance on oral antibiotics.[7,26,27] Future prospective randomized trials would be valuable to better define the safety and efficacy of spironolactone and how it compares to other treatments for acne such as oral antibiotics.

Conflicts of interest

None disclosed.

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