

Frequency of Treatment Switching for Spironolactone Compared to Oral Tetracycline-Class Antibiotics for Women With Acne: A Retrospective Cohort Study 2010-2016

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ABSTRACT

Background: Long-term oral antibiotic use in acne may be associated with a variety of adverse effects including antibiotic resistance, pharyngitis, inflammatory bowel disease, and breast and colon cancer. Spironolactone may represent an effective and safe alternative to oral antibiotics for women with moderate to severe acne, however comparative studies are lacking.

Methods: Using the OptumInsight™ Clinformatics™ DataMart, we conducted a retrospective analysis of the frequency of switching to a different systemic agent within the first year of therapy among women with acne who were started on either spironolactone or an oral tetracycline-class antibiotic between 2010-2016, after controlling for age, topical retinoid, and oral contraceptive use.

Results: Among women with acne who were started on spironolactone, 14.4% were prescribed a different systemic agent within one year, compared with 13.4% started on an oral tetracycline-class antibiotic. After adjusting for age, topical retinoid, and oral contraceptive use, the odds ratio for being prescribed a different systemic agent within one year was 1.07 (95% CI 0.99-1.16) for those prescribed spironolactone when compared with oral tetracycline-class antibiotics and the risk difference was 0.007 (95% CI -0.002-0.017).

Conclusions: Based on the observation of similar switching between the two groups, spironolactone may have similar clinical effectiveness to that of oral tetracycline-class antibiotics. While ultimately large clinical trials are needed to determine the optimal management strategy for women with moderate to severe acne, these results provide additional support that spironolactone represents an effective treatment for women with acne.

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INTRODUCTION

Acne is one of the most common diseases worldwide, affecting 85% of adolescents. In addition, acne often persists into adulthood, with over 50% of women reporting acne between 20-29 years of age and over 35% between 30-39 years of age.[1,2] While topical agents are typically sufficient for mild acne, moderate to severe acne often requires treatment with systemic agents, such as oral antibiotics, spironolactone, and isotretinoin.[3]

Oral antibiotics are the most common systemic agent used in the treatment of acne and dermatologists prescribe more antibiotics per capita than any other specialty.[4,5] However, antibiotic use may be associated with a variety of adverse outcomes including antibiotic resistance, pharyngitis, inflammatory bowel disease, and colon and breast cancer.[6–15] As a result, there have been calls to reduce overuse of antibiotics throughout medicine and multiple guidelines regarding the treatment of acne recommend limiting the duration of therapy with oral antibiotics.[16–20,3,21]

For women with moderate to severe acne, spironolactone may represent an effective, safe, and well-tolerated alternative to oral antibiotics and its use is becoming more common over time.[5,22–27] However, despite expert opinion supporting the use of spironolactone in the treatment of acne, spironolactone is not approved by the Food and Drug Administration for this indication and clinical evidence demonstrating the effectiveness of spironolactone is limited to small studies.[24–27] The objective of this study was to compare the outcomes with spironolactone and oral tetracycline-class antibiotics among a large, broadly representative population of women with acne. Specifically, this study sought to characterize the frequency with which women who are started on either spironolactone or an oral tetracycline-class antibiotic subsequently switch to a different systemic agent within the first year of therapy, since this switching may reflect treatment failure, whether due to lack of efficacy, side-effects, cost, or other reasons.[28]

METHODS

Data Source

This study was a retrospective analysis using the OptumInsight™ Clinformatics™ DataMart (OptumInsight, Eden Prairie, MN) between 2010 and 2016. The OptumInsight Clinformatics DataMart includes de-identified commercial claims data for approximately

12-14 million annual covered lives in the United States. The patient population included in the dataset are broadly representative of the demographics of the United States population with respect to gender, age, and geographic distribution. These data include both medical and pharmacy claims, as well as patient demographic information such as age and gender.

Study Design and Study Population

Inclusion criteria were (1) women who were enrolled in the OptumInsight Clinformatics DataMart with at least two claims associated with an International Classification of Diseases (ICD) Ninth or Tenth Revision code for acne separated by 12 months, (2) at least 6 months of continuous enrollment in the dataset before the start date of the index course of therapy without any prescriptions for spironolactone, an oral antibiotic, or isotretinoin during this period, (3) at least 12 months of continuous enrollment in the dataset after the start of the index course of therapy, and (4) who were between 16 and 35 years of age at the start date of the index course of therapy were included in the study. Previous studies have validated the accuracy of ICD codes to identify patients with acne.[29] A 6-month period of continuous enrollment before the index course of therapy was chosen to increase the probability that the index course of therapy was the initial treatment for these patients. An age cutoff of 35 years was chosen since acne is less common after this age and to reduce the likelihood of including patients with rosacea rather than acne.[2] Exclusion criteria included an ICD code for rosacea, since systemic antibiotics are also commonly used for this condition.

Prescriptions for spironolactone, oral antibiotics, and isotretinoin were identified by their National Drug Codes. Prescriptions were consolidated into courses of therapy with the start date defined as the date of the first prescription of the series and the end date defined as the date of the last prescription in the series plus the number of days of medication supplied. To account for non-adherence that could result in delays between prescriptions, prescriptions separated by fewer than 30 days were considered to be part of the same course of therapy.[30–36] Courses shorter than 30 days were excluded to avoid including prescriptions for acute illnesses (eg, Lyme disease, Rocky Mountain Spotted Fever). The index therapy was defined as the first course of therapy with either spironolactone or an oral tetracycline-class antibiotic prescribed to patients who had not received any previous courses of oral antibiotics, spironolactone, or isotretinoin.

The primary outcome was the frequency with which patients were switched to a course of therapy or to combination therapy with a different systemic agent used in the treatment of acne (ie, oral antibiotic, spironolactone, or isotretinoin) within the first year after starting treatment with either spironolactone or an oral tetracycline-class antibiotic.[28,37] Since switching may reflect treatment failure, either due to lack of efficacy, side-effects, cost, or other reasons, this outcome was selected as a surrogate marker for clinical effectiveness. Given that patients with acne are often young and without significant comorbidities, and since systemic acne treatments typically have narrow indications, any observation of switching is likely to have clinical relevance. In addition, prior work to evaluate clinical effectiveness of antibiotics using large administrative datasets has taken a similar approach.[28] Secondary outcomes included the timing of the change in therapy and the percentage of patients on each systemic therapy at time points 90, 180, 270, and 360 days after starting the index medication. In addition, subgroup analyses were conducted among adolescents, who were defined as being age 16 to 20 at the start of treatment, and adults, who were defined as being age 21 or older as the start of treatment.[35] Subgroup analyses were also performed comparing the three most commonly prescribed oral tetracycline-class antibiotics to spironolactone.

Statistical Analysis

Descriptive statistics are presented using means, medians, and percentages as appropriate for the outcomes of interest. In addition, the odds ratio and absolute risk difference for switching to a different systemic agent within the first year of therapy were calculated using logistic regression. Since topical retinoids and oral contraceptive pills are effective agents in acne and are also often prescribed to women on spironolactone and oral antibiotics, we adjusted for whether the patient had received any prescriptions for topical retinoids or oral contraceptives prior to starting the index therapy or concurrently with the index therapy, in addition to adjusting for age at the start of treatment, using a multivariable logistic model.[38–41] In any observational study, there is a concern that unmeasured confounding could lead to biased estimates. Since claims data do not contain information about acne severity, which could be a potential confounding variable, a formal sensitivity analysis was performed to assess the impact of differing acne severity between the spironolactone and oral tetracycline-class antibiotic groups on the primary outcome of interest.[42] Statistical analyses were performed in Stata 14 (StataCorp, College Station, Texas) and R version 3.1 (The R Foundation for Statistical Computing, Vienna, Austria). The Institutional Review Board of the University of Pennsylvania has granted a blanket exemption for all research completed at the University of Pennsylvania using OptumInsight data.

RESULTS

Cohort

The characteristics of the study population are summarized in Table 1. There were 6,684 and 31,614 unique women who were started on spironolactone and oral tetracycline-class antibiotics as the index systemic therapy, respectively. The most frequent tetracycline-class antibiotics prescribed were

TABLE 1.

Characteristics of the Study Population

	Spironolactone			Tetracycline		
	Adolescents (N=1,139)	Adults (N=5,545)	Overall (N=6,684)	Adolescents (N=17,349)	Adults (N=14,265)	Overall (N=31,614)
Age at time of index therapy, y, median (IQR)	18 (17-19)	28 (25-32)	27 (22-31)	17 (16-19)	27 (23-31)	20 (17-26)
Prior treatment with topical retinoid, n (%)	557 (48.9)	1835 (33.1)	2392 (35.8)	8473 (48.8)	6892 (48.3)	13768 (43.6)
Prior treatment with oral contraceptive, n (%)	519 (45.6)	3227 (58.2)	3746 (56.0)	3658 (21.1)	7369 (51.7)	11027 (34.9)
Days in Optum prior to index therapy, median (IQR)	2404 (968-3730)	1544 (628-3089)	1657 (661-3268)	2214 (1009-3651)	1452 (640-2898)	1843 (798-3408)
Days in Optum after index therapy, median (IQR)	948 (645-1436)	914 (623-1368)	918 (625-1376)	1116 (726-1628)	1048 (697-1530)	1086 (714-1588)

minocycline (34%), doxycycline hyclate (33%), extended-release minocycline (21%), doxycycline monohydrate (8%), and low-dose extended-release doxycycline (3%).

Frequency of Therapeutic Switching

Among women with acne who were started on spironolactone, 14.4% were prescribed a different systemic agent within 1 year. Among women with acne who were started on oral tetracycline-class antibiotics, 13.4% were prescribed a different systemic agent within 1 year (Table 2). When adjusted for age, topical retinoid, and oral contraceptive use, the odds ratio for being prescribed a different systemic agent within one year was 1.07 (95% CI 0.99-1.16) for those prescribed spironolactone when compared with oral tetracycline-class antibiotics and the risk difference was 0.007 (95% CI -0.002-0.017). The number of women needed to treat with an oral tetracycline-class antibiotic instead of spironolactone to prevent one instance of switching was 143 women.

Subgroup and Secondary Analyses

Among adolescent women, the adjusted odds ratio for being prescribed a different systemic agent within one year was 1.58 (95% CI 1.35-1.86) for those prescribed spironolactone when compared with oral tetracycline-class antibiotics and the risk difference was 0.060 (95% CI 0.039-0.080). The number of adolescent women needed to treat with an oral tetracycline-class antibiotic instead of spironolactone to prevent one instance of therapeutic switching was 17 women. Among adult women, the adjusted odds ratio for being prescribed a different systemic agent within one year was 0.94 (95% CI 0.86-1.03) for those prescribed spironolactone when compared with oral tetracycline-class antibiotics and the risk difference was -0.007 (95% CI -0.018-0.004).

Compared to spironolactone, doxycycline was the oral tetracycline-class antibiotic that was least likely to be switched. The adjusted odds ratio for being prescribed a

TABLE 2.

Frequency of Switching to Alternative Systemic Agents Within the First Year of Therapy With Either Spironolactone or an Oral Tetracycline Antibiotic

	Spironolactone			Tetracycline		
	Adolescents (N=1,139)	Adults (N=5,545)	Overall (N=6,684)	Adolescents (N=17,349)	Adults (N=14,265)	Overall (N=31,614)
Spironolactone	-	-	-	3.10%	7.70%	5.20%
Tetracycline	11.90%	8.70%	9.20%	-	-	-
Other Antibiotic†	3.50%	1.80%	2.10%	4.50%	3.00%	3.80%
Isotretinoin	4.10%	3.80%	3.90%	5.80%	4.40%	5.10%
Any Systemic Agent	18.50%	13.50%	14.40%	12.70%	14.30%	13.40%

†Other antibiotic includes trimethoprim-sulfamethoxazole, amoxicillin, cephalexin, and azithromycin.

TABLE 3.

Median Days Before Switching to Alternative Systemic Agents for Women With Acne Who Were Started on Spironolactone or an Oral Tetracycline Antibiotic

	Spironolactone			Tetracycline		
	Adolescents (N=1,139)	Adults (N=5,545)	Overall (N=6,684)	Adolescents (N=17,349)	Adults (N=14,265)	Overall (N=31,614)
Spironolactone, days, median (IQR)	-	-	-	204 (98-294)	154 (74-253)	167 (83-266)
Tetracycline, days, median (IQR)	131 (61-235)	102 (52-211)	106 (55-220)	-	-	-
Other Antibiotic†, days, median (IQR)	101 (58-233)	135 (67-224)	131 (61-228)	174 (86-271)	147 (78-246)	166 (84-262)
Isotretinoin, days, median (IQR)	204 (92-291)	164 (105-257)	167 (102-265)	209 (125-287)	187 (113-280)	200 (21-282)

†Other antibiotic includes trimethoprim-sulfamethoxazole, amoxicillin, cephalexin, and azithromycin.

different systemic agent within one year was 1.28 (95% CI 1.16-1.42) for those prescribed spironolactone when compared with doxycycline hyclate, 0.99 (95% CI 0.90-1.09) for those prescribed spironolactone when compared with minocycline, and 1.10 (95% CI 0.99-1.23) for those prescribed spironolactone when compared with low-dose extended-release minocycline.

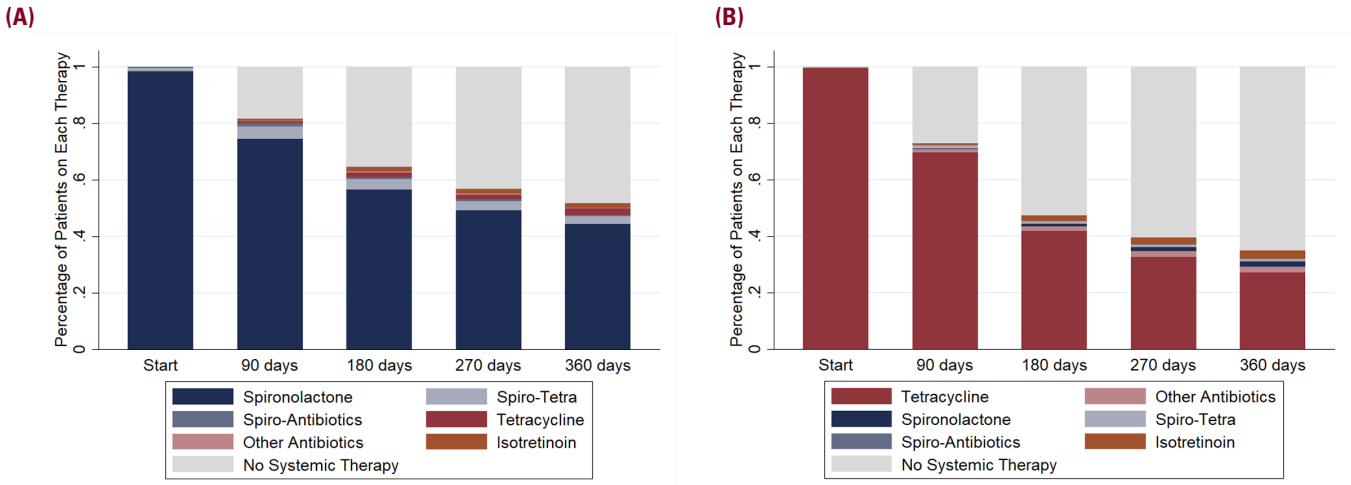
Switching from spironolactone to isotretinoin occurred after a median of 167 days (IQR 102-265 days). Switching from oral tetracycline-class antibiotics to isotretinoin occurred after a median of 200 days (IQR 121-282 days) (Table 3). Figure 1 summarizes the systemic agents being prescribed to patients at time points 90, 180, 270, and 360 days after starting either spironolactone or an oral tetracycline-class antibiotic.

A sensitivity analysis to assess the potential impact of differing acne severity between the spironolactone and oral tetracycline-class antibiotic groups on the primary outcome is available in Table 4. In this analysis, the adjusted odds ratio did not change substantially from the original estimate across a range of values for the prevalence of severe acne between the two groups. In many plausible scenarios, the odds ratio for switching becomes smaller and favors spironolactone. In other scenarios, the odds ratio does become more significant, but under most plausible scenarios, the odds ratio does not become larger than 1.16 (95% CI 1.08-1.26).

DISCUSSION

In this large, retrospective study, the frequency of switching to another systemic agent within the first year of treatment

FIGURE 1. Systemic therapies being prescribed following the index therapy. Systemic therapies prescribed at the start date of the index therapy and at 90, 180, 270, and 360 days after starting spironolactone (A) or an oral tetracycline-class antibiotic overall (B). Other antibiotics includes trimethoprim-sulfamethoxazole, amoxicillin, cephalexin, and azithromycin.
Spiro-Tetra: Combined therapy with spironolactone and a tetracycline. Spiro-Antibiotics: Combination therapy with spironolactone and another non-tetracycline antibiotic.



was similar among women with acne who were started on spironolactone compared with those started on oral tetracycline-class antibiotics. In addition, the frequency of switching to isotretinoin was more common among women who were started on oral tetracycline-class antibiotics than those started on spironolactone. Since switching may reflect treatment failure, whether due to lack of efficacy, side-effects, cost, or other factors, these results suggest that spironolactone may have similar clinical effectiveness to oral tetracycline-class antibiotics, particularly for adult women.

TABLE 4.

Sensitivity Analysis

In this sensitivity analysis, we evaluated the potential impact of differing prevalence of severe acne between the group started on spironolactone and the group started on oral tetracycline-class antibiotics. This analysis is important because the claims data used in this study do not contain information about acne severity. As a result, if either the spironolactone or the oral tetracycline-class antibiotic group were to include patients with more severe acne, this difference could bias our results to favor the group with less severe acne (of note this is a theoretical risk and there may in fact be no significant difference in acne severity between the two groups). To determine the impact of this potential source of bias, in this analysis we simulated theoretical scenarios where we assume a difference in acne severity between the two groups. We varied the prevalence of severe acne between 0.15 and 0.35 and we varied the odds of switching therapy for patients with severe acne compared to those with moderate acne from 1.1 to 2.0. Notably, after accounting for acne severity, the adjusted odds ratio did not change substantially from the original estimate. Additionally, for many plausible scenarios, the odds ratio for switching becomes smaller and favors spironolactone. In other scenarios the odds ratio does become more significant in favor of oral tetracycline-class antibiotics, but under most plausible scenarios, the odds ratio does not become larger than 1.16 (95% CI 1.08-1.26). These results highlight that a theoretical difference in severity of illness between the two groups is unlikely to have a significant effect on the primary outcome.

Prevalence of severe acne for those started on spironolactone	Prevalence of severe acne for those started on oral tetracycline antibiotics	Odds of switching if severe acne versus moderate acne	Adjusted odds ratio for switching if started on spironolactone (95% CI)
0.15	0.25	1.3	1.10 (1.02-1.19)
0.25†	**0.25†**	**1.3†**	**1.07 (0.99-1.16)†**
0.35	0.25	1.3	1.04 (0.96-1.13)
0.25	0.15	1.3	1.04 (0.96-1.13)
0.25	0.35	1.3	1.10 (1.02-1.19)
0.15	0.25	1.1	1.08 (1.00-1.17)
0.25	0.25	1.1	1.07 (0.99-1.16)
0.35	0.25	1.1	1.06 (0.98-1.15)
0.25	0.15	1.1	1.06 (0.98-1.15)
0.25	0.35	1.1	1.08 (1.00-1.17)
0.15	0.25	1.5	1.12 (1.04-1.21)
0.25	0.25	1.5	1.07 (0.99-1.16)
0.35	0.25	1.5	1.02 (0.95-1.11)
0.25	0.15	1.5	1.02 (0.95-1.11)
0.25	0.35	1.5	1.12 (1.03-1.21)
0.15	0.25	2.0	1.16 (1.08-1.26)
0.25	0.25	2.0	1.07 (0.99-1.16)
0.35	0.25	2.0	0.99 (0.92-1.07)
0.25	0.15	2.0	0.98 (0.91-1.07)
0.25	0.35	2.0	1.16 (1.07-1.25)

†Bolded results represent the base case scenario

Compared to oral antibiotics, spironolactone represents an enticing therapeutic alternative for women with moderate to severe acne, with a favorable side-effect profile.[43] While spironolactone is pregnancy category C and contraception is recommended for patients on spironolactone due to concerns about potential feminization of the fetus, oral tetracycline-class antibiotics are also contraindicated in pregnancy and are category D.[44,45] Although there have been concerns about a potential association between spironolactone and breast cancer based on animal studies, large population-based studies have not confirmed such a risk;[43,46,47] in contrast, there is evidence that pronged antibiotic use may be associated with increased risk of breast and colon cancer.[7,14] In addition, recent work has suggested that potassium monitoring is not required in young, healthy women.[48] Given that oral antibiotics are included in the first-line therapeutic regimens for moderate to severe acne, spironolactone may represent a favorable alternative therapy, especially for adult women.[3]

In addition, smaller studies have suggested that spironolactone is effective for women with all types of acne, not only for women with acne on the lower face or acne characterized by flares associated with the menstrual cycle.[22,23,25] It is likely that spironolactone is underutilized in the treatment of acne in women and increased utilization of spironolactone may decrease reliance on oral antibiotics and associated complications from antibiotic use. Since oral antibiotics are currently used much more often than spironolactone, the opportunity to increase the use of spironolactone for the treatment of acne in women is substantial.[5]

In subgroup analyses, spironolactone compared favorably to oral tetracycline-class antibiotics among adults, while it performed inferiorly to oral tetracycline-class antibiotics among adolescents. There are several potential explanations for this finding, including that spironolactone is less effective for adolescents than adults, that adolescents who are prescribed spironolactone have more severe acne than adults, or that therapeutic expectations differ among adolescents than adults. This latter explanation is important to consider, as adolescents may expect more rapid improvement in their acne or have more significant concerns about acne scarring than adults. It is also possible that hormonal factors may be less influential in adolescent acne and hence spironolactone may be less effective in this population.

Of note, a recent meta-analysis comparing oral contraceptive pills to oral antibiotics in the treatment of acne found that while

both treatments had similar efficacy at 6 months, oral antibiotics were more efficacious at 3 months.[38] Given this evidence that therapies that address the hormonal etiology of acne, such as oral contraceptive pills and spironolactone, may have slower onset of action when compared with oral antibiotics, oral tetracycline-class antibiotics may represent a more effective strategy for those looking for rapid improvement in their acne. Initial combination therapy with oral tetracycline-class antibiotics and spironolactone, with eventual tapering of the oral antibiotics and maintenance with spironolactone is another potential approach to consider in this population. Finally, it is important to consider that over 80% of adolescent women started on spironolactone as the index therapy are not prescribed a subsequent systemic agent within the first year of treatment and that the number needed to treat with an oral tetracycline-class antibiotic to prevent one instance of switching was 17, suggesting that for many adolescent women, spironolactone is an effective therapy for their acne.

Many patients who were started on either spironolactone or oral tetracycline-class antibiotics were found to be receiving no systemic therapy at a later point during the first year of follow-up. This finding could be a result of periods of remission induced by the systemic agent, successful maintenance with topical therapies alone, discontinuation of therapy due to guideline recommendations (ie, limiting antibiotics to 3 months), or patients who stopped seeking care with systemic agents for their acne. While it is difficult to assess which factors were the greatest contributors, topical retinoids have been shown to maintain results following an initial treatment period with oral antibiotics, so it is possible that many of these patients started on either spironolactone or oral tetracycline-class antibiotics were subsequently able to maintain their improvement with topical therapies alone.[39–41]

When compared to spironolactone, doxycycline hyclate was less likely to be switched than either minocycline or low-dose extended-release minocycline. Although these results should be interpreted with caution due to potential confounding by indication, these findings are consistent with a recent Cochrane review which found no evidence to support minocycline as being more effective than other tetracycline-class antibiotics.[49] Given the potential safety concerns associated with minocycline, doxycycline may be preferable over minocycline for the treatment of acne vulgaris in this patient population.[50,49]

This study has several strengths, including its large size with over 6,000 women treated with spironolactone. In addition, the broadly representative population included in the OptumInsight Clinformatics DataMart gives this study a high level of generalizability and the use of claims data minimizes potential loss to follow-up that could occur in a single-center observational study.

The results of this study should be interpreted in the context of the study design. Any retrospective, claims based analysis has the potential for treatment selection bias. Since claims data lacks information on acne severity, we cannot exclude that patients treated with spironolactone may have a different acne severity than those treated with oral antibiotics. However, the sensitivity analysis demonstrates that plausible differences in acne severity between the groups are unlikely to have a significant effect on the primary outcome. While we are unable to assess the reasons for switching, and thus cannot measure therapeutic *efficacy*, since switching reflects some form of treatment failure, whether due to lack of efficacy, side-effects, cost, or other reasons, this outcome is likely a reasonable measure of clinical *effectiveness* in a real-world setting. Importantly, as used in the clinical practice scenarios captured in the dataset, spironolactone appears to be effective when compared with oral antibiotics. However, because of these potential source of bias, the results should be interpreted with caution when attempting to generalize to other patient populations. Although it is possible that we were unable to capture treatment failure among patients who were never seen in follow-up, given that moderate to severe acne is challenging to manage with over the counter agents alone, it is likely patients would continue to follow-up for subsequent care if their acne remained uncontrolled. Finally, we are not able to capture information about adverse effects associated with treatment, although prior studies have suggested that spironolactone is generally well tolerated.[48,51,52]

In summary, spironolactone has similar rates of switching when compared to oral tetracycline-class antibiotics for the treatment of acne vulgaris, especially among adult women. As a result, spironolactone may represent an effective and safe alternative to oral antibiotics for women with moderate to severe acne. Increased utilization of spironolactone is a potential opportunity to improve antibiotic stewardship and reduce complications associated with antibiotic use. While ultimately large clinical trials are needed to determine the optimal management strategy for women with moderate to severe acne, these results provide additional support for the use of spironolactone in this patient population.

DISCLOSURES

The authors have no conflicts to declare.

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