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REVIEW ARTICLE

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Topical ketoconazole for the treatment of androgenetic alopecia: A systematic review

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Abstract

Androgenetic alopecia (AGA) is common and associated with significant psychosocial distress. Treatment options are needed for patients that do not adequately respond to first line treatments of finasteride or minoxidil. Topical ketoconazole has been proposed as a promising treatment. The goal of this systematic review was to evaluate the efficacy of topical ketoconazole in the treatment of AGA. A systematic literature search was conducted within the MEDLINE database using the key terms "ketoconazole" and "alopecia." Forty-seven papers were screened for inclusion, of which nine were assessed for eligibility. Seven articles were included in the qualitative synthesis, including two animal studies (total of 40 participants) and five human studies (total of 318 participants). Murine studies demonstrated a significant increase in mean ratio of hair regrowth to denuded area in the ketoconazole treatment groups compared to controls. Human studies reported increased hair shaft diameter following ketoconazole use. One study reported a significant increase in pilary index (percent anagen phase × diameter) following treatment. Studies also demonstrated clinical improvement of AGA based on photographic assessment and subjective evaluation. Topical ketoconazole is a promising adjunctive or alternative therapy in the treatment of AGA. Randomized controlled trials are needed.

KEYWORDS
androgenetic alopecia, androgenic alopecia, ketoconazole

1 | INTRODUCTION

Androgenetic alopecia (AGA) is the most common type of hair loss in men (Hamilton, 1951). Hair loss of this type predominately involves the fronto-parietal, midfrontal, or postero-superior scalp (Hamilton, 1951). Prevalence varies by age and race, with older Caucasian men most commonly affected. A staggering 50% of Caucasian men have AGA by age 50 (Sinclair, 1998). AGA is associated with significant psychosocial distress, including preoccupation about future alopecia, stigmatization, and perceived decreased attractiveness (Cash, 1992). Predisposing factors for AGA include genetics and the presence of circulating androgens (Kaufman, 2002). High levels of 5α-dihydrotestosterone (DHT), a hormone that binds to androgen receptors in scalp hair follicles, are thought to drive AGA (Ellis, Sinclair, & Harrap, 2003).

Topical minoxidil and oral finasteride are the only Food and Drug Administration approved treatments for AGA. Numerous studies support their efficacy for this indication (Adil & Godwin, 2017; Kaufman, Olsen, Whiting, et al., 1998; Savin, 1987). However, not all patients experience adequate response with these first line agents and some cannot tolerate the adverse effects (Kaufman et al., 1998). Therefore, additional treatment options are needed. Potentially promising

therapies include dutasteride, low-level laser light therapy, platelet-rich plasma, and surgical hair transplantation (Alves & Grimalt, 2016; Leavitt, Charles, Heyman, & Michaels, 2009; Olsen, Hordinsky, Whiting, et al., 2006; Jimenez, Wikramanayake, Bergfeld, et al., 2014).

Recent studies have supported the efficacy of topical ketoconazole for AGA. Ketoconazole is an imidazole derivative and potent antifungal agent that inhibits ergosterol synthesis (Borgers, Van den Bossche, & De Brabander, 1983; Van Cutsem, 1983). Ketoconazole is thought to exert anti-inflammatory effects through inhibition of 5-lipooxygenase (Cutsem, Gerven, Cauwenbergh, Odds, & Janssen, 1991; English, 2018; Magro, Rossi, Poe, & Manhas-Bhutani, 2011). In addition, ketoconazole blocks testosterone synthesis, thus decreasing DHT, and further supporting the theoretical role of ketoconazole in the treatment of AGA (Pont, Williams, Azhar, et al., 1982). Herein, we conduct a systematic review of topical ketoconazole as a treatment for AGA.

2 | MATERIALS AND METHODS

2.1 | Search strategy

Three reviewers (PV, JF, RM) conducted a systematic literature review using the MEDLINE database in March 2019. The key terms "ketoconazole" and "alopecia" linked by the Boolean operator "and" were queried in PubMed and Embase to provide the papers for review. Articles met inclusion criteria if they were published from 1951 to 2019 and satisfied the following: (1) studies specifically assessed the effects of topical ketoconazole on hair growth in humans or animals, (2) studies were prospective in nature, and (3) studies used a reproducible method to qualify or quantify hair changes in the experimental arm. The reviewers performed the study selection process independently, with discrepancies presented to the corresponding author for final determination.

2.2 | Data extraction

In accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, the reviewers (PV, JF, RM) independently assessed the quality and methodology of each study (Moher, Liberati, Tetzlaff, et al., 2009). Extracted data for each study included: study type and design; experimental subject characteristics; sample size; mode, dosage, and frequency of ketoconazole application; duration of treatment and adjuvant experimental treatments; and outcome. Aside from the biases inherent to study designs, additional sources of bias were identified.

3 | RESULTS

The database search yielded 47 articles, which were screened for reproducible prospective studies that assessed the use of topical ketoconazole for hair growth in humans or animals. Review papers and unrelated results were eliminated. Seven prospective studies were included in the qualitative synthesis, including two animal studies and five human studies. Figure 1 outlines the selection process. Table 1 summarizes the study details and outcomes of the included articles.

3.1 | Animal studies

A prospective study by Jiang, Tsuboi, Kojima, and Ogawa (2005) examined the effect of 2% ketoconazole solution, administered five times per week, on hair growth in shaved mice. Ratios of hair regrowth to denuded area were significantly greater in the ketoconazole group than the ethanol control group, with a ratio 0.61 (p = 0.006) on the 21st day. Similarly, a prospective murine study by Aldhalimi, Hadi, and Ghafil (2014) separated 20 shaved mice into four groups for 3 weeks of treatment with: (1) ketoconazole 2% solution, (2) minoxidil 5% solution, (3) minoxidil 5% solution plus tretinoin 0.1%, and (4) control (95% ethanol). There was significant hair growth in all of the experimental groups. Ketoconazole significantly increased both the mean ratio of hair regrowth to denuded hair (15.98 ± 3.42, p < 0.05) and mean diameter of hair follicles in micrometers (2.71 ± 0.18, p < 0.05) when compared to the control group (1.49 ± 0.17 and 1.53 ± 0.09, respectively). As the murine coats were androgen insensitive, the authors concluded that ketoconazole has additional

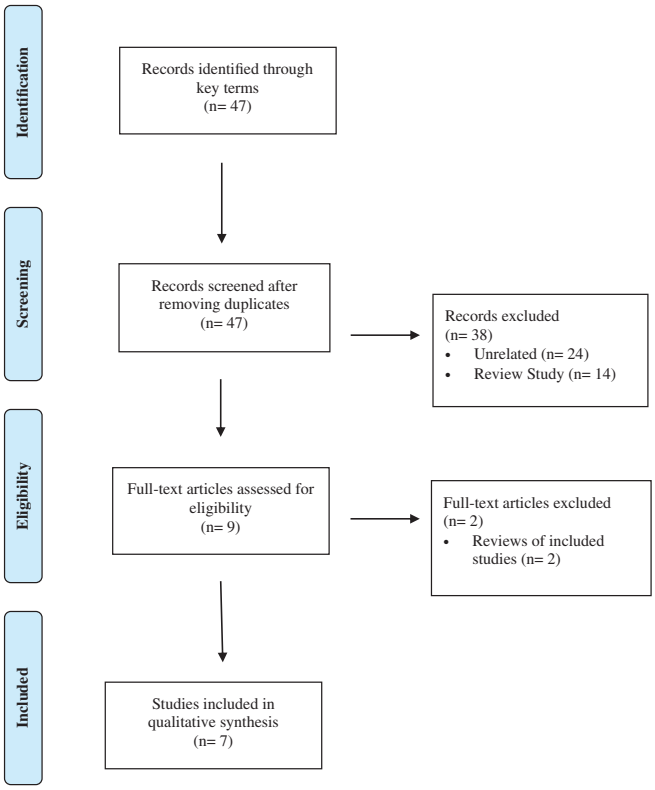

FIGURE 1 PRISMA flow diagram of included studies

TABLE 1 Summary of studies included in the systematic analysis

Authors	Quality assessment (OCEBM)	Study design	Subjects	Study size (# with ketoconazole)	Mean age	Ketoconazole dosing	Length of treatment	Adjuvant treatment	Drug comparison	Outcome measure
Jiang et al.	3	Non-randomized control	Mice	20 (10)	7 weeks	Twice daily, 2% solution, 5 days per week	3 weeks	None	None	Increased hair regrowth ratio
Aldhalimi et al.	3	Non-randomized control	Mice	20 (5)	N/a	Once daily, 2% solution 0.1 mL	3 weeks	None	Minoxidil and minoxidil/tretinoin	Increased hair regrowth ratio and follicle diameter
Rafi and Katz	4	Prospective clinical study	Human	15 (10)	40.8 years	2% shampoo, 2–3 times per week	3 months	NuH, [a]finasteride, minoxidil	NuH, ketoconazole/NuH ketoconazole finasteride	Patient recognition of hair growth
Inui and Itami	4	Prospective clinical study	Human	6 (6)	34.8 years	2% lotion, almost daily	6 months to 1 year	None	None	Hair regrowth via clinical evaluation
Khandpur et al.	2	Prospective randomized clinical study	Human	100 (10)	24.9 years	2% shampoo, three times weekly	1 year	1 mg oral finasteride daily	1 mg finasteride daily, finasteride daily with minoxidil 2% solution BID, or 2% minoxidil BID	Hair growth (patient and dermatologist perceptions)
Pierard et al., Study 1	3	Prospective non-randomized control	Human	39 (27), 22 (11)[b]	N/a	2% shampoo, 2–4 times weekly	21 months	None	Unmedicated shampoo	Pilary index (% anagen phase × hair shaft diameter)
Pierard et al., Study 2	3	Prospective non-randomized clinical	Human	8 (4)	N/a	2% shampoo, once daily	6 months	None	2% minoxidil lotion and unmedicated shampoo	Hair density, hair shaft diameter, mean sebaceous gland area
Henry et al.	2	Prospective randomized clinical trial	Human	150 (50)	N/a	1% shampoo, 2–3 times weekly	6 months	None	1% piroctone olamine and 1% zinc pyrithione	Hair shedding, anagen percentage, hair diameter, hair density, sebum excretion rate

[a]NuH is a proprietary blend of finasteride, dutasteride, and minoxidil.
[b]Age-matched controls without AGA.

effects on androgen insensitive follicles. The applicability of these findings to human subjects is unknown.

3.2 | Human studies

In a prospective study by Rafi and Katz (2011), 15 men were treated with a combination of NuH Hair (finasteride, minoxidil, and dutasteride), minoxidil foam, oral finasteride, and ketoconazole shampoo. Ten of the 15 patients used ketoconazole 2% as part of their therapy. Photographs were taken at 0, 1, 3, 5, and 9 months. All 15 patients experienced significant new hair growth. Only one patient used NuH Hair and ketoconazole alone, and no patients used ketoconazole alone, limiting the ability to discern the effect of topical ketoconazole on hair growth. The study was also limited by subjective evaluation of hair growth, and the varied combinations of products used by individual patients.

A small prospective study conducted by Inui and Itami (2007) included six male patients with AGA treated with 2% ketoconazole lotion daily. Clinical pictures were used to assess response. Three patients demonstrated improvement with ketoconazole. Two men with Grade II vertex and Grade Va hair loss (Hamilton-Norwood classification) showed hair regrowth after several months. Hair loss recurred in one patient when he stopped using ketoconazole, but growth began again upon resumption of use. The third patient had some increase in vertex hair growth at 1-year follow up. Limitations included the lack of a control group and quantitative outcome measure, inconsistent follow up, and inconsistent use of ketoconazole by subjects.

A larger study of 100 male patients with Hamilton Grades II–IV AGA was conducted by Khandpur, Suman, and Reddy (2002). There were four treatment groups: (1) 1 mg oral finasteride daily, (2) 1 mg oral finasteride daily with minoxidil 2% solution twice daily, (3) 2% minoxidil twice daily, and (4) 1 mg oral finasteride daily with 2% ketoconazole shampoo three times weekly. Ten patients were treated with ketoconazole. Patients were assessed every 3 months for 1 year. Outcomes included patient perception of hair loss and growth, subjective evaluation by dermatologists, global photographic assessment, and cessation of treatment. The mean score of hair growth was greatest when finasteride was combined with minoxidil or ketoconazole, with no significant difference between these two groups. No significant side effects were reported. Ketoconazole efficacy was not assessed independently in this study, limiting results.

Piérard-Franchimont, De Doncker, Cauwenbergh, and Pierard (1998) evaluated the effects of ketoconazole shampoo on AGA in two studies. The first was a prospective study of 39 men with AGA (Grade 3 vertex, according to Hamilton-Norwood classification); 27 were treated with 2% ketoconazole shampoo 2–4 times weekly; and 12 subjects used unmedicated shampoo. In addition, there was a control group of 22 age-matched men who had no personal or family history of AGA, of which half received ketoconazole shampoo and the other half received non-medicated shampoo. The study participants were assessed every 3 months for a total of 21 months. Results were reported as pilary index (PI), defined as A (percentage of hairs in anagen assessed on trichogram) $\times$ D (average hair shaft diameter at 1.5 cm from the bulb). At 6 months, the ketoconazole group yielded a PI index increase, which plateaued after 15 months. The PI of the unmedicated shampoo users with AGA decreased linearly over time. In the control subjects (no AGA), PI remained stable throughout the study for both control groups.

The second prospective study by Piérard-Franchimont et al. (1998) included eight males with Grade 3 vertex AGA; four were treated with 2% ketoconazole shampoo; and four were treated with 2% minoxidil lotion plus unmedicated shampoo. Hair shaft diameter and sebaceous gland area were assessed via computer analysis of punch biopsies at baseline and after 6 months. The results showed a 7% increase in the median hair shaft diameter for both the ketoconazole shampoo group and the minoxidil group. The ketoconazole group showed an 18% increase in hair density compared to an 11% increase in hair density for the minoxidil group. The ketoconazole group also demonstrated a 19.4% decrease in the mean sebaceous gland area, which, in contrast, was *increased* by 5.3% in the minoxidil plus unmedicated shampoo group. Scalp sebaceous glands affected by hair loss bind androgens with greater affinity and capacity than their hairy counterparts (Sawaya, Honig, & Hsia, 1989).

A prospective study by Henry et al. (2003) was conducted in 150 men with telogen effluvium and AGA. The men were randomly assigned to three groups receiving either 1% ketoconazole, 1% piroctone olamine, or 1% zinc pyrithione. Hair density was unchanged, although hair shedding was decreased in all groups at the end of the study period (ketoconazole group by 17.3%, piroctone olamine group by 16.5%, and the zinc pyrithione group by 10.1%). The anagen hair percentage was also increased in all groups. Mean hair shaft diameter was increased in the ketoconazole and piroctone olamine groups and decreased in the zinc pyrithione group. In this study, all three shampoos improved telogen effluvium, with no significant impact on AGA.

4 | DISCUSSION

AGA is a common dermatologic complaint with significant psychosocial ramifications, in need of effective adjunctive and alternative therapies. Of the reviewed studies, all supported the use of ketoconazole for the treatment of AGA in some regard. The dosing of ketoconazole at 2% was consistent throughout the studies, apart from one human study, which treated subjects with 1% ketoconazole shampoo. Frequency of treatment ranged from twice weekly to daily use. There were positive results even with the most infrequent use of 2–3 times per week (Henry et al., 2003), suggesting that this may be an adequate regimen for the use of topical ketoconazole in the treatment of AGA. Varying study methodology and strength of evidence limit the application of these results, although the lack of side effects supports the use of topical ketoconazole.

Studies varied in their means of assessing effects on hair growth. Three human studies reported the effect of ketoconazole on hair shaft diameter. This is relevant because, in AGA, there is hair follicle

miniaturization (Whiting, Waldstreicher, Sanchez, & Kaufman, 1999). Miniaturization leads to a decrease in terminal hairs and an increase in fine, hypopigmented vellus hairs (Whiting, 1998). All three studies noted an increase in hair shaft diameter from baseline as a result of ketoconazole use. Two studies reported this as a percent increase (5.4% in Henry et al. (2003) and 7% in Piérard-Franchimont et al. (1998)), and the third reported it as a pilary index (Piérard-Franchimont et al., 1998). The effect of ketoconazole shampoo on hair density was reported by two studies with differing results; one study reported an increase in hair density (Piérard-Franchimont et al., 1998), whereas the other reported no change (Henry et al., 2003). The increased hair shaft diameter resulting from ketoconazole use likely explains the impression of fuller hair noted in subjective clinical evaluation of hair regrowth. Further studies are needed to determine the impact of ketoconazole on hair density.

Ketoconazole increased the ratio of hair regrowth to denuded area in both murine studies. This raises the possibility of a non-androgenetic role of ketoconazole in hair regrowth. This could be due to anti-inflammatory properties of ketoconazole and/or conversion of follicles out of the telogen resting phase. In AGA, hair follicles experience a brief anagen phase of growth and prolonged telogen (resting) phase, causing new hairs to be shorter (Piérard-Franchimont & Piérard, 2001). However, hair regrowth in individuals using ketoconazole, but without a diagnosis of AGA, was not found in human studies. The study by Piérard-Franchimont et al. (1998) included a control group of age-matched men without AGA. In this group, the pilary index remained unchanged throughout the study regardless of use of ketoconazole or unmedicated shampoo. The reason for this difference between humans and mice is unclear.

Although large-scale prospective studies are lacking, the existing literature shows promise for the use of ketoconazole in AGA. Likely due to its anti-inflammatory, anti-androgenetic, and anti-fungal effects, ketoconazole has a role as an adjunctive or alternative therapy. This may be especially applicable in patients with concomitant seborrheic dermatitis, as the use of topical ketoconazole for the treatment of malassezia-related conditions is well described (Choi, Juhasz, & Atanaskova, 2019; Savin & Horwitz, 1986).

In females, the prevalence of AGA is 30% in Caucasian women over the age of 30 (Norwood, 2001). Compared to their male counterparts, females have thinning of the frontal and parietal scalp with retention of the frontal hairline (Price, 2003). In women, minoxidil has shown efficacy, whereas finasteride has not (Adil & Godwin, 2017; Price, Roberts, Hordinsky, et al., 2000). However, minoxidil has limited efficacy, with one study showing a clinical improvement in only 32% of patients (De Villez, 1985). Adverse effects of minoxidil include irritant and allergic contact dermatitis and hypertrichosis of non-scalp areas (Melis et al., 2012). Topical ketoconazole may provide a safe alternative in this population.

With lack of significant side effects, ketoconazole is a low-risk addition to the treatment regimen of any patient with AGA. Randomized controlled trials are needed to further determine ketoconazole's utility, both as monotherapy and as an adjunctive, in the treatment of AGA.

5 | CONCLUSION

First line therapy for androgenic alopecia remains the FDA-approved treatments of oral finasteride and topical minoxidil. There is limited evidence for increased hair shaft diameter and hair regrowth in human subjects following topical ketoconazole treatment. Topical ketoconazole shows promise as a low-risk adjunctive or alternative therapy in the treatment of AGA.

CONFLICTS OF INTEREST

Dr. Schoch serves on a medical advisory board for Janssen Biotech Inc. The other authors have no relevant conflicts of interest to disclose.

DECLARATIONS

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

AUTHORS' CONTRIBUTIONS

JF, PV, and RM contributed to article selection/review and manuscript writing. All authors read and approved the final manuscript.

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