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Comparative Efficacy of Oral Minoxidil and Topical Minoxidil in Treating Androgenetic Alopecia: A Systematic Review and Meta-Analysis

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Abstract **Background:** Androgenetic alopecia (AGA) is the most common disorder of hair loss in men and women. Minoxidil is one of the drugs that are widely used for the treatment of hair loss and commercially available as oral or topical preparations. This systematic review with meta-analysis was thus intended to compare the efficacy and safety profile of oral minoxidil and topical minoxidil in the treatment of AGA. **Methods:** A systematic literature search was conducted across seven major databases: PubMed, Scopus, Web of Science, Cochrane Library, Embase, CINAHL and PsycINFO. After close filtering, four studies were selected for meta-analysis where the efficacy and safety of oral and topical minoxidil for the treatment of AGA were studied. **Results:** Meta-analytic results did not express a statistically significant superiority of oral minoxidil over the topical minoxidil in promoting healthy hair growth, that is, the odds ratio 2.23 (95% CI: 0.84, 5.93) with a p-value 0.11 for a test of overall effect and Z = 1.60, with heterogeneity (Tau^2=0.00); meaning homogeneity among the studies. The incidence of adverse events was also more in the oral minoxidil compared to the oral finasteride. However, it included hypertrichosis, tachycardia and scalp pruritus with OR, 3.33 (95% CI: 1.40, 7.90) and p-value of 0.006. Qualitatively, the studies unveiled that oral and topical minoxidil have efficacy in the treatment of AGA but to different degrees of efficacy and tolerability. **Conclusion:** The clinical benefits of oral and topical minoxidil were the same when used in the treatment of AGA, however, hair density improved better with topical minoxidil and adverse effects were minimum.

Key Words Androgenetic Alopecia, Minoxidil, Hair Growth, Oral Minoxidil, Topical Minoxidil, Systematic Review

INTRODUCTION

Androgenetic alopecia (AGA), a very complex and multifactorial disease with the impairment of gradual miniaturization in hair follicles, is a condition rather severely disabling to more than a million individuals in the world who can severely interfere with quality of life, self-esteem and psychological well-being [1]. It arises from the dynamic interplay between a multiplicity of genetic, hormonal and environmental factors, such as the effect of testosterone converting to dihydrotestosterone (DHT) by the enzyme 5α-reductase, leading to activation of the androgen receptor and subsequent miniaturization of hair follicle morphology [2]. The process further gets complicated with the presence of multiple molecular pathways, which involves Wnt/β-catenin signaling pathways, sonic hedgehog signaling pathways, Fibroblast Growth Factor (FGF) signaling pathways and Platelet-Derived Growth Factor (PDGF) signaling pathways that leads to progressive thinning of hair on the scalp [3-4].

Thus, the pathophysiology of AGA leads to decreasing hair density, alteration from terminal towards vellus-like hairs and increasing miniaturization of the hair follicles that causes a reduction in hair growth rate as well as increase hair fall. Generally, it is accompanied with other comorbidities, such as hypertension, diabetes and cardiovascular disease, which add on to the complexity of this condition [5-6].

The therapeutic landscape for AGA has witnessed much evolution over the last few years and in its management, minoxidil is certainly one of the cornerstones. Minoxidil, a potassium channel opener originally designed as an antihypertensive, was also developed as a topical agent, where it proved to be effective in stimulating hair growth and attenuating hair loss through increased flow to the scalp, extension of the anagen phase of hair growth and stimulation of hair follicles into the anagen phase from telogen [4,7-8]. The atomic mechanisms of action investigated for minoxidil are opening of ATP-sensitive potassium channels, inhibition of apoptosis and stimulation of hair growth-promoting genes including Vascular Endothelial Growth Factor (VEGF) and fibroblast growth factor-7 (FGF-7) [9].

Oral minoxidil also entered the scene as a potential therapeutic agent in exploiting systemic effects on hair growth. Minoxidil increases the rate of hair growth and slows down hair loss by prolonging anagen duration, reducing the length of the telogen phase and stimulating hair matrix cell proliferation [10]. It has been claimed to possess anti-inflammatory and anti-fibrotic effects, which could contribute to the beneficial effects observed in AGA.

Indeed, although there exist oral and topical formulations of minoxidil, the comparative efficacy of the two formulations remains indefinite until date in the treatment of AGA, with most existing studies generating discordant outcomes [11]. The choice of treatment for AGA is not very well established and patients as well as clinicians face a not-so-simple decision-making process while choosing between oral and topical minoxidil [12]. This systematic review and meta-analysis therefore provides an opportunity for the synthesis of the evidence that would then be used to critically evaluate the comparative efficacy of oral minoxidil and topical minoxidil as treatments for AGA, hence leading to evidence-based treatment decisions and to guiding future research.

METHODS

Eligibility Criteria

The PECO (Population, Exposure, Comparator and Outcome) protocol for this review was developed in accordance with the PRISMA reporting guidelines [13] and is described below-

Population

The population under consideration were patients with AGA an abnormality characterized by a progressive form of hair loss because of the transformation of testosterone into DHT.

Exposure

The exposure of interest is oral minoxidil and topical minoxidil, which are formulations of minoxidil used to treat AGA.

Comparator

Of interest was the comparison of the relative efficacy of oral minoxidil compared to topical minoxidil in treating AGA.

Outcome

The outcome of interest was the efficacy of oral minoxidil and topical minoxidil in initiating hair growth, reducing hair loss and improving patient-reported outcomes of patients with AGA.

Table 1 describes the inclusion and exclusion criteria that we developed for the purpose of this review.

Database Search Protocol

A literature search through seven databases was conducted, namely PubMed, Scopus, Web of Science, Cochrane Library, Embase, CINAHL and PsycINFO. The search strings were constructed using Boolean operators and MeSH terms of AGA, minoxidil and hair growth as depicted in Table 2.

Protocol for Data Extraction

A standardized data extraction form was developed to extract relevant data from included studies. The following items were determined for extraction: study characteristics (e.g., study design, sample size, duration), participant characteristics (e.g., age, sex, hair loss severity), intervention characteristics (e.g., dose, frequency, duration) and outcome data (e.g., hair growth, hair loss, patient-reported outcomes).

Protocol for Assessing Bias

We have assessed the risk of bias in the included studies by applying Cochrane's RoB 2.0 tool [14]. This tool evaluates the presence or absence of a risk of bias across five domains, which include bias resulting from the process of randomization, bias related to deviations from planned interventions, bias from missing outcome data, bias due to inappropriate measurement of the outcome and bias from selective reporting of the result.

Statistical Analysis Protocol

The pooled data from the included studies were assembled using the RevMan 5 (v. 5.4.1) statistical analysis software, assuming a Random Effects (RE) model in place for accounting for the assumed heterogeneity among studies for calculations of dichotomous outcomes like the efficacy of oral vs topical minoxidil regarding positive hair growth recorded across participants and incidence of adverse events. To determine the heterogeneity between studies, I^2 statistic was utilized. A value of 50% or more has been considered as presenting moderate to high heterogeneity. Forest plots were generated to visually represent the outcome from the meta-analysis and were then used to develop representations of ORs and 95% CI for each outcome and inspected for visual outliers/anomalies.

RESULTS

Article Selection Schematics

As shown through Figure 1, the databases revealed 213 records, no record was found in the registers. From 26 records as duplicates were excluded along with none for other reasons leaving a total of 187 records to be screened. Of

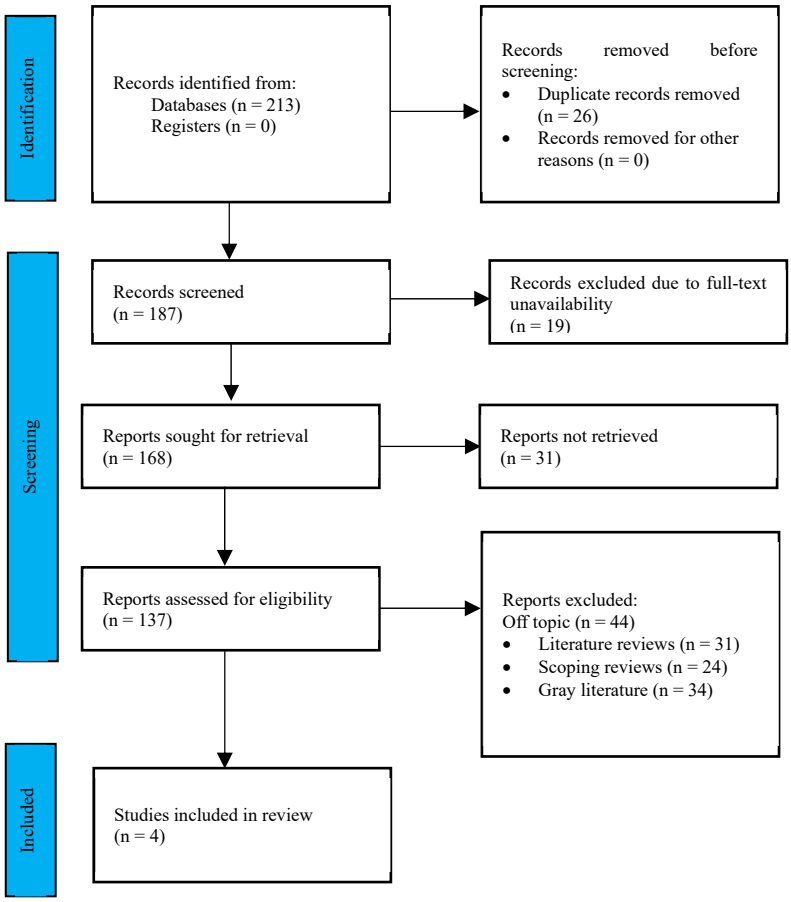

Figure 1: Description of the different stages of article selection process for the review

Table 1: Selection criteria devised for this review

Inclusion criteria	Exclusion criteria
Studies comparing oral minoxidil with topical minoxidil in treating androgenetic alopecia	Studies not comparing oral minoxidil with topical minoxidil
Randomized controlled trials (RCTs) and observational studies	Non-interventional studies, case reports, and reviews
Studies published in English language	Studies published in languages other than English
Studies conducted on human subjects	Studies conducted on animals or in vitro models
Studies reporting outcomes related to hair growth, hair loss, and patient-reported outcomes	Studies not reporting relevant outcomes

Table 2: Search strings utilised across the databases

Database	Search string
PubMed	(("Androgenetic Alopecia"[Mesh] OR "Hair Loss"[Mesh]) AND ("Minoxidil"[Mesh] OR "Rogaine"[Mesh]) AND ("Oral"[Mesh] OR "Topical"[Mesh]))
Scopus	(TITLE-ABS-KEY("Androgenetic Alopecia" OR "Hair Loss") AND TITLE-ABS-KEY("Minoxidil" OR "Rogaine") AND TITLE-ABS-KEY("Oral" OR "Topical"))
Web of Science	(TS=("Androgenetic Alopecia" OR "Hair Loss") AND TS=("Minoxidil" OR "Rogaine") AND TS=("Oral" OR "Topical"))
Cochrane Library	(MeSH descriptor: [Androgenetic Alopecia] explode all trees AND MeSH descriptor: [Minoxidil] explode all trees AND MeSH descriptor: [Oral] explode all trees OR MeSH descriptor: [Topical] explode all trees)
Embase	('androgenetic alopecia'/exp OR 'hair loss'/exp) AND ('minoxidil'/exp OR 'rogaine'/exp) AND ('oral'/exp OR 'topical'/exp)
CINAHL	(MH "Androgenetic Alopecia" OR MH "Hair Loss") AND (MH "Minoxidil" OR MH "Rogaine") AND (MH "Oral" OR MH "Topical")
PsycINFO	(DE "Androgenetic Alopecia" OR DE "Hair Loss") AND (DE "Minoxidil" OR DE "Rogaine") AND (DE "Oral" OR DE "Topical")

these, 19 full-text could not be retrieved for their exclusion and reports of 168 were sought for retrieval. However, 31 reports could not be retrieved and thus only 137 reports were left for eligibility assessment. The review studies excluded are as follows: Off-topic: 44 reports. Such ones have been excluded. Other literature reviews that had excluded studies included other reviews apart from scoping reviews, a total of 31, gray literature reports, 24 and 34. A total of 4 clinical trials [15-18] were found to be within the inclusion criteria.

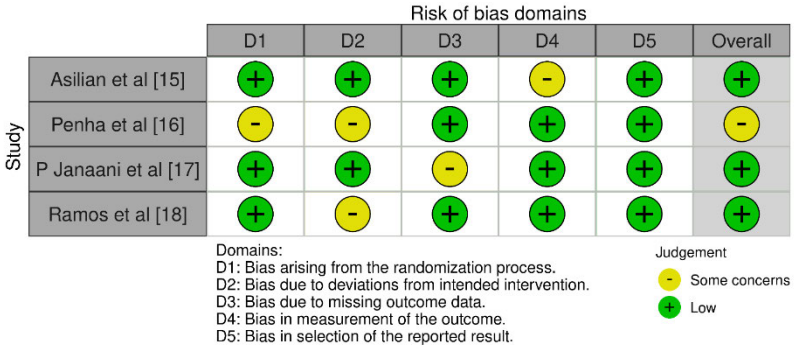

Figure 2: Bias levels assessed across the included trials

Observed Levels of Bias

Varying levels of bias were seen across the included trials with an overall low risk of bias in Asilian *et al.* [15], Janaani *et al.* [17] and Ramos *et al.* [18] (Figure 2). However, Penha *et al.* [16] had some concerns. Asilian *et al.* [15] had a very low risk in all domains except D4 in which bias concerning the measurement of an outcome existed and D3 in which bias resulting from missing outcome data was observed, respectively. Penha *et al.* [16] had concerns with regard to D1 or bias related to the process of randomization as well as with regard to D2 or bias because of deviations from the planned interventions. Ramos *et al.* [18] had concerns in only D2. All the studies had low risk in D5- bias arising from the reporting of the selected result. Most the studies had generally low overall risk of bias.

Baseline Variables Analyzed

The included trials as shown in Table 3 [15-18] differed in respective sample sizes, study designs and durations. For example, the sample size varied between 52 and 90 patients, with two studies having a smaller patient sample of 65 and 66 patients [15,17]. The study durations also varied from 6 months to 24 weeks, with two studies having a short duration of 24 weeks [16,18]. There were three randomized comparative studies [15,16,18] in the study design category and the other was a RCT [17]. Two were open-label studies [16,18], where both participants and researches knew the treatment assignments. Participants were males and females in the respective studies, with one study recruiting male participants exclusively [17] and another female participants exclusively [18].

Outcomes Observed

The study by Asilian *et al.* [15] revealed that the oral and topical minoxidil groups both exhibited a significant increase in mean hair diameter and the topical showed significant improvements in hair density. Satisfactory therapy with few side effects was observed in both groups: one case of orthostatic hypotension occurred in the oral group.

Penha *et al.* [16] found no statistical differences in mean hair diameter between oral and topical minoxidil groups. However, the topical group did show clinical improvements in hair density at all scalp points with a statistically significant difference on the vertex, being 24% better with oral minoxidil. Terminal hair density increased significantly in the oral group on the vertex.

Janaani *et al.* [17] reported that the most common side effects in the oral minoxidil group were hypertrichosis (49%) and headache (14%); there were greater discontinuations in the topical group due to adverse events. The mean change in terminal hair density at the vertex from baseline to week 24 was 23.4 hairs/cm2 (95% CI, -0.3 to 43.0; p = 0.09) for the oral group.

Ramos *et al.* [18] found that the terminal hair density was superior when PRP was combined with topical minoxidil compared with oral minoxidil. Oral minoxidil reduced vellus hair density but not terminal and all groups reduced diversity in hair diameter. Total hair density increased by 12% (95% CI 8.0%-16.1%) with oral and 7.2% (95% CI 1.5%-12.9%) with topical minoxidil (p = 0.09). The side effects observed were hypertrichosis at 27% and tachycardia in the oral group and scalp pruritus at 19% in the topical group.

Meta-Analysis Observations of Efficacy of Oral vs. Topical Minoxidil Observed

Figure 3 shows the forest plot illustrating the effect of oral vs topical minoxidil on stimulating positive hair growth as measured by OR. The pooled effect of oral minoxidil in stimulating positive hair growth was nonsignificant with an OR of 2.23 (95% CI: 0.84, 5.93) and p-value 0.11. The test for overall effect had a Z-score of 1.60. Notably, heterogeneity analysis was such that a Tau^2 of 0.00 was reported signifying that there was an overall homogeneity of the studies and no noteworthy variation in the results obtained as the Chi^2 value reported was 0.01 (df = 2, p = 0.99) and an I^2 value of 0%. The statistics point out that oral minoxidil did not bring out any statistical superiority for the topical use of minoxidil concerning the promotion of healthy hair growth. Since the studies are relatively homogenous and the overall test was not significant, it suggests that the outcome observed came out fairly and without biasness, such that the effect of oral minoxidil for positive hair growth was not any better than that of topical minoxidil.

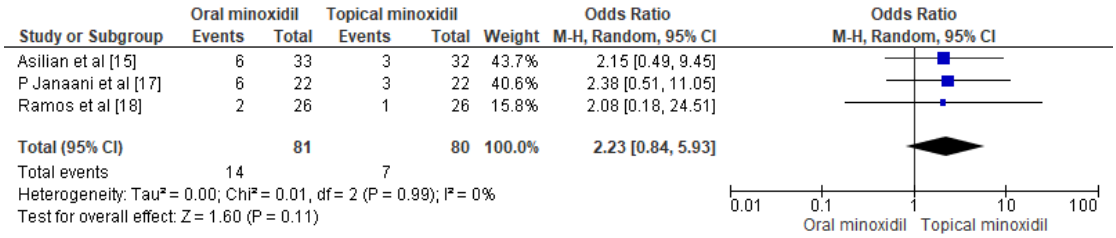

Figure 3: Efficacy of oral vs topical minoxidil in terms of positive hair growth recorded across the participants

Table 3: Included trials and their observed inferences

Study	Sample size	Study type	Duration	Key outcomes	Adverse effects	Statistics	Overall inference observed
Asilian *et al.* [15]	65 patients (32 topical, 33 oral)	Randomized, comparative study	6 months	Both groups showed significant improvements in mean hair diameter. Topical group had significant improvements in hair density. High patient satisfaction in both groups.	Few adverse effects. One case of orthostatic hypotension in oral group, managed with diet. Mild, reversible minoxidil-induced telogen effluvium and hypertrichosis in both groups.	No significant differences in mean hair diameter between groups. Topical group showed significant improvements in hair density at all scalp points.	Both oral and topical minoxidil are effective, with topical showing better hair density improvements and fewer adverse effects.
Penha *et al.* [16]	90 participants (35 topical, 33 oral)	Randomized, open-label, comparative study	24 weeks	Oral minoxidil superior to topical on vertex (24% difference) but not frontal scalp. Significant increases in terminal hair density for oral group on vertex.	Hypertrichosis (49%) and headache (14%) most common in oral group. Topical group had more treatment discontinuations due to adverse events.	Mean change in terminal hair density from baseline to week 24 on vertex: 23.4 hairs/cm2 (95% CI, -0.3 to 43.0; p = 0.09) for oral group.	Oral minoxidil shows greater efficacy on vertex, but with more adverse effects. Topical minoxidil has lower efficacy but better tolerability.
Janaani *et al.* [17]	66 male participants (22 per group)	Randomized controlled trial	32 weeks	PRP+topical minoxidil had superior terminal hair density. Oral minoxidil better at reducing vellus hair density. All groups showed reduction in hair diameter diversity. Increases in regulatory T cells and signaling molecules across groups.	Not reported	At 32 weeks, PRP+topical minoxidil significantly increased terminal hair density compared to oral (p = 0.03) and topical (p = 0.02) groups. Oral group had significantly decreased vellus hairs compared to PRP+ topical group (p = 0.02).	Combining PRP with topical minoxidil achieves superior terminal hair density. Oral minoxidil is more effective in reducing vellus hair density.
Ramos *et al.* [18]	52 female participants (26 per group)	Randomized, open comparative study	24 weeks	12% increase in total hair density with oral, 7.2% with topical (non-significant difference). Significant increase in terminal hair density only in oral group. Improved global photographic assessments and quality of life scores in both groups.	Hypertrichosis (27%) and increased heart rate in oral group. Scalp pruritus (19%) in topical group.	Total hair density increased by 12% (95% CI 8.0%-16.1%) with oral and 7.2% (95% CI 1.5%-12.9%) with topical minoxidil (p = 0.09).	Low-dose oral minoxidil is an effective alternative to topical minoxidil in female pattern hair loss, with some advantages in increasing terminal hair density but more adverse effects.

Meta-Analysis Observations of Adverse Events

The forest plot in Figure 4 illustrates OR of adverse events associated with oral minoxidil compared to topical minoxidil. The plot has three categories of adverse events: hypertrichosis, TE and scalp pruritis. Findings are that the adverse events were much lower in using topical minoxidil compared to oral minoxidil. In the hypertrichosis group the OR was 3.58 (95% CI: 0.40, 32.06); heterogeneity was significant ($Tau^2 = 0.92$, $Chi^2 = 1.56$, $df = 1$, $p = 0.21$, $I^2 = 36\%$). In the TE group the OR was 2.54 (95% CI: 0.71, 9.09); the test for overall effect was not significant ($p = 0.15$). Scalp pruritis OR: 5.47 (95% CI: 0.89, 33.57), trend towards significance. ($p = 0.07$). On cumulative analysis for all adverse events, the OR was: 3.33 (95% CI: 1.40, 7.90); $p = 0.006$, indicating topical minoxidil is associated with fewer adverse events compared with oral minoxidil.

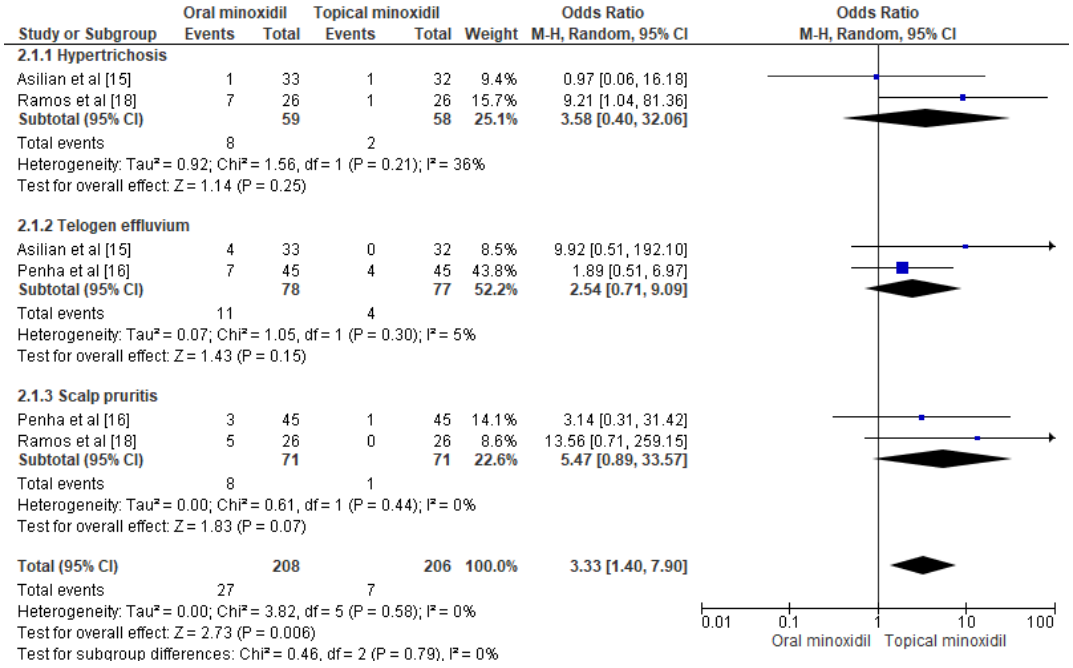

Figure 4: Adverse events recorded

DISCUSSION

After comparative analysis of findings from the included studies [15-18], a broad inference can be drawn about the safety and efficacy of oral and topical minoxidil in the treatment of alopecia. Based on the findings of the studies, both oral and topical minoxidil have proved to stimulate hair growth. However, there exist difference in the rates of efficacy and tolerability of the two treatments in alopecia.

Asilian *et al.* [15] and Ramos *et al.* [18] have reported similar results wherein topical minoxidil provides better improvement of hair density but with fewer side effects than oral minoxidil. However, in the context of Ramos *et al.* [18], there is an added advantage of PRP together with topical minoxidil to achieve superior terminal hair density.

Contrarily, Penha *et al.* [16] and Janaani *et al.* [17] yield opposite results as oral minoxidil is a better medication for the vertex with higher side effects. Penha *et al.* [16] in their study expresses 24% difference to favor oral minoxidil on the vertex, but also says that the risk of hypertrichosis as well as headache is increased on consuming oral minoxidil as concluded by the findings of Janaani *et al.* [17].

Interestingly, Ramos *et al.* [18] seem to appear on the opposite side of the divide, as low-dose oral minoxidil is a promising alternative to topical minoxidil for female pattern hair loss. Even though oral minoxidil has a higher incidence of side effects, its benefits include increased terminal hair density.

On closer observation, the evidences are classified into two groups: those that marked the advantage of topical minoxidil (Asilian *et al.* [15] and Ramos *et al.* [18]) and those in which oral minoxidil has greater curative potential though accompanied by more side effects (Penha *et al.* [16] and Janaani *et al.* [17]). The degree of similarity among the studies varies because Asilian *et al.* [15] was in high concordance with Ramos *et al.* [18], but Penha *et al.* [16] and Janaani *et al.* [17] had a moderate degree of similarity.

Extensive use of minoxidil for its effectiveness in alopecia treatment has been witnessed, including AGA, Alopecia Areata (AA) and scarring alopecia. Several studies have described minoxidil's efficacy in AGA treatment management. Within some reports, it was evident that patients had objective clinical improvement, reduced shedding and increased hair length [19]. An Asian cohort study showed remarkably excellent results in all patients receiving daily combination of 1 mg finasteride, 2.5 mg minoxidil and 5% topical minoxidil twice daily [18]. The satisfaction of the patients was very high at 96% and 80% after 6 and 12 months. Also, minoxidil is used to treat AA with either used alone or with another agent [18].

Minoxidil has further been reported in several studies to stimulate hair regrowth; one study showed that patients suffering from AA, who had used 5 mg minoxidil twice daily, increased terminal hair regrowth up to 19 percent. Another study demonstrated increased hair growth with concomitant minoxidil and oral tofacitinib in cases resistant to 5% topical minoxidil for the management of AA [20]. There are very few case reports of minoxidil in the treatment of scarring alopecia Like Lichen Planopilaris (LPP) and Frontal Fibrosing Alopecia (FFA). From these, the drug is reported to induce hair growth in these conditions [21-22]. Other reports by authors also showed that Minoxidil is effective in other hair disorders such as pseudopelade of Brocq and monilethrix.

Minoxidil has also been shown to be tolerated quite well in both females and males while the most reported adverse events were hypertrichosis, tachycardia and fluid retention [5]. Generally, these are mild side effects that do

not necessitate discontinuation of therapy. Contraindications are few and include drug hypersensitivity and history of pheochromocytoma [23-26]. A dosage adjustment should be considered in the following patients with a serious renal condition or on dialysis. Severe hepatic impairment should also be closely monitored [3]. Routine laboratory monitoring is not necessary and minoxidil is considered safe in women of childbearing age, although it should be withdrawn when conception is attempted due to its category C pregnancy and excretion in breast milk.

Similar to our review, Devjani *et al.* [1] further emphasized that AGA is chronic in nature and influenced by genetic and environmental factors. They further added that there are few available treatments for the condition as such and FDA-approved drugs for the disease are only two: topical minoxidil and oral finasteride. Alternatively, oral minoxidil was studied by Randolph *et al.* [27] and Villani *et al.* [28]. The outcome of the study confirmed that oral minoxidil was effective as an alternative for topical minoxidil as a treatment for AGA. Low doses between 0.25 and 5 mg/day have proved to stimulate hair growth successfully. Our results, therefore, appear to be supported by these studies, which suggest that oral minoxidil is an alternative to topical minoxidil.

Lemes *et al.* [29] conducted a review of literature regarding the pediatric populations usage of minoxidil. This was marked by the absence of any corresponding guideline on its pediatric use. The necessity for further studies on the safety and efficacy of minoxidil in pediatric patients was thus emphasized. However, our review is not focused on pediatric populations, but our results are most indicative that minoxidil may be an effective treatment option for AGA in adults.

Gupta *et al.* [30] carried out a comprehensive overview of topical minoxidil on the action mechanism, pharmacokinetics and clinical efficacy. Our results agreed with theirs, which was on the effectiveness of topical minoxidil to promote hair growth among men and women who have AGA.

Klein *et al.* [31] compared the therapeutic results of patients treated with low-dose oral minoxidil, LDOM, solitary versus those treated with LDOM in combination with topical minoxidil. Their results failed to show significant differences in hair density or caliber between the two treatment groups, but they conclude that LDOM alone could be an effective therapy option for AGA. Our findings were consistent with theirs by pointing towards the possible benefits of oral minoxidil as an alternative to topical minoxidil.

Clinical Recommendations

Considering better tolerability as well as equal efficacy with oral minoxidil, clinicians should consider topical minoxidil as an ideal treatment for AGA. The combination of platelet-rich plasma with topical minoxidil should be taken up for study as a promising approach to attaining higher terminal hair density. It would also be important to define standard measures for hair growth and adverse events in future studies. It would also be interesting to perform efficacy and safety studies of oral as well as topical minoxidil in bigger, more diverse populations.In addition, we recommend longer study lengths and more rigorous study designs in order to finally determine long-term gains and side effects of these treatments. This could be attained via standardization of oral and topical minoxidil dosing, as well as through more objective means of hair growth and adverse events measurement. The studies must also seek to attract more heterogeneous participants, both male and female, in order to obtain a result with greater generalizability.

CONCLUSIONS

Based on our review, we conclude that oral and topical minoxidil alike promote hair growth in AGA but differ according to their efficacy and tolerability. By our results, topical minoxidil could be associated with a better improvement in hair density and fewer adverse events in comparison with oral minoxidil, especially when more effective at the vertex but also accompanied by more side effects. The combination of PRP with topical minoxidil might achieve superior terminal hair density with fewer side effects.

Limitations

Our review had several limitations that might have affected the accuracy and generalizability of our findings. First, the study designs, durations and sample sizes differed among the included trials, which may introduce bias and reduce the precision of our estimates. Basically, the few low-power studies with participants reduced the power to detect significant differences that could be associated between oral and topical minoxidil. Additionally, the study's definitions of hair growth and adverse events also vary from one study to the other, thereby influencing outcome reporting varied to some extent.

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