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REVIEW PAPER

An overview of incidence and mechanisms promoting weight gain as an adverse effect of oral minoxidil therapy for androgenetic alopecia

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ABSTRACT

Introduction and aim. Androgenetic alopecia, with a mechanism based on the excessive response of hair follicles to androgens, affects a majority of people at some point in their lives, prompting them to seek therapy. Current treatment options for this condition include oral minoxidil, a medication associated with an adverse effect of fluid retention, potentially resulting in weight gain for certain individuals. In contemporary scientific literature, there aren't many articles focusing solely on this specific side effect. The objective of this review is to explore links between taking oral minoxidil and fluid retention leading to weight gain in patients with androgenetic alopecia by examining available studies in order to understand the mechanisms behind this phenomenon and the dose dependence of fluid retention.

Material and methods. A review of the literature was performed to find connections between oral minoxidil therapy and water retention-induced weight gain.

Analysis of the literature. Clinical trials have demonstrated that low dose oral minoxidil therapy, within the range of 0.5 to 5 mg daily, leads to an improvement in both hair count and density. The incidence of side effects such as hypertrichosis, fluid retention, headache, dizziness, and insomnia, is relatively infrequent. Fluid retention rates varied between 0.22% in the Tanaka study and 10% of patients in the Panchaprateep study. The discontinuation of treatment was necessary in some instances, with the highest rate of 2.4% cases in the Jimenez-Cauhe study. A comparative analysis of studies on oral minoxidil use for refractory hypertension, within the range of 10 to 40 mg daily, revealed that nearly all patients required adding a diuretic to control fluid retention. Some patients discontinued the treatment due to the severity of side effects. In instances of minoxidil overdose, serious complications, including generalized edema, myocardial infarction, stroke, and pleural effusion, were observed. Across these studies, all patients recovered following the discontinuation of minoxidil treatment. The underlying mechanism behind oral minoxidil induced sodium and fluid retention, contributing to weight gain, is associated with alterations in the neurohumoral system, increased plasma renin activity, changes in renal hemodynamics with relocation of the blood circulation from outer to inner cortex, and tubular effect that can be connected to minoxidil ability to act as an opener of potassium channels in the thick ascending limb of the loop of Henle causing greater reabsorption of sodium and chloride.

Conclusion. The frequency and severity of water retention promoting weight gain in individuals taking oral minoxidil are dose dependent. In most patients, minoxidil is a safe and effective treatment option for androgenetic alopecia. In some cases, due to rapid weight gain of 5 pounds or more, adding a diuretic or discontinuation may be required. Further research is necessary to better understand the mechanisms and dose dependence of minoxidil induced fluid retention, which promotes weight gain.

Keywords. androgenetic alopecia, fluid retention, minoxidil side effects, oral minoxidil

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Introduction

Androgenetic alopecia (AGA) is a condition preset by genetic factors that affects up to 50% of men and women.[1] The underlying process leading to AGA is an excessive response of hair follicles to androgens.[2] Over time, dihydrotestosterone (DHT) causes the gradual miniaturization of terminal hair, leading to balding especially of the temples and the crown. Hair is an important part of an individual's self-image, thus the consequences of androgenetic alopecia are largely psychological.[1,2] According to recent studies, approximately 60% of women and 30% of men suffering from AGA experience emotional distress that can lead to anxiety and depression.[3] Nowadays, therapies for AGA include oral minoxidil, oral finasteride and dutasteride, platelet-rich plasma, low-level light therapy, and hair transplantation.[4] Minoxidil, being a direct acting peripheral vasodilator, was first introduced to general medicine in the 1970s as a treatment for refractory hypertension. The initial trials of this drug displayed an adverse effect of hypertrichosis in 80% of patients, which led in 1981 to the development of a topical minoxidil solution and in 1987 to creating low dose oral minoxidil (LDOM) therapy for AGA.[5] However, despite causing improvements in both hair diameter and density, the medicine seems to have also an array of possible adverse effects, such as weight gain, fluid retention, pericardial effusion, hypertrichosis, hirsutism, GI intolerance, hypotension, tachycardia, headache, periorbital oedema, and insomnia.[6-8]

Aim

In this review, we aim to explore the prevalence and mechanisms of oral minoxidil induced water retention leading to weight gain in patients with AGA.

Material and methods

For this review, PubMed, Medline, and Google Scholar were searched to find articles concerning the impact of LDOM therapy for AGA and the prevalence of adverse effects, with an emphasis on fluid retention leading to possible weight gain. As a comparison, we also analyzed minoxidil treatment for refractory hypertension and oral minoxidil overdose. We performed a search using the keywords "androgenetic alopecia", "oral minoxidil", "low dose oral minoxidil", "minoxidil adverse effects", "minoxidil fluid retention", "minoxidil weight gain."

Articles underwent a careful analysis and were included based on their relevance to our review. The inclusion criteria encompassed abstracts and full text-format published articles, including review articles, randomized control trials, and clinical trials, written in English. We excluded duplicates and articles irrelevant to our topic. The initial search, employing the keywords and criteria present in this study, resulted in identification of 237 publications consisting of abstracts and full texts. Following this, duplicate and irrelevant scientific papers were excluded. Figure 1 illustrates the inclusion and exclusion criteria applied during this process. Subsequently, a total of 115 manuscripts were identified for detailed evaluation, which led to the selection of 42 articles and reports that are incorporated in this literature review.

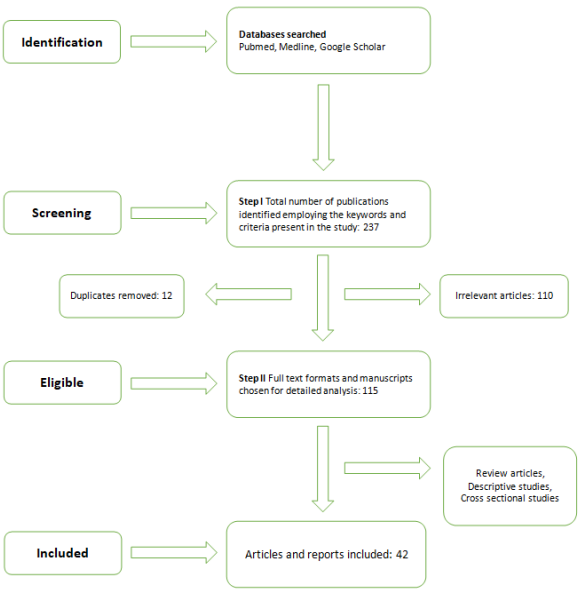

Fig. 1. A flow chart figure displaying the sequential steps from the initiation of the literature research to the finalization of chosen publications

Analysis of the literature

Hair anatomy and hair growth cycle

Hair is a structure that consists of terminally differentiated keratinized dead cells. In its composition, we can distinguish the follicle and the shaft (Fig. 2).[9] The division of the hair follicle separates the upper part, including the infundibulum and the isthmus, from the lower part, consisting of the bulb and the suprabulbar region. The bulb includes the dermal papilla that is a group of specialized mesenchymal fibroblasts, capillaries along with nerve endings, and the hair matrix built by quickly proliferating keratinocytes. Hair follicles remain anchored in the subcutis layer and undergo the phases of the hair growth cycle. The hair shaft, built by trichocytes, is visible above the skin.[9-11] The normal hair growth cycle (Fig. 3) is divided into 4 phases: growth (anagen), involution (catagen), resting (telogen), and shedding (exogen).[9,12] The anagen phase lasts 2-7 years, which makes it the longest part of the cycle. In this phase, cells at the lower part of the hair divide rapidly, simultaneously cells of the matrix migrate outward. The catagen phase lasts around 3 weeks and is a period of short transition. In this phase, the hair shafts lose their connections to the papillae and contract. The telogen phase lasts around 3 months. In this phase, the matrix regresses and the papilla retracts to a location near

the bulge. No significant proliferation or apoptosis happens in this phase. In the exogen phase, active hair shed and new hair continue to grow.[9]

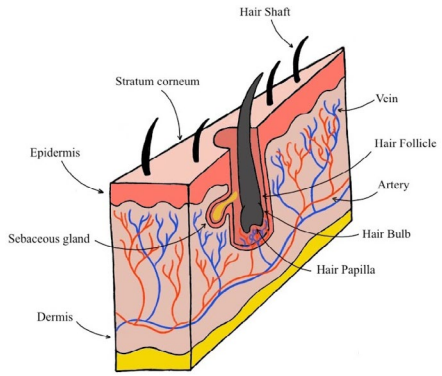

Fig 2. Anatomy of the hair[9]

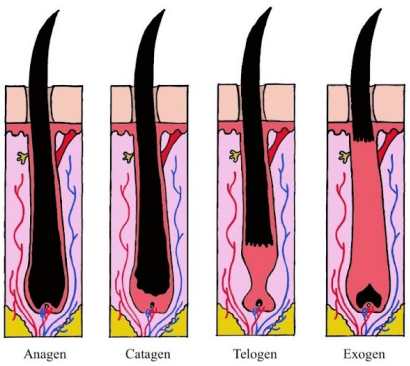

Fig 3. Hair growth cycle[9]

At any given moment, around 85–90% of the hair remains in the anagen phase, 2% of the follicles are in the catagen phase, and 10–15% in the telogen phase.[12,13] However, according to the newest data, this percentage of telogen hair can be overestimated, and in reality, only 3.6% remain in this phase.[14]

Androgenetic alopecia

Androgenetic alopecia is the most prevalent type of hair loss worldwide and affects approximately 30% of men and 20% of women in their 30s, increasing to 50% of men and 40% of women in their 50s. This further increases to 80% of men and 50% of women by the time they reach their 70s. The disease starts after puberty, progresses with age, and is the most common among Caucasians.[1,2,12,15-17] Hair loss usually starts after puberty on the frontal hairline with bitemporal recession, subsequently it's followed by diffuse thinning of the hair and eventually balding on the vertex. As AGA progresses, the bald spot at the crown connects with the frontal receding hairline, leaving only an island of hair at the frontal scalp. With the further progression of AGA, the island disappears. At this point, hair is left only in the occipital and parietal zones. The Hamilton Norwood scale is typically used to analyze the degree of AGA in men, while the Ludwig scale is used to assess the extent of AGA in women. AGA might be a factor contributing to a higher risk of type 2 diabetes, cardiovascular disease, and benign prostatic hyperplasia.[18-23] The mechanism of AGA has both a genetic and hormonal background, with excessive response of the hair follicles to androgens being the main factor. Over time androgens promote gradual miniaturization of terminal hair into intermediate and vellus hair. This process clinically manifests itself as continuous hair shortening and thinning, leading to hair loss among patients with AGA.[12,24] Moreover, elevated blood levels of dihydrotestosterone and 5-alpha reductase type 2 are frequent in patients with AGA. DHT has 10 times higher affinity to androgen receptors and is a strong hormone promoting the development of male characteristics, whereas 5-alpha reductase type 2 is an enzyme converting testosterone into DHT in the hair follicles. Even though blood levels of testosterone may not vary between patients with and not affected by AGA, the blood concentrations of unbound testosterone are elevated in individuals with AGA.[1,12,25] AGA is usually perceived as a minor dermatologic condition. However, it has been observed that about 60% of female patients and 30% of male patients with AGA frequently suffer from emotional distress, leading to anxiety as well as depression.[2,3]

Nowadays, there are continuously more new treatment options available for AGA. These include topical and oral minoxidil, topical and oral finasteride, oral spironolactone, topical pyrilutamide, intradermal botox injections, platelet-rich plasma, low-level light therapy, microneedling, and finally hair transplant. In this review, we're going to focus solely on the increasingly popular off- label use of oral minoxidil therapy for AGA.[12,15]

Hypertension

In this literature review, along with exploring the impact of LDOM treatment on patients with androgenetic alopecia, we're also reporting the adverse effects associated with the use of higher doses of oral minoxidil therapy among individuals with refractory hypertension. High blood pressure, being one of the most frequently occurring chronic illnesses leading to premature deaths in the world population, is defined as average systolic blood pressure (SBP) ≥ 140 mmHg, average diastolic blood pressure (DBP) ≥ 90 mmHg, or usage of antihypertensive agents.[26] Resistant hypertension, being the most severe form of hypertension, can be diagnosed when more than 3 antihypertensive drugs (diuretic included) belonging to different classes at the highest doses recommended are not able to reduce the blood pressure.[26-28]

Minoxidil

Oral minoxidil is a direct acting arteriolar vasodilator. The drug was first introduced in general medicine in

the 1970s as a treatment option for refractory hypertension, dosed at 10 to 40 mg daily with a maximal recommended dose not exceeding 100 mg.[5,6,29,30] Even though minoxidil has a plasma half-life of approximately 3 to 4 hours, its blood pressure lowering effect may persist for up to 72 hours, which implies the accumulation of the drug in the body.

As a result of reaction with sulfotransferase, minoxidil transforms into minoxidil sulfate. Being the active metabolite, minoxidil sulfate opens ATP-sensitive K^+ channels located in arterial smooth muscle cells, leading to hyperpolarization of the sarcolemma, which inhibits Ca^{2+} entry and causes vasodilation. This mechanism promotes hypotensive effect. Minoxidil induced arteriolar vasodilation can activate the sympathetic nervous system through aortic and carotid baroreceptors impulses, causing tachycardia, as well as an increased plasma renin activity that leads to aldosterone synthesis. That's why, when used among patients with resistant hypertension, minoxidil should be prescribed along with beta blocker to prevent tachycardia and a diuretic to avoid sodium and fluid retention.[5,8,30-32] The adverse effects of oral minoxidil are dose dependent, and besides an increase in heart rate as well as possible water retention, they include hypertrichosis affecting about 80% of individuals, hirsutism, postural hypotension, fatigue, dizziness, nausea, pericardial effusion, periorbital edema, GI intolerance, and insomnia.[6-8,31-35] The reported high prevalence of hypertrichosis among patients using minoxidil led in 1981 to the development of 5% topical minoxidil solution applied on the scalp, and subsequently in 1987, low dose oral minoxidil treatment. Off-label LDOM therapy dosed at 0.5-1 mg daily for women and 2.5–5 mg daily for men appears to be very effective in individuals suffering from AGA with a relatively good safety profile. Recently, this treatment is gaining popularity among patients because oral administration is simply easier than applying the topical solution. In 1988 minoxidil solution in concentration of 2% was approved by FDA, and in 1998 minoxidil 5% solution gained acceptance for topical use. Oral minoxidil to this day is an off-label treatment for AGA. The Polish Dermatological Society since 2018 recommends in men 5% minoxidil solution applied once or two times a day on the scalp with a provided applicator and in women 2% minoxidil solution used topically on the hair two times a day or 5% minoxidil solution used topically on the hair once a day as a treatment of first choice. Once applied, minoxidil solution should remain on the scalp for at least 2 hours to absorb. Both oral and topical minoxidil are not recommended for children and during pregnancy.[5,6,24,36,37] The exact mechanism of minoxidil hair growth promotion is not entirely known. By opening ATP-sensitive K^+ channels in arterial smooth myocytes of the scalp, leading to vasodilation, minoxidil increases the blood flow and allows a better delivery of oxygen and nutrients to the hair. Through inducing the Wnt/β-Catenin pathway, it elevates VEGF concentration in the cells of dermal papilla, and promotes vascularization as well as prolongs the growth phase of hair cycle. It is also reported that minoxidil inhibits interleukin 1α and prostacyclin synthesis at the same time promoting leukotriene B4 and prostaglandin E2 production, therefore it presents anti-inflammatory properties. Minoxidil might also act as an antiandrogen by inhibiting the expression of 5α-reductase, which converts testosterone to DHT, and inducing 17β-dehydrogenase in the hair follicles to quicker transform testosterone to its less biologically active forms. Due to lack of full understanding how exactly minoxidil causes hypertrichosis, further studies are required.[5,8]

Mechanism of minoxidil induced fluid retention leading to possible weight gain

The metabolism of oral minoxidil mainly happens in the liver, where it conjugates with glucuronic acid. After metabolization, minoxidil gets eliminated from the body through the kidneys. Even though it takes approximately 3 to 4 hours from administration to excrete the drug, the vasodilating effect remains for roughly 72 hours. Oral minoxidil has been linked to retention of sodium and fluid leading to weight gain, pericardial effusion with unknown mechanism, pulmonary hypertension caused by high pressure in the pulmonary artery along with increased cardiac output, and in extreme cases, coronary heart disease resulting potentially from the increased oxygen demand due to higher heart rate as well as cardiac output. Sodium and fluid retention causing weight gain is dose dependent and occurs due to alterations in neurohumoral system, increased plasma renin activity, changes in renal hemodynamic including relocation of the blood circulation from the outer to the inner kidney cortex, along with directly tubular effects that can be connected to minoxidil's ability to act as an opener of potassium channels. Through activating the potassium channels located in the thick ascending limb of the loop of Henle, minoxidil boosts the activity of Na^+ $2Cl^-$ K^+ cotransporters and leads to greater reabsorption of sodium and chloride. Minoxidil can promote rapid 5 pounds or more weight gain. Early identified fluid retention is easier to manage with diuretics. Therefore, a patient's weight should be monitored daily to pinpoint individuals experiencing fluid retention. In some cases, discontinuation of minoxidil treatment may be required due to extreme fluid retention.[31,32,35]

Clinical findings of oral minoxidil weight gain

In this segment of the review, we will display a short summary regarding side effects of LDOM therapy for AGA, oral minoxidil dosed at 10–40 mg daily as a treat-

ment for refractory hypertension, and oral minoxidil overdose, with emphasis on fluid retention. Through this process, we found the link between dosage of oral minoxidil and prevalence of sodium and fluid retention, leading to weight gain, which in some cases caused discontinuation of treatment.

Across the 5 studies regarding the use of LDOM treatment for AGA, an improvement of hair count and density was observed. The incidence of side effects was low. The most common adverse effects included: hypertrichosis, fluid retention along with lower limbs edema, headache, dizziness, and insomnia.[6,24,37-39] Fluid retention led to discontinuation of treatment in several individuals.[6,37,39]

Across the 4 studies, when minoxidil was used as an antihypertensive agent, in 1 review the safety profile was similar to LDOM therapy for AGA because low doses of minoxidil were used, whereas in 3 trials the incidence of side effects was higher.[30,33,40,41] Many patients required adding a diuretic to control sodium and fluid retention, leading to weight gain.[30,33,41] Some patients had to discontinue the use of minoxidil because of the severity of side effects.[33,40,41]

In 2 studies displaying minoxidil overdose, the most severe side effects were observed. These included generalized edema, myocardial infarction, stroke, passing out, prolonged tachycardia, fluid retention and pleural effusion.[36,42] Intubation and use of a diuretic was needed.[42] Patients recovered after discontinuation of the treatment.[36,42]

LDOM therapy for AGA clinical trials

In the multicenter study conducted in 2021 by Sergio Vano-Galvan et al. 1404 patients mostly with AGA 82.4% (1157 patients) who received LDOM for not less than 3 months were analyzed in order to describe the safety profile of this treatment. The dosing was titrated in 1065 patients and fixed in 339, so in fact 2469 cases could be analyzed. The doses ranged from 0.03 mg to 15 mg. Adverse effects affected 20.6% (509 patients). The displayed side effects were hypertrichosis 15.1% (374 patients), dizziness 1.7% (43 patients), fluid retention and pedal edema 1.3% (32 patients), tachycardia 0.9% (21 patients), headache 0.4% (9 patients), periorbital edema 0.3% (7 patients) and insomnia 0.2% (6 patients). The treatment was discontinued in 1.7% (43 patients). Fluid retention led to discontinuation in 8 cases. The incidence of side effects was similar in AGA and other alopecia types. The authors conclude that LDOM is a safe treatment option for alopecia with infrequent side effects. Based on their data, they propose to start dosing for females from 0.5 mg a day and increase by 0.25 mg every 12 weeks to a max dose 2.5mg, for males from 2.5mg a day and increase by 1.25 every 12 weeks to a max dose 5mg.[6] In a prospective open labeled and single arm study conducted in 2020 by Panchaprateep and Lueangarun, 30 males with AGA were given 5mg of oral minoxidil daily. The study duration was 24 weeks. After this time both efficacy as well as safety of the drug were assessed. All of the patients displayed improvement in hair count and density. Most common side effect was hypertrichosis 93% (28 males). Pedal edema affected 10% of the participants (3 males). In this study minoxidil was found both safe and effective. However, the authors of this trial emphasized that oral minoxidil should be used with caution among patients with high blood pressure and elevated risk of congestive heart failure.[38] In the interventional trial conducted between January 2017 to May 2020 performed by Sanabria et al. 435 participants taking LDOM (≤5 mg/d) at 3 trichology clinics in Brazil were interviewed regarding possible adverse effects of this drug in AGA treatment. The most common side effects were hypertrichosis reported by 55.4% (117 females and 124 males), headache 9% (22 females and 17 males) and insomnia 7% (14 females and 15 males). Generalized edema was reported by 1.1% of patients (3 females on 1mg oral minoxidil and 2 males on 2.5mg and 5mg). Lower limbs edema affected 6% of participants (19 females and 6 males). Facial edema affected 1% of participants (2 females and 3 males). All in all 6 patients discontinued using low dose oral minoxidil treatment for androgenetic alopecia due to fluid retention in the body. The results indicated that LDOM is a relatively-safe option for AGA, but patients should be warned about possible adverse effects including hypertrichosis, headaches, insomnia and edema.[37] In the controlled study conducted in 2019 by Jimenez-Cauhe et al. 41 males with AGA were included. The focus of this trial was to assess the effectiveness and possible side effects of LDOM in men. The doses prescribed in this study were 2.5 mg (10 participants) and 5 mg (31 participants) for at least 6 months. Clinical images before and after therapy were assessed by 3 dermatologists. 37 patients displayed clinical improvement, 4 showed stabilization and no worsening was observed. The most common side effect was hypertrichosis 24.3% (10 males) and lower limbs edema 4.8% (2 males). All in all, 1 patient discontinued the treatment due to pedal edema. Fluid retention affected patients taking 5 mg of oral minoxidil daily. The conclusion of the study states that oral minoxidil treatment at 5 mg daily brought positive effects and its safety profile was acceptable. In order to determine optimal dosing further controlled studies need to be conducted.[39] In a study conducted by Tanaka et al. between 2011 and 2017 a total of 18918 Asian men with AGA were prescribed a combination therapy consisting of oral finasteride 1mg once a day, topical minoxidil with concentration 5% and oral 2.5mg minoxidil twice a day as well as 4 ml per procedure injectable solution containing lidocaine, minoxidil, retinyl palmitate, caffeine, amino acids, vitamins and panthenol once a month. The aim of this study was evaluation of efficacy and safety of the combination therapy for AGA in Asian men. In order to

analyze the results photographs were taken before and after. After the treatment all patients displayed significant improvement. According to this study side effects affected 4.2% of the participants (802 males). Most common were pain due to injection 3.4% (651 participants) and slight bleeding in 0.3% (56 participants). When it comes to edema, swelling was observed in 0.22% (42 patients). Other side effects were itching and erythema linked to the use of topical minoxidil as well as decreased libido linked to the use of oral finasteride. Tanaka and coauthors conclude their study with a statement that their combination therapy is both effective and safe, however further studies are necessary to assess the safety of the therapy if higher doses are used.[24]

Minoxidil therapy used to treat hypertension clinical trials

In a multicentric retrospective review in 2023 Jimenez-Cauhe et al. analyzed 254 patients that had received LDOM as a treatment for alopecia in the past and had had high blood pressure or arrhythmia at that time. Side effects appeared in 6.8% (26 patients) and these were dizziness 3.1% (8 patients), water retention 2.6% (7 patients), other adverse effects included tachycardia, headache, general feeling of weakness. Six participants discontinued LDOM of hypertension due to adverse effects. The authors concluded that treatment of hypertension and with low dose oral minoxidil displays an advantageous safety profile.[40] In a clinical trial conducted in 1981 by Hagstam et al., minoxidil was prescribed to 25 patients suffering from refractory hypertension. At the beginning of this study 18 patients were diagnosed with kidney failure, presenting high serum creatinine levels. Soon after the onset of this trial 6 patients discontinued the treatment due to adverse effects or inability to control high blood pressure and only 19 individuals remained receiving the treatment for 0.5 to 4.5 years. Minoxidil had to be combined with beta-blocker and diuretic in order to reduce its side effects. During the treatment, all of the patients developed fluid retention that was kept under control with the use of diuretics. One patient died; however, it was not caused by minoxidil, but by the high uremia linked to starting dialysis. The authors found minoxidil to be successful in treating hypertension in patients with advanced renal disease.[33] In a clinical trial conducted in 1980 by Meier et al. 11 patients with severe hypertension impossible to control with conventional therapy were given diazoxide 400mg daily and minoxidil 17.7 mg daily in a crossover approach. Both treatments managed to decrease blood pressure. Both caused hypertrichosis, more severe with minoxidil. Both caused sodium and fluid retention leading to weight gain, which could be controlled with diuretic therapy.[30] In a clinical trial conducted in 1979 by Joekes et al. 47 patients with refractory hypertension received oral minoxidil 5-40 mg daily for up to 57 months. In 45 out of 47 patients a decrease in blood pressure was achieved on this drug. When it comes to adverse effects: 3 patients had to withdraw oral minoxidil due to sodium retention causing congestive heart failure, 2 female patients discontinued treatment because of hirsutism, 1 patient because of postural hypotension. In 34 patients due to sodium retention adding a diuretic was required. The authors of the study were unable to tell if adding the diuretic is always necessary. They claimed that if no edema, weight gain or postural hypotension were observed, minoxidil could be prescribed "well alone."[41]

Oral minoxidil overdose

In a multicentric retrospective review in 2022 by Moreno-Arrones et al. the authors focused their attention on 12 women (0.7% of patients) who developed serious side effects out of 1700 patients taking LDOM for AGA from January 2018 to October 2020. The dosing varied from 0.5mg to 1mg daily. When it comes to side effects: generalized oedema affected 6 patients, passing out affected 6 patients, stroke affected 1 patient and myocardial infarction affected 1 patient. After analyzing the composition of capsules that patients were receiving it turned out that they were taking higher doses than prescribed because of a compounding error at the pharmacy (the doses really varied between 50mg and 1000mg per pill). The patient who had a stroke received a 1000 times higher dose than the prescribed one and the patient who experienced myocardial infarction took a 200 higher dose. Out of the 12 women described in this case report, generalized edema affected those that took between 50 mg and 500mg of minoxidil. While the woman who took 50 mg presented swelling of the whole body in the first week, with higher doses this side effect appeared after the first intake. All women fully recovered after discontinuation of treatment. The authors concluded that the most severe side effects happened due to a pharmacist error at the dose at least 10 times higher than used in LDOM. Furthermore, they stated that adverse effects are dose dependent and while taking regular doses the safety of this treatment is high.[36] In a case report presented by Farell and Epstein from 1999 the authors describe an overdose of minoxidil. Patient drank a bottle containing 5% minoxidil solution resulting in a total dose of 3g oral minoxidil. Adverse effects were severe hypotension, prolonged tachycardia as well as fluid retention alongside pleural effusion. Intubation, antihypotensive agents and several days of furosemide therapy were necessary. In this case fluid retention and pleural effusion caused by oral minoxidil overdose were managed with furosemide.[42]

Conclusion

Oral minoxidil is an increasingly popular off label treatment option for AGA. Some patients find it more convenient than recommended by the Polish Dermatological

Society topical solution. Clinical findings have shown that both incidence and severity of adverse effects, including sodium and fluid retention leading to weight gain among individuals taking oral minoxidil are dose dependent. Low dose oral minoxidil treatment for patients with androgenetic alopecia based on 0.5 to 2 mg daily for women and 2.5 to 5 mg daily for men is proved to be effective with a relatively good safety profile.[5,6] Besides hypertrichosis, which is highly prevalent, the occurrence of other side effects including water retention and lower limbs edema appears to be low in this group, not exceeding 10% of the patients. Only in several cases due to severity of oedema discontinuation of the treatment was necessary. Furthermore, in this review we provided a comparison of the frequency and gravity of LDOM therapy adverse effects to those occurring in the treatment involving oral minoxidil to cure refractory hypertension dosed at 10 to 40 mg daily and an oral minoxidil overdose. With higher doses the incidence of side effects was respectively higher. Edema affected the majority of the patients and adding a diuretic was needed. The most extreme adverse effects occurred during oral minoxidil overdose, which required intensive care in some individuals.

The mechanism of minoxidil induced sodium as well as fluid retention and subsequently weight gain is based on the drug's ability to affect the neurohumoral system, increase plasma renin activity and change renal hemodynamic along with promoting a direct tubular effect. These processes can cause a rapid weight gain of 5 pounds or more that if detected early can be in most of the cases easily managed with the use of a diuretic. Some patients may require discontinuation of the treatment due to severe oedema. After ceasing treatment fluid retention resolves on its own.

Even though low dose oral minoxidil therapy is a very effective and mostly safe treatment option for androgenetic alopecia, the adverse effects in some individuals are quite severe, therefore further studies are necessary to fully understand the mechanism and dose dependance of water retention leading to weight gain in patients taking LDOM therapy for AGA.

Declaration

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Author contributions

Conceptualization, M.P. and Ł.C.; Methodology, Ł.C.; Software, J.F.; Validation, A.K. and M.P.; Formal Analysis, J.F.; Investigation, Ł.C., M.P., A.K. and J.F.; Resources, M.P., A.K. and J.F.; Data Curation, Ł.C.; Writing – Original Draft Preparation, Ł.C. and M.P.; Writing – Review and Editing, Ł.C., M.P., A.K. and J.F.; Visualization: M.P.; Supervision: M.P., A.K. and Ł.C., Project Administration, Ł.C., M.P., A.K. and J.F.

Conflict of interest

The authors declare no conflicts of interest.

Data availability

Not applicable.

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