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Review

Erectile dysfunction from mechanisms to medicines with a focus on the application of topical Minoxidil

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Abstract

Introduction: Erectile dysfunction (ED), for multifactorial reasons, is one of the biggest current quandaries among men worldwide and results in other complications such as reduced quality of life of the patient and his sexual partner, impotence, and psychiatric problems.
Objectives: Understanding of disease etiology, penile anatomy, erectile physiology, therapeutic mechanisms, and effective molecular pathways all play key roles in determining a therapeutic approach. This project is based on the study of topical minoxidil's effectiveness in treating ED.
Methods: To perform a comprehensive overview of the subject, we performed a triple-keyword combination search to assess recent studies of ED.
Results: The most common formulation used in these studies was 2% minoxidil solution. Except for cases studied in paralytic patients, topical treatment with minoxidil appears to elicit a mild erectile response; however, this finding is insufficient to confirm the effectiveness of this topical treatment.
Conclusions: Although evidence to confirm the therapeutic properties of minoxidil in ED is limited, combination therapy and the use of modern formulations of minoxidil are promising options for treating ED in the future.

Keywords: minoxidil; transdermal formulation; erectile dysfunction; topical therapy; impotence.

Introduction

Erectile dysfunction (ED) is the persistent inability to attain and maintain an erection adequate to have satisfactory sexual intercourse, according to the National Institutes of Health (NIH) Consensus Development Conference on Impotence.[1] By definition, ED is a more precise term than impotence, because in ED only the ability to attain and maintain an erection is lost, while sexual desire and the ability to reach orgasm and ejaculation may remain intact.[2] Erectile dysfunction can be classified into 2 main subgroups, (1) primary ED, which occurs from early puberty, prevents the experience of regular sexual activity from the beginning of sexual maturity, and (2) secondary ED, due to various reasons, which may occur at different ages and prevents the patient from having regular sexual activity as before.

Because ED is usually temporary and related to emotional conditions and life problems, it may disappear as these issues are resolved, without the need to visit a doctor and be examined. However, the complete cure of ED depends on the underlying causes. Patients who experience longer-lasting ED, for example, for several months, should be evaluated medically and treated if necessary.[3] Although ED is not considered a fatal morbidity, it is closely correlated to many underlying diseases, including cardiovascular disease, and may adversely affect psychosocial health. Thus, ED may have a significant impact on the quality of life of patients and their partners.[4]

In this study we aimed to update clinical research into the pathophysiology of erectile dysfunction and the underlying treatments. This review also includes discussion of the application of minoxidil as a popular topical drug for treating ED.

Methods

The current project was performed based on the main perspectives of reported efficacies in clinical trials, including various formulations of topical minoxidil in diverse conditions to diminish ED incidence or probability. The predetermined searches were accomplished in the PubMed and Scopus search engines. To fetch various clinical trials and similar approaches, the intermingled keywords [Minoxidil] + [Topical/Transdermal formulations] + [Erectile dysfunction] were utilized. The results of this 3- component search were integrated and categorized as follows. PubMed results were confined to advanced searches in abstracts and titles without using MeSH terms. Other investigations have been holistically performed based on the concentration of

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the textuality of each section or on an ad hoc foundation. The consistence of the context from a systematic, scientific, and didactic point of view was reinspected and revised appropriately.

Results and discussion

Physiology of erection

Penile erection is the consequence of neurological and vascular events that coordinate with hormonal and psychological triggers. Eventually, penile rigidity occurs due to increased intracorporal pressure from corporal smooth muscle relaxation and increased blood flow in the arteries.[5–7] Penile erection can be triggered by direct stimulation of the genital organ (reflex parasympathetic erection) or through stimulation of central pathways (psychogenic erection).[8] The thalamus regulates psychogenic erection and limbic system, which control the spinal sympathetic (Tl-L2) and parasympathetic (S2-S4) centers.[7]

Cholinergic and nonadrenergic-noncholinergic nerves relax the smooth muscles of the corpus cavernosum by proerectile neurotransmitters such as nitric oxide (NO), intestinal vasoactive peptide (VIP), and prostaglandins.[7] NO, which plays a more prominent role than other neurotransmitters in relaxing smooth muscles, is synthesized by NO synthase (NOS) and released from endothelial cells, and activates the enzyme guanylate cyclase (GC), producing cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP).[9]

VIP is injected intracavernosally for treatment of ED and has a synergistic effect in concomitant administration with acetylcholine.[7] VIP activates the enzyme adenylate cyclase (AC) and produces cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP).[10–12] Both cGMP and cAMP lead to hyperpolarization of smooth muscle cells by activating the sodium-potassium channel, thereby reducing the intracellular calcium concentration and relaxing the smooth muscle corpus cavernosum.[11,12] As the enzyme 5-phosphodiesterase breaks down cGMP, a primary therapeutic goal in patients with ED is to regulate the function of this enzyme. Details of the mentioned molecular pathways are shown in Figure 1.

Other proerectile neurotransmitters include the following.

1. Acetylcholine does not directly affect the corpus cavernosal smooth muscle cells but modulates the release of NO from endothelial cells in the relaxation process.[7,13,14]

2. CGRP is released from the ends of neurons leading to the corpus cavernosum and directly affects smooth muscle relaxation. Intracavernosal injection of CGRP combined with alprostadil (prostaglandin E1) is one way to treat ED.[7,15]

3. Substance P promotes corpus cavernosum relaxation. The function of substance P depends on the endothelial release of NO.[7,16]

4. Pituitary adenylate cyclase–activating polypeptide (PACAP) is structurally similar to VIP and has a relaxant effect on the corpus cavernosum.[7,17]

5. ATP can be injected either intracavernosally or intraarterially and has a relaxant effect on the corpus cavernosum.[7]

6. Histamine improves erection by activating H2 receptors and can be administered by intracavernosal injection (ICI) in men with ED.[18,19]

7. Oxytocin, present in the hypothalamus, is released from oxytocinergic neural terminations and therefore plays a role in modulating the central neural pathway of erection.[7,20]

8. Dopamine, like oxytocin, plays a role in the hypothalamus's central neural pathway of erection, which is rich in dopaminergic receptors.[21]

9. Serotonin (5-Hhydroxytryptamine [5-HT]) regulates and modulates the sympathetic and parasympathetic output and can be injected peripherally.[7,20]

On the other hand, antierectile neurotransmitters such as noradrenaline (norepinephrine), neuropeptide Y (NPY), and γ-aminobutyric acid act as counterpoints to the neurological and hormonal factors that cause erections.[7]

The equilibrium between the levels of these factors plays a crucial role in creating or preventing an erection (Figure 2).

Pathophysiology of ED and risk factors

Organic and nonorganic ED

The normal function of the smooth muscle of penile blood vessels and corpus cavernosum depends on the intactness of all neurological, vascular, and hormonal factors.[22] Although the function of the peripheral nervous system in erection has been thoroughly examined, the role of the central nervous system has not been completely clarified. Regions of the frontal and limbic cortex modulate sexual response along with direct or intermediate stimulation of the septal area.[23] In the evaluation of some men with epilepsy and ED, the nature of the disorder, primarily in penile stiffness, suggests a neurogenic rather than vasogenic origin and is better identified by assessing both nocturnal penile tumescence and stiffness.[24]

At the National Institutes of Health (NIH) Consensus Development Conference on Impotence in December 1992, organic etiologies were reported in approximately 75% of ED cases.[10,25,26] Organic ED primarily results from cardiovascular diseases, spinal cord injury, and neurodegenerative disorders, which lead to impairment of blood flow and nerve messages to the penis.[27] Central neurological disorders, including Parkinson disease, epilepsy, Alzheimer disease, and stroke defects, can also lead to ED.[22,28]

Other nonorganic causes of ED are diabetes mellitus, hypercholesterolemia, drug side effects, and poor lifestyle habits such as smoking, obesity, stationary lifestyle, and drug and alcohol addiction.[6,10] Psychological disorders such as depression, anxiety, lack of self-confidence, etc., are the most prevalent causes of nonorganic causes of ED.[2,3,29] Diabetic neuropathy and localized nerve damage due to injury or surgery are among the peripheral neurological diseases that lead to an increase in the stimulus threshold of the penis and, thus, a decrease in its sensitivity.[22]

Age-related ED

Erectile dysfunction was previously thought to be an inevitable consequence of aging, so little attention was paid to this sexual problem of the elderly.[30] The prevalence of ED in men younger than 50 years is 9%-39% and in men older than 70 years is 40%-80%.[3] However, increased recognition of the importance of sexual satisfaction in elderly patients and their complaints about not having and maintaining a normal erection have led to more attention and research in this field. Sexual problems are relatively common in elderly patients and are frequently related to general health issues or specific sexual disorders. Andropause or androgen deficiency occur in elderly patients through decreases in glandular function and testosterone production, along with an increase in the blood concentration of sex hormone–binding globulin (SHBG), which reduces the bioavailability of testosterone and leads to impotence, decline in penile sensitivity, and ED.

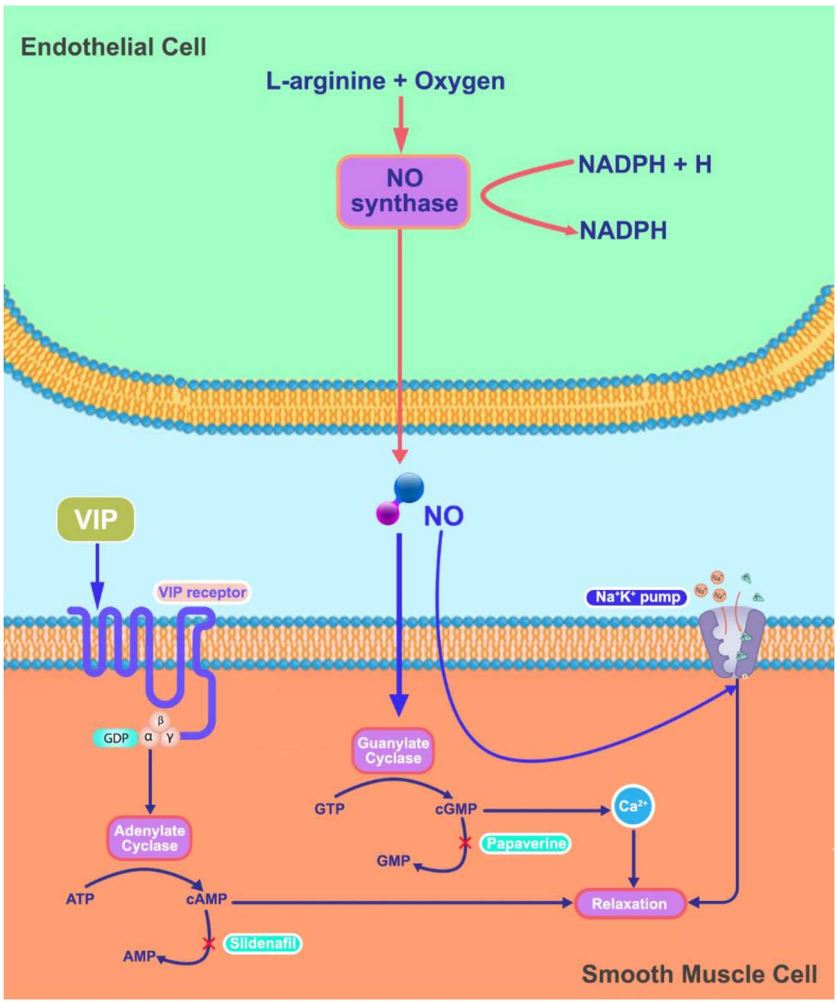

Figure 1. Molecular pathways in the process of erection; stimulants as well as different inhibitors act in different points of this pathway.

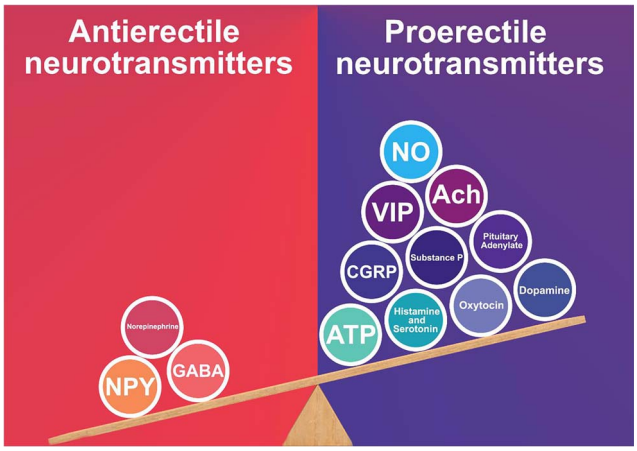

Figure 2. Influential neurotransmitters effective in erectile function; changes in the equilibrium of these factors are effective in causing or obliterating contractions that exert influence on erection.

Testosterone is involved in libido, penile tissue integrity, and NOS expression. The incidence of hypogonadism in older men is 30% of men in their 60s and 80% in their 80s and 90s.[22,31] In addition to aging, alcoholism may cause hormonal changes and eventually ED by upsetting the androgen-estrogen balance.[22,31] Chronic age-related diseases that impair sexual function include cardiovascular events such as hypertension, hyperlipidemia, and atherosclerosis; chronic neurological disorders including stroke, dementia, and depression;[22,31] hormonal disturbance and hypogonadism due to testicular failure (primary hypogonadism) or hypothalamic and pituitary insufficiency (hypogonadotropic hypogonadism);[29] and diabetes, a disease that leads to multiorgan dysfunctions. Because older people take many medications, side effects of some medicines may cause iatrogenic ED, especially psychiatric drugs, thiazides, and beta-blockers. If possible, erectile function can be restored in these cases by changing the class or dose of the medication.[22,31]

Drug-related ED

Medications can affect sexual ability in several ways,[4] such as the following.

1. Antidepressants such as tricyclic antidepressants, MAOIs (monoamine oxidase inhibitors), lithium, SSRIs (selective serotonin reuptake inhibitors), and benzodiazepines indirectly cause ED by reducing libido,
2. Antihypertensive drugs, including diuretics, beta-blockers, methyldopa, clonidine, reserpine, guanethidine, and verapamil affect cardiovascular function.
3. Drugs such as phenothiazines, antipsychotic drugs (risperidone, olanzapine, and clozapine), and H2 antagonists

(cimetidine and ranitidine) that cause hyperprolactinemia, which leads to ED, impotence, breast enlargement, testicular dysfunction, and infertility in men.

4. Endocrine hormones, such as antiandrogens, H2 antagonists (cimetidine), estrogens, and testosterone.

Management steps for treatment of ED

Basic measures

In the first step of ED treatment management, psychosocial counseling, lifestyle modification, sexual relationship evaluation, and a thorough medical evaluation of other underlying causes might be helpful. Patients who complain of ED should also be examined for corresponding diseases associated with the induction of ED.[2,3,32] Studies have shown that lifestyle modification and elimination of ED risk factors by the patient can reduce the risk of ED by up to 70%.[2–4,28,29] According to complaints of medication-induced ED, changes in medication may help patients regain the ability to have a normal erection.[3,29] Sometimes the patient is in perfect physical health but has depression or conflict with his partner and therefore cannot achieve a full erection until these problems are resolved.[2,3,29]

Oral medication

Oral therapy is the most common way to take ED medications, including phosphodiesterase type 5 (PDE5) inhibitors. NO donors, such as minoxidil and nitroglycerin (NTG), increase cGMP and cAMP production by increasing the activity of guanylate cyclase and adenosine cyclase.[11] On the other hand, reduction of cGMP and cAMP degradation occurs with specific inhibitors of PDE, such as sildenafil, tadalafil, vardenafil, and the nonspecific PDE inhibitor papaverine.[11] Sildenafil (Viagra) was introduced to the pharmaceutical market in 1998, and during the first 6 years after its introduction more than 20 million men were medicated with Viagra. Subsequently, vardenafil (Levitra) was authorized in 2003, providing patients with a substitutional choice. Several months later, also in 2003, tadalafil (Cialis), also known as the "weekend pill" for maintaining 36-hour effectuality that allowed more sexual spontaneity, was also introduced.[33] Avanafil (Stendra) is one of the latest FDA-approved drugs for ED, which has a very high specificity for inhibiting PDE5 with fewer side effects.[34,35]

Although these drugs are taken orally as the first line of treatment for ED, some men do not get enough response to achieve complete sexual intercourse. In addition to lack of an adequate response, some factors such as the occurrence of various side effects (such as headaches, hot flashes, indigestion, and respiratory infections), drug interactions (especially with CYP3A4 inhibitors), and widespread contraindications, especially among cardiovascular patients using nitrate medicines (such as NTG, isosorbide dinitrate, and isosorbide mononitrate), have led researchers to seek alternative approaches.[36]

Nonoral medication

The next steps in ED treatment include transurethral therapy, intravenous injection, topical therapy, and the application of medical devices (such as vacuums and rings). Intracavernous injection therapy is not very popular with patients due to its side effects, such as priapism and pain. Topical therapy is well tolerated owing to its greater efficiency, fewer whole-body systemic side effects, and easiery application method.[25]

Surgery

The last step in ED treatment is the use of invasive treatments, including penile prostheses and penile vascular surgeries.[2,37,38]

In the following information, among the cases mentioned in the second line of treatment, we focus on the local effects of non-PDEI vasoactive agents, including topical minoxidil.

Non-PDEI vasoactive topical medicines

Alternative routes of administration of vasoactive drugs for treating ED that are less threatening than injection therapy are explored in this section. Agents approved by the FDA for other indications or other ways of administration, including alprostadil, organic nitrates, minoxidil, papaverine, and yohimbine, have been tested via topical administration on the glans penis or penile shaft. Although the FDA does not currently approve these therapies, they may be effective, as well as other medications.[2,4,39,40] The challenge with topical therapy is to reach complete absorption, ie, agents applied on penile skin must permeate fascial layers and the tunica albuginea, which means thick layers of collagen.[3,41] Organic nitrate, minoxidil, aminophylline, co-dergocrine mesylate, and vasoactive intestinal polypeptide have previously been described as topical cavernosal smooth muscle relaxants with varying degrees of success and rate of side effects.[42] To protect the partner, condoms are recommended with the use of aminophylline, co-dergocrine mesylate, minoxidil cream, or the NO donor isosorbide dinitrate are used.[22,43] The use of glycerol trinitrate, minoxidil, and papaverine gel has been investigated in various studies, with the results that were variable but mainly disappointing.[44] In the following section, we address examine each of these agents separately.

Prostaglandin E1

Notwithstanding the achievement of PDE5Is, prostaglandin E1 (PGE1, also known as alprostadil) has been tested with various dosing methods as an alternative therapy for ED, predominantly for patients who had unsatisfactory results with PDE5Is medication .[45] Topical alprostadil is the most commonly administered synthetic PGE1 for ED. PGE1 promotes corporal smooth muscle laxity, preponderantly by activation of adenylate cyclase and the pursuant agglomeration of 3′5′-cAMP. This process is independent of the NO-cGMP pathway and does not require preliminary sexual stimulation.[46] The cream formulation of PGE1 (Vitaros/Virirec) incorporates the advantages of alprostadil with a formulation that is convenient to use.[47] Alprostadil cream is a particular combination containing alprostadil as the active pharmaceutical ingredient, a penetration booster (dodecyl-2-*N*, *N*-dimethylamino propionate [DDAIP]), and an ester of *N*-dimethylalanine and dodecanol called HCl. The mentioned penetration-enhancing complex provisionally slackens tight junctions located in the dermal epithelial cells, subsequent to its interplay on the plasma membrane with the hydrophilic zone of the phospholipid bilayer.[48] Numerous studies have also been reported that have investigated transdermal strategies for treating ED, including transdermal conveyance of NTG, PDEIs, phentolamine, and papaverine.

Testosterone

Testosterone is a pivotal androgen in men that is produced in the testicles and adrenal cortex. Recently, the direct effects

of different testosterone levels on the structural, biochemical, and physiological characteristics of the penis and the pathways associated with erection have become apparent. Animal findings and studies of castrated individuals have shown that lowering testosterone levels not only directly affects the NO pathway but also changes the hemodynamics of the penis as well as smooth muscle tone in a way that makes ED inevitable.[49] Monotherapy with gel-formulated testosterone restored erectile function but its effect is limited in hypogonadal men,[49] ie, the most efficacious approach for sexual impairment in hypogonadal males is testosterone therapy. It operates by re-establishing erections as commonly evaluated with International Index of Erectile Function (IIEF) scores. This effect will be more tangible in these patients if the gel is used concomitantly with oral sildenafil.[50] Numerous assessments have illustrated the advantages of merged testosterone and sildenafil therapy in generating acceptable erectile reactions in hypogonadal males who did not react to sildenafil monotherapy.[51]

Papaverine

Topical transmission of papaverine through the penile shaft would be a superb substitutive and lower-priced therapy for patients undergoing long-term medication for ED.[52] Transdermal papaverine gel does not seem to cause severe adverse effects after administration to the penile shaft. A 15%-20% formulation of papaverine elevates intracorporal pressure due to the increased blood flow to the penis. The outcome of transdermal papaverine in altering blood flow to the phallus is dose dependent. However, topical therapy with papaverine is not as beneficial as an intracavernous medication injection. Nevertheless, transdermal formulations of papaverine may have promising outcomes at higher concentrations or in amalgamation with diverse skin penetration boosters. Transdermal administration avoids many difficulties related to ICI medication, and the represented outcomes on boosting penile arterial flow via transdermal administration of locally acting papaverine gel formulation warrant further evaluation.[53]

Nitroglycerine

Transdermal NTG is a feasible and practical strategy for treating impotence and ED, and NTG-treated patients exhibited erections sufficient for regular sexual intercourse.[54] After sexual stimulation, topical NTG works by increasing blood flow in the cavernous arteries, causing an increase in factors related to erection, such as stiffness and diameter of the penis. This effect was observed in a group study by Nunez and Anderson, in which 3 impotence patients were successfully treated with NTG ointment.[47]

Minoxidil

Topical minoxidil formulations, which influence follicular cells, have been utilized for hair regrowth in recent decades,. Elevated fenestration in the follicular capillary membrane around anagen bulbs was illustrated by electron microscopy after administration of topical minoxidil 4% solution.[55] This affirmative outcome of topical minoxidil stimulation of hair regrowth is chiefly attributable to its active metabolite, minoxidil sulfate, which is converted by sulfotransferase.[55] However, minoxidil might generate undesirable vascular outcomes. As a direct-acting peripheral vasodilator, minoxidil decreases blood pressure in systolic and diastolic sessions by decreasing peripheral vascular resistance.[56] Minoxidil also provokes PGE2 synthesis by switching on prostaglandin endoperoxide synthase-1 and suppressing prostacyclin generation. Furthermore, minoxidil increases the expression of the PGE2 receptor, which is the most upregulated in thebeta-catenin pathway of dermal papilla cells.[55] Minoxidil can accelerate nail growth with proven vasodilatory characteristics.[57] As an alpha-adrenergic antagonist, minoxidil is a potent vasodilator and antihypertensive agent used in refractory hypertension. Because minoxidil relaxes vascular and other smooth muscle cells, it was also tested topically on the glans penis to treat ED[5,7,58] and was also suggested for use in the long-term treatment of organic impotence.[59]

Minoxidil in treatment of ED

Mechanism of action

The primary mechanism of action of minoxidil is opening potassium channels in the membrane of vascular smooth muscle cells.[12] Minoxidil does not have a direct vasodilatory effect; however, its metabolite minoxidil O-sulfate does have an immediate vasodilatory impact on arterial smooth muscle, causing a reduction in peripheral resistance and blood pressure. Nevertheless, the detailed mechanism of action of minoxidil in ED treatment is not completely clear. Topical minoxidil is a prodrug, which means that to be effective, it would have to be metabolized through the liver and then recirculated to the penis.[60,61] In 1999, a study showed that NO significantly affected penile smooth muscle relaxation and erectile function. Minoxidil is considered a donor of NO. Topical minoxidil as a nitric acid donor increases cGMP, relaxing smooth muscle. Therefore, topical minoxidil was expected to positively affect ED.[10,11,22] Such topical activity of minoxidil contrasts with the hypothesis that this prodrug requires hepatic metabolism to become vasoactive.[62] In a study by Kim and McVary on minoxidil and NTG, it was found that the penis can absorb these substances and that their effects on the hemodynamics of the penis are direct and local (Figure 3).[63]

Formulation, dosing, and effectiveness

A study by Radomski et al showed increased effectiveness of 2% minoxidil solution (1 mL applied on the glans penis 20 minutes before sexual intercourse) over NTG and placebo by demonstrating increased penile blood flow, diameter, and rigidity.[64] The commercially available form is a 2% solution, and the manufacturer suggests a maximum dose of 1 mL (0.28 mg).[25] It was found that topical minoxidil solution 2% (1 mL administered on the glans penis) compared to NTG (2.5 g, 10% ointment administered on the penile shaft) is more effective t. The results showed that minoxidil was more effective in increasing the diameter, stiffness, and arterial flow to the penis.[7,53,58,65–68] Another study on 10 individuals with neurogenic impotence revealed the effectiveness of minoxidil in the elevation of penile circumference and rigidity relaxation.[69] Topical minoxidil solution was also more effective than placebo or NTG in facilitating erections with fewer side effects.[70–72]] In a small double-blind trial of 33 men, minoxidil solution 2% (1 mL on glans penis) showed acceptable results. This research was assessed based on comparing the outcome of minoxidil solution vs placebo and NTG 10% ointment (2.5 g on the penile shaft) in a prospective manner.[73] Finally, the results showed that topical minoxidil not only causes fewer local side effects but also

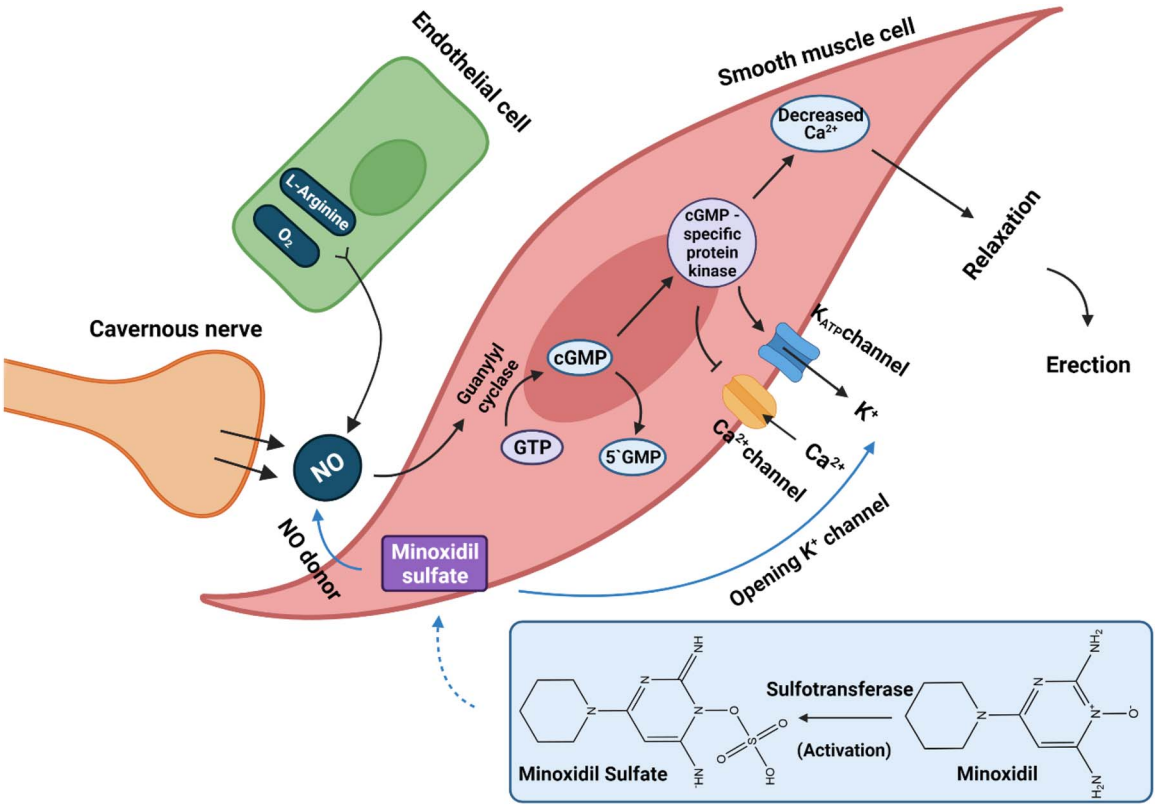

Figure 3. Functional roles of minoxidil in erectile-related pathways. After applying structural changes and becoming an active metabolite, Minoxidil affects the erection process in 2 ways.

performs better than placebo and NTG ointment in increasing the diameter, stiffness, and arterial blood flow of the penis, especially in neurogenically impotent patients.[54,61,74] Then, in 1994, another study investigating the topical use of minoxidil cream showed a slight improvement in penile blood flow in 22 men with impotence who also had diabetes.[75] Under laboratory conditions, applying 1 mL of a 2% minoxidil solution to the glans penis caused more significant penile tumescence, rigidity, and arterial function changes. However, when the same doses of minoxidil were used in a clinical approach, this drug appeared to be of minimal utility in improving patients' sexual activity.[12,31,37,38] One mL of Minoxidil (2%) has been tested in 18 spinal cord lesioned (SCL) men when applied as an aerosol spray to the glans penis. This topical application of minoxidil caused a minimal response subjectively and objectively.[76,77] In this study, which was performed comparatively alongside other methods such as papaverine intracorporeal injection (range 30%-100% and median 77% successful) and utilizing a vacuum constriction device (range 30%–80% and median 57% successful), topical minoxidil caused less tumescence and rigidity in the penis than other methods (range 0%-15% successful).[76] When the results could not be amplified, 28 significant responses were reported by Cavallini with a combination of minoxidil and capsaicin.[7,78] Another similar study found that 2% topical minoxidil solution is ineffective when applied to the penis to treat ED. A higher concentration, a different delivery medium, or a different chemical composition may yield better results.[64]

Side effects

Patients using topical minoxidil experienced fewer episodes of local burning, hypotension, and headache than patients using NTG or placebo. In addition to a better safety profile, topical minoxidil is either more effective or better absorbed than NTG.[73] In an uncontrolled study, 15 men with spinal cord injury tested 1 mL of 2% minoxidil on their torso. A total of 4 paraplegic men with complete dorsal surface lesions reported an erectile response. Three of these 4 patients preferred to continue this noninvasive treatment compared to the intracerebral injection of prostaglandin E1. No side effects appeared, and minoxidil was well tolerated on the skin surface of the penis. The results showed that this treatment should be tested before starting aggressive therapy in men with spinal cord injury.[79] An evaluation of the quality of the 1986 study by Beretta et al. of transcutaneous minoxidil (1 mL of a 2% solution) found that 4 of 15 patients had a full erection, and only 1 patient had a mild headache. In this research, 8 out of 19 patients reached the satisfactory erection needed for vaginal penetration.[79,80] Systemic effects resulting from topically administered minoxidil are unlikely but theoretically could occur if the drug is overused. Skin abrasion or irritation such as excoriations, psoriasis, or sunburn can increase the systemic absorption of topical minoxidil.[60]

Combination of minoxidil with other ED therapies

It was reported that management of impotence using a vacuum contraction device and topical minoxidil is more effective than monotherapy, and the results also indicated that the use of minoxidil before the vacuum contraction device might help reduce the time of use of the device, increase device efficiency, and in some cases prevent the use of the tightening ring.[81] Cecchi et al. also evaluated vacuum therapy with topical minoxidil in 18 patients. These authors found that this combination increased erectile quality, reduced device use time, and avoided the need for tightening rings with a 12/18 ratio.[82]

Different results have been reported in clinical studies on the erectile effects of minoxidil. This striking difference may be due to other criteria in assessing the erectile response, ie, in the clinical studies, only patients achieving erections adequate for vaginal penetration were considered responders.[25,29] In experimental studies, subcutaneous treatments such as NTG, minoxidil, yohimbine ointment, PGE, and topical papaverine gel showed fewer side effects but failed to cause a rigid erection. Another study in 2002 tested topical minoxidil, NTG, and papaverine alone and with a skin penetration enhancer but resulted in limited success.[83,84] Intraurethral (IU) application of minoxidil (2% solution) to the isolated phallus developed more intracorporal pressure (ICP) compared to topical minoxidil and other topical pharmacotherapies. The topical application of NTG (ointment 2%) was less practical than IU and topical forms of minoxidil. Although both topical and UI applications of NTG and minoxidil increase intracorporal pressure, rigidity is remarkably lower than with intracorporal papaverine injection.[85] Several vasoactive drugs (2% NTG, 15%-20% gel of papaverine, and 2% solution or gel of minoxidil) have been used for topical application to the penis. No topical treatments have been approved, and their role in the treatment of ED is currently unknown.[29,32,39] In experimental studies, transdermal ointment or paste of NTG, minoxidil, and prostaglandin E1 failed to induce erectile stiffness, apparently due to the insufficient transmission of the drug through the skin.[6,52] These treatments have had only limited success, perhaps in less severe ED.[86] Studies show that the levels of rigidity reported fall well below accepted values for an erection that is satisfactory for sexual intercourse.[26,28,87] However, today, it can be said that topical minoxidil is considered an adjunct therapy to improve the quantity and quality of erection without affecting sexual desire.[88] Furthermore, combined with a transdermal booster, topical minoxidil does not improve erections sufficiently to ensure its general use.[89] Achieving a functional erection with topical application of vasoactive drugs has been limited but tremendously successful in patients with psychiatric and neurological disorders compared with those with vascular disease.[90,91] Topical drug delivery is a simple, reversible, noninvasive, spontaneous treatment option for ED. Still, the efficacy of this application must be facilitated by an enhanced degree of skin and tunica permeation. Absorption through the skin of the penis is slow and uncertain, and topical application of papaverine, prostaglandin E1, minoxidil, and NTG has been performed without much success. The use of transdermal enhancers was then evaluated and reached the clinical trial stage.[87,92] No significant reports show complete efficacy for the topical application of agents such as papaverine, NTG, and minoxidil.[38,93] Although generally safe, these treatments are not effective beyond 24%-40%, and lack of uptake through the tunica albuginea is the main challenge in transdermal delivery of topical therapies.[94] However, the formulations of minoxidil-loaded nano-ethosomes (ethosomal systems that are nanocarriers of fat-based vesicles that contain a high percentage of ethanol and are used to deliver high-performance therapeutic agents to deep layers throughout the skin) was prepared for transdermal delivery. Prepared nanoethosomal formulations at 2% phosphatidylcholine and 30% ethanol showed rapid enhancement in transdermal permeability of compared hydroethanolic or phospholipid ethanolic solutions of minoxidil.[95]

Conclusion

Recently, topical and transdermal therapies have become increasingly crucial for treating ED due to fewer side effects, interactions, and contraindications to systemic medications. Meanwhile, minoxidil as a peripheral vasodilator has shown a doubtful role in the topical treatment of ED. There is a balance of data confirming success and reports of minoxidil's ineffectiveness as a topical treatment agent in ED. Reasons for this equilibrium include the lack of clear transparency of the drug's functional pathway, multiple physical barriers in the structure of the penis preventing drug uptake, uncontrolled physicochemical properties of the drug, and the lack of study of minoxidil in modern formulations such as nanoemulsions, transferosomes, bilosomes, nanoliposomes, centrosomes, nanoethosomes, liposomes, optimized multilayer vesicles (MLVs), and nanosized colloidal systems such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Almost all of the findings regarding topical treatment of ED with minoxidil were limited to the classic formulations. If topical minoxidil is evaluated in newer formulations, it may have completely different and surprising effects due to improved local absorption.

Coadministration of intracavernosal therapies (such as papaverine, phentolamine, prostaglandin E1, yohimbine, or an adrenoceptor-antagonist), systemic medications (such as PDE5Is), or other transdermal agents (such as NTG, PGE1, papaverine, and PDE5Is) with topical minoxidil may produce a better erectile response in comparison with monotherapy. Further studies are needed on combination therapies and modern formulations to confirm the efficacy of topical minoxidil in treating ED.

Our discussion in this article includes the use of minoxidil alone as a topical treatment for ED. However, studies have shown that combination therapy and different medications are more effective than monotherapy.

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