Prostaglandins as a Topical Therapy for Erectile Dysfunction: A Comprehensive Review

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ABSTRACT

Introduction: Erectile dysfunction (ED) is a substantial cause of dissatisfaction among many men. This discontentment has led to the emergence of various drug treatment options for this problem.

Objectives: Unfortunately, due to various interactions, contraindications, and side effects, systemic therapies such as phosphodiesterase-5 inhibitors (including sildenafil, tadalafil, vardenafil, avanafil, etc.) are not welcomed in many patients. These problems have led researchers to look for other ways to reduce these complications.

Methods: This article holistically reviews the efficacy of topical prostaglandins and their role in treating ED. We sought to provide a comprehensive overview of recent findings on the current topic by using the extensive literature search to identify the latest scientific reports on the topic.

Results: In this regard, topical and transdermal treatments can be suitable alternatives. In diverse studies, prostaglandins, remarkably PGE1 (also known as alprostadil), have been suggested to be an acceptable candidate for topical treatment.

Conclusion: Numerous formulations of PGE1 have been used to treat patients so far. Still, in general, with the evolution of classical formulation methods toward modern techniques (such as using nanocarriers and skin permeability enhancers), the probability of treatment success also increases. **Hamzehnejadi M, Tavakoli MR, Homayoun F et al. Prostaglandins as a Topical Therapy for Erectile Dysfunction: A Comprehensive Review. Sex Med Rev 2022;10:764–781.**

Key Words: Erectile Dysfunction; Transdermal Prostaglandin; Drug Interaction; Alprostadil; PGE1

INTRODUCTION

According to the definition, erectile dysfunction (ED) is the persistent inability to create or maintain a penile erection with sufficient quality.[1] Adequate erections are essential for penetration and durability of sex, and there is a clear connection between ED and infertility in men.[2] The issues of sex, primarily related to a man's strength, may cause embarrassment and stress, leading to frustration in the person relative to this subject.[3] This problem causes mental health problems such as depression and loss of confidence by reducing patients' quality of life.[3] ED remains untreated because the patient is reluctant to report it.[1] That is why the physician should examine the patients at risk.[4] The physician should talk to the patient about psychosocial issues, sexual records, and psychological factors.[1] Appropriate and timely intervention to return earlier to sexual performance provides a higher quality of life.[1] ED treatment improves patient and partner satisfaction and improves overall health.[5]

Erectile Function

The erection of the penis is the result of a complex neurovascular process in which nerves, endothelium, sinusoidal tissues, blood vessels, and smooth muscle cells are all intertwined.[6] Knowing the physiology of smooth muscles, nitric oxide pathway neurophysiology, and penile anatomy is crucial for a deeper understanding of erectile physiology. Penile erectile tissues, vascular and cavernosal smooth muscle, and supportive structures

Received March 29, 2022. Accepted June 9, 2022.

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https://doi.org/10.1016/j.sxmr.2022.06.004

are essential to tumescence. The human penis comprises 3 cylindrical structures connected by tunica albuginea, ligaments, and muscles. The paired corpora cavernosa and a single corpus spongiosum house the urethra. The complex yet perfectly regulated interplay between these erectile tissues, veins, and nerves is essential for penile erection. Collagen fibers provide good rigidity to support high pressures during erection and flexibility due to the elastin content.[7]

The tone of smooth muscle (arterial and trabecular) of the penis determines hemodynamic events that maintain or eliminate erection. Penis erections require reduced penis smooth muscle tone. The contractile activity of the penile muscle is regulated by several factors: adequate levels of agonists (neurotransmitters, hormones, and endothelium-derived substances), sufficient expression of receptors, the integrity of the transduction mechanisms, calcium homeostasis, interaction between contractile proteins, and effective intercellular communication among smooth muscle cells. The balance between relaxant and contractile factors determines the result of the penile smooth muscle tone.[8] Sexual stimulation causes the secretion of neurotransmitters from the cavernous nerve terminals.[9] Impulses of the brain, typically through the paths of the sympathetic (inhibiting norepinephrine release), parasympathetic (releasing nitric oxide and acetylcholine), and systematic (releasing acetylcholine), produce a normal rigid erection. The erectile tissue of the penis, especially the cavernous smooth muscle and the smooth muscles of the arterial endothelium, play a fundamental role in the erection process. These muscles are typically contracted by sympathetic secretions and muscle contractors secreted by the endothelium. In fact, when the penis is flaccid, vascular and cavernosal smooth muscles are in a tonically contracted state. This limits the amount of arterial blood flow so that partial oxygen pressure (pO2) approaches venous blood. Erection is caused by the relaxation of cavernosal and vascular smooth muscles, leading to sinusoidal relaxation, arterial dilation, and venous compression.[7,9] Sinusoidal expansion leads to mechanical compression of the venous network under the trunk between the contractile sinusoids and the hard tunica albuginea. This leads to a decrease in venous outflow and increased sinusoidal blood clogging. Consequently, penile blood pO2 rises to 90 mmHg (closer to arterial oxygen levels), and the intracavernous pressure increases to 100 mmHg. The amalgamation of these events leads to penile erection, with the penis going from a flaccid state to the complete erection phase. Contraction of the ischiocavernosus muscle during erection further increases pressure during the rigid erection phase (Figure 1).[10,11]

Many endogenic compounds are involved in erectile function. Androgens generally increase libido and frequent sexual action.[12] These are essential for penile tissue growth and maintaining erectile function.[13] On the other hand, androgens, by adjusting neurotransmitters' synthesis and function, influence the contraction and relaxation of smooth muscle in the erectile tissues.[14] Oxytocin can also facilitate erectile function and male sexual behavior. In the hypothalamus's PVN (paraventricular nucleus), oxytocinergic neurons are located in extrahypothalamic brain areas and the spinal cord, which influences erectile function.[6] Acetylcholine is also required to relax smooth vascular muscles via muscarinic receptors. It is involved in the regulation of erection by releasing NO from endothelial cells.[9] NO from nerves and possibly endothelia plays a crucial role in initiating and maintaining intracavernous pressure elevation, penile vasodilatation, and the penile erection dependent on cyclic GMP synthesized with activation of soluble guanylyl cyclase by NO in smooth muscle cells.[15] Therefore, nitric oxide is released as a synthesized mediator of vascular endothelium and plays a role in penis function as a neurotransmitter.[15,16]

Etiology

ED can have a neurogenic, psychogenic, or endocrinologic basis.[17] Risk factors for causing ED include tobacco and alcohol consumption, obesity and sedentary lifestyle, stress, and depression.[1] Damage to blood vessels and smooth muscle that leads to changes in the blood flow to the penis, as well as deformation and deviation of the penis, are among the main ED factors.[18,19] Poor mental health, physical weakness, and fragile psychological health can also lead to ED.[20] In addition, variables such as age, cardiovascular disease, including coronary artery disease, heart attack, hypertension, hyperlipidemia, diabetes, urinary tract injury, endocrine disease, and neurological factors, are closely related to ED,[5,21–23] and people with these diseases should be screened for erectile function.[1]

Physiological and biochemical changes in penis structure may also play a role in ED.[24] Abnormalities of the endocrine system and hormonal causes such as adrenal insufficiency, hypothyroidism, hyperthyroidism, hypogonadism, and hyperprolactinemia are other causes of ED and impotence.[11,25] Also, testosterone deficiency is one of the common reasons for ED.[26]

Management

The choice of appropriate treatment depends on the severity and cause of ED's disease, the patient's general health, and the treatment preference of the patient and his partner.[27] ED treatment includes pharmacotherapy and non-drug therapy. Pharmaceutical treatment mostly includes treatment with oral drugs such as phosphodiesterase-5 inhibitors.[28] Other therapies include diet and lifestyle modifications, physical therapy, vacuum erection devices (VED), testosterone therapy, low-intensity extracorporeal shock wave therapy, penile injections, penile prostheses, and surgery.[28–31]

Lifestyle Modifications. Improving lifestyle and proper management of individual diseases is the most helpful treatment modality. Lifestyle changes can, in addition to preventing the progression of the disease, improve the initial symptoms of ED.[30] With a healthy lifestyle, proper diet, and adequate mobility, we can enhance sexual function and prevent ED.[32] Lifestyle

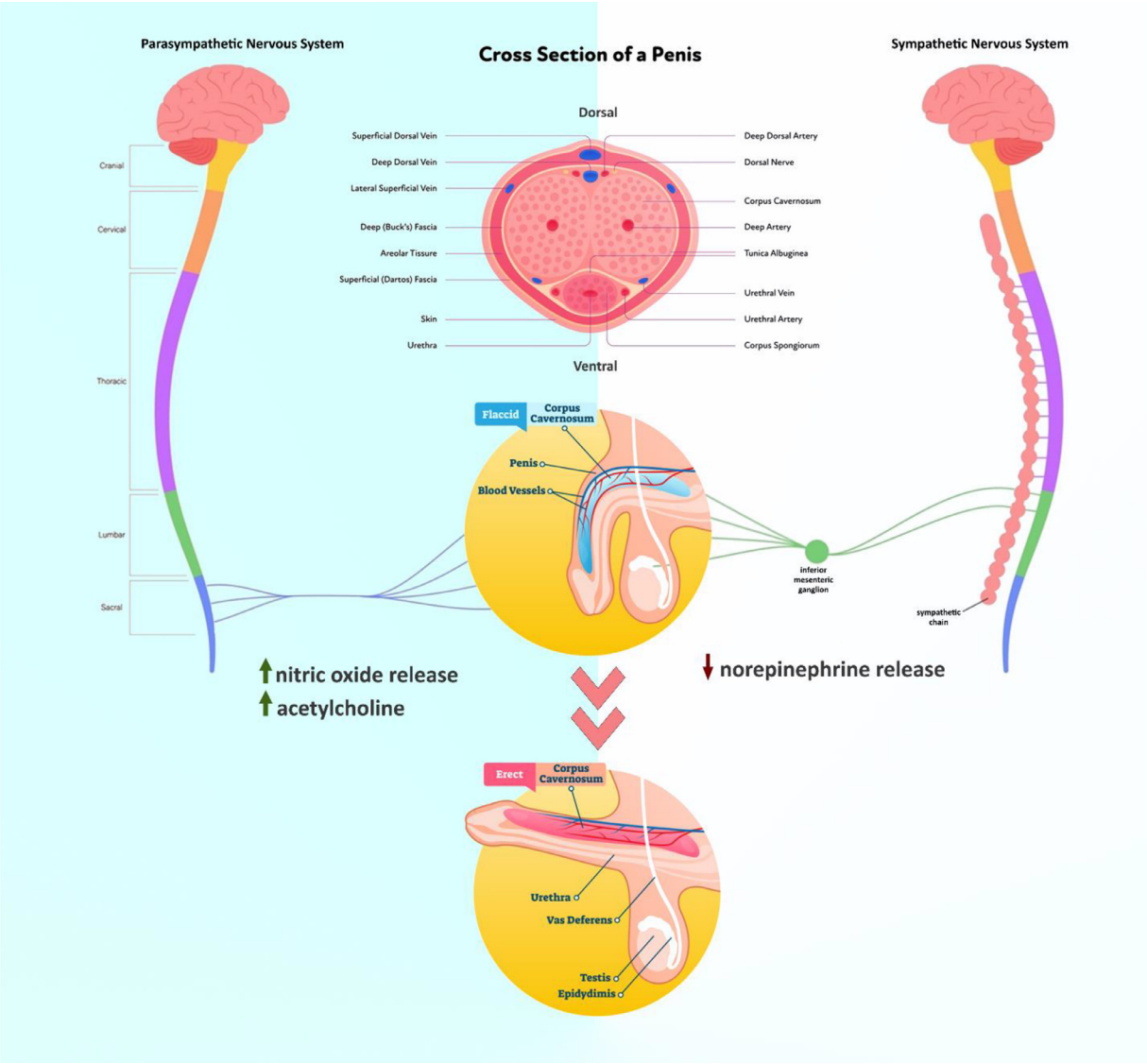

Figure 1. Physiology, anatomy, and neural pathways related to the mechanism of erection along with the primarily involved neurotransmitters; erection is the result of a complex change in neurological, vascular, and hormonal events, all of which play a direct role in completing this process. Figure 1 is available in color online at www.smr.jsexmed.org.

changes and modification of risk factors should be considered before any drug or psychological treatment.[27]

Oral Treatment. In ED, NO release is reduced, leading to abnormalities in smooth muscle relaxation. In this regard, PDE5Is are the most common drug treatment and first-line treatment of ED.[29,33] With inhibition of PDE5, these drugs keep cGMP levels high and effectively prolong NO activity in the penis artery.[29,34] Sildenafil, vardenafil, tadalafil, and avanafil, are the most effective drugs in this category which differ only in onset and duration of effects and side effects.[27–29,35]

Intracavernousal Injection (ICI). ICI treatment is considered the second-line treatment of ED. The main advantage of this type of treatment is that the obtained erection is predictable and occurs quickly.[31] In ICI, the PDE5I non-responsive patient is treated using vasodilating drugs such as alprostadil and papaverine.[35,36]

Vacuum Erection Devices (VED). In this method, a device is placed on the penis and filled to create a vacuum, draws blood into the penis, and causes an artificial erection.[27,30,31,35]

Testosterone Therapy. Although the therapeutic role of testosterone is limited, it plays a vital role in maintaining adequate erectile function.[31,37] The primary function of testosterone in men's sexual response is to regulate the time of erection and synchronize the erection of the penis with sex. Testosterone levels

are reversed by increasing the severity of ED.[38] As a dilator of the arteries of the penis and the sinuses of the cave, testosterone facilitates an erection.[39]

Penis Prosthesis. The third line of treatment for ED is using a prosthesis, which is used if other methods have failed.[30,31] Despite these protocols, we still need more effective therapies to improve long-term erections. Promising future treatment strategies, including gene and cell therapy, may lead to the treatment of ED.[31]

History of ED's Topical Therapy

Some medicines, such as tadalafil, sildenafil, minoxidil, alprostadil, yohimbine, papaverine, testosterone, aminophylline, co-dergocrine, and nitroglycerin, were studied for their ability to treat ED when applied topically.[40–49] Limited skin penetration is a common problem with transdermal medication administration; causes include the compound's physicochemical characteristics, low partition ability, and the stratum corneum's strong barrier capabilities.[50]

Phosphodiesterase-5 (PDE5) Inhibitors. Tadalafil. Tadalafil is clinically recommended, even in resistant patients, because of its extended duration of action (36 hours). It causes less than 0.1 percent vision impairment due to PDE6′s lower inhibitory impact than sildenafil and vardenafil.[51] Topical tadalafil was shown effective in many trials to treat male reproductive system problems. The use of PEG400, hydroxypropyl-beta-cyclodextrin (HPCD), and tween 80 not only improved tadalafil solubility but also the AUC of tadalafil gel rose by 223% compared to the tadalafil solution.[51]

Lipid nanocarriers (LNC) can be utilized to improve tadalafil permeability to the skin. According to Baek et al., one of the effective LNC systems is tadalafil loaded on lipid nanocarriers made from glycerol monostearate (solid lipid), oleic acid (solid lipid), and twin 80 (solid lipid - surfactant). Compared to the tadalafil solution, the tadalafil-loaded LNC dispersion with ethanol and limonene as skin influx enhancers had the most significant flux.[52]

According to Ismail and co-workers, the use of tadalafil, sialorphin, and NO to produce topical gel nanoparticles was described in an experimental study. Erectogenic drugs were entrapped in nanoparticles and administered to rats' glans and penile shaft. A control group of rats received non-loaded nanoparticles, administered in the same region and the same manner as the experimental group. Compared to the control group, the experimental group showed a substantial erectile and raised intracavernosal pressure response.[53]

The penetration enhancer-containing tadalafil-loaded nanoliposomes (penetrosomes) were produced by the hydration-sonication technique, according to Mehanna and co-workers.[54] Penetrosomes and ultraelastic nanoliposomes are suitable carriers for delivering tadalafil transdermally to treat ED.[55]

Sildenafil. Topical administration of sildenafil citrate (SC) directly to the cavernosa provides optimum efficacy and rapid onset with the lowest dose and minimal side effects, according to a phase I pharmacokinetic and safety experiment, which was the central claim of the recent research.[56,57] According to Bhattacharya et al., topical application of sildenafil citrate in cream or lotion form in a dosage range of 28–56 mg induced an erection in 30 minutes with prolonged sexual stimulation.[58]

Topical treatment with bilosomes (a flexible lipid vesicular nanocarriers made of bile salts such as deoxycholic acid, sodium cholate, deoxycholate, taurocholate, glycocholate, or sorbitan tristearate as active surface agents[59]) could provide higher therapeutic efficacy.[56] In-vitro study results showed enhancement for permeation of the drug from the transdermal transfersomes (are a type of elastic or malleable vesicle that can convey giant molecules through intact mammalian skin and are administered in a non-occlusive manner[60]) by 5-fold in comparison with drug suspension.[61] Another study evidenced that nano-transfersomal films enhance the transdermal permeation and the bioavailability of SC.[62] Researchers tested the effects of a topical SC gel vs SC oral tablet on ED. Transdermal SC administration was found to have a considerably faster onset of action and fewer adverse effects. The nanocarriers created in this work increased SC transdermal penetration, potentially resulting in a quicker onset and longer duration of pharmacological activity.[50,63,64]

Vasodilators. Nitrates, PGE1, papaverine, minoxidil, aminophylline, and co-dergocrine are vasodilating drugs used topically to treat ED.[48] Topical vasodilators such as minoxidil, PGE1, papaverine, and nitroglycerin are typically safe, but their effects are restricted to 24%–40%.[65–69] The sorts of effective topical vasodilators in ED will be presented in the following sections:

Papaverine. Local use of a papaverine-containing ointment enhanced cavernous artery diameter, according to Doherty et al.[70] Phase I of a placebo-controlled non-blinded study tested the effects of 15% and 20% papaverine base gels applied to the scrotum, perineum, and penis. The authors found that topical papaverine enhanced reflex erections in those with spinal cord injury by 36%.[71–73] Despite this, some studies reported no significant effect of topical papaverine on penile blood flow.[47,52,68,72]

According to Montorsi and colleagues, a 50:30:20 percent volume ratio of caproic acid, ethanol, and water is an appropriate penetration enhancer for topical administration of papaverine HCl for systemic absorption.[41] Compared to the classic papaverine HCl gel, the papaverine HCl-loaded trasferosomes displayed more excellent pharmacological outcomes in controlling ED.[70,74]

Minoxidil. Minoxidil, an alpha-adrenergic antagonist, relaxes arterial smooth muscles directly.[75] Following topical administration of minoxidil cream, Clark et al. observed a slight improvement in penile blood flow in 22 diabetic males.[76] In another study, topical minoxidil was much more effective than nitroglycerin,

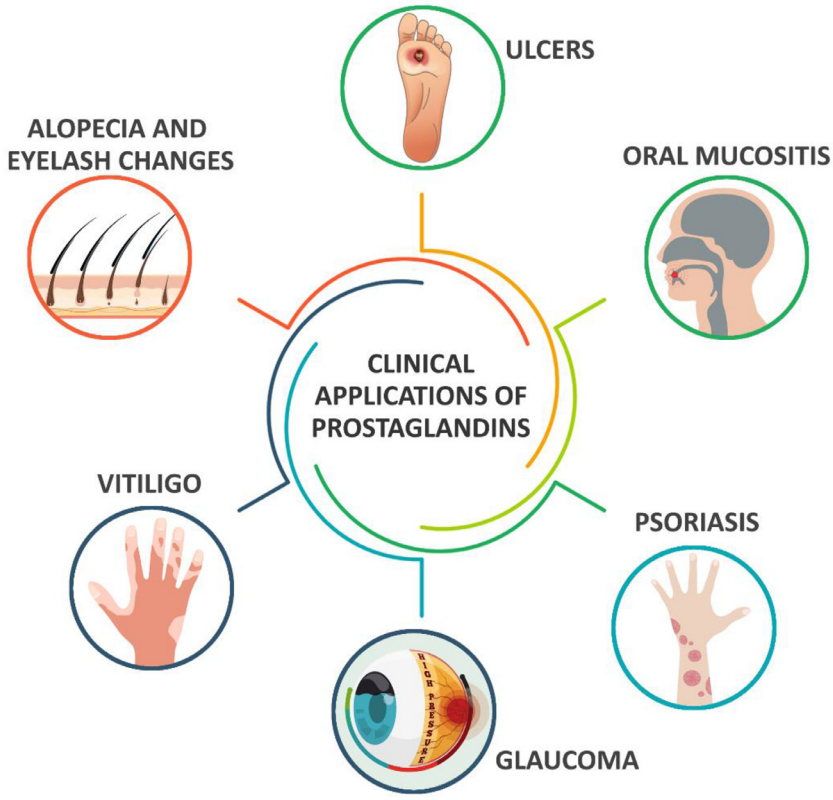

Figure 2. Therapeutic records of topical prostaglandins; the topical effectiveness of these compounds has been evaluated locally in many diseases. Figure 2 is available in color online at www.smr.jsexmed.org.

which itself was more effective than the placebo.[64,70,77–81] Besides, an aerosol spray of minoxidil was studied on the glans penis in spinal cord lesioned men (SCL). The topical use of minoxidil induced a little, if any, subjective and objective effect.[82] With a slight impact, transdermal minoxidil has been shown to produce a 4/15 complete erection in ED patients.[79]

Nitroglycerin. After sexual stimulation, nitroglycerin paste promotes tumescence by increasing blood flow in the cavernous arteries.[83] However, there is little evidence of nitroglycerin as a topical agent in a natural setting that allows for normal sexual function. Nunez and co-workers presented 3 cases of impotence that were successfully treated with nitroglycerin ointment applied topically.[84]

Testosterone. Transdermal testosterone therapy is more successful than intramuscular or oral testosterone therapy. According to Khera, et al., hypogonadal men treated with Testim (testosterone 1%) topical gel and followed for 12 months had higher total testosterone and free testosterone levels and vastly enhanced sexual function. All of the categories investigated, including patients taking PDE5Is and those who had previously used testosterone replacement therapy, reported enhancement in sexual function compared to baseline scores.[85]

In another study, in hypogonadal patients with ED, testosterone gel (T-gel) efficacy was studied alone and in a mix with oral sildenafil. In hypogonadal patients who have failed to respond to testosterone supplementation alone, a combination of sildenafil and T-gel treatment improves ED.[86] According to another study, testosterone is helpful when added to this PDE5I regimen, but only in hypogonadal males with baseline testosterone levels of less than 3 ng/Ml.[87]

Topical Prostaglandins Applications

Prostaglandin analogs, particularly topical types like latanoprost, PGE2, alprostadil, and bimatoprost, are used to treat a variety of cutaneous disorders (Figure 2) that we will investigate in the following:

Alopecia and Eyelash Changes. The prostaglandin analog latanoprost is used to treat glaucoma. It can cause iridial and periocular hyperpigmentation and eyelash changes such as pigmentation and increased thickness, length, and quantity.[88] Hypotrichosis and eyelash alopecia can only be treated with prostaglandin analogs, regardless of the cause. As a sign of alopecia areata, these drugs can impact frontal fibrosis alopecia and eyebrow hypotrichosis.[89]

Vitiligo. Topical prostaglandin E2 (PGE2) treatment on the skin of mice has been demonstrated to increase melanocyte density.[90] PGE2 promotes melanocyte proliferation and has stimulant and immunomodulatory properties. Topical PGE2 is suitable for localized, stable vitiligo because of its effectiveness and safety.[91] With narrowband ultraviolet B phototherapy, the effect of latanoprost as a potential treatment for vitiligo, specifically periocular vitiligo, on skin repigmentation could be enhanced.[92]

Psoriasis. After a few days of topical application of the PGE2 gel and the gel alone to psoriatic lesions in 10 individuals, all PGE2-treated lesions improved; however, complete healing was not attained.[92,93]

Oral Mucositis. Yazdanian et al. reported that PGE2 tablet 0.5 mg used locally could minimize the extreme discomfort of radio chemotherapy-induced oral mucositis, according to various research.[92]

Glaucoma. For individuals with ocular hypertension (OHT) or glaucoma, topical prostaglandin analogs such as travoprost and bimatoprost may be more effective in decreasing intraocular pressure (IOP).[94–96] In terms of IOP reduction, bimatoprost had the best efficacy, whereas latanoprost had the best tolerability.[97] In treating primary open-angle glaucoma, topical prostaglandin F2 (PGF2) analogs can be employed.[98] Also, PGD2 or its equivalents may be beneficial in treating glaucoma, according to another study.[99]

Ulcers. Nine patients with persistent leg ulcers were treated with topical PGE2 dispersed in hydrocolloid granules, and the results were reported. These findings indicate that topical PGE2 effectively treats leg ulcers.[100] The effects of a prostaglandin E1-cyclodextrin clathrate compound in an ointment are investigated. According to these data, topical use of PGE1 CD ointment increased wound healing under ischemia conditions during the first week of treatment. They also suggest that PGE1 CD ointment could be a topical therapy for ischemic skin ulcers in the early phases of inflammation.[101]

Table 1. The search strategy of the manuscript

Constant keyword 1	variable keywords [X]	Constant keyword 2
Prostaglandin -	Topical	ERECTILE DYSFUNCTION (ED)
Alprostadil	Transdermal	
	Gel	
	Cream	

METHODOLOGY

This job was done based on the manner of effectuality, clinical administration, and diverse formulations of topical prostaglandins in various forms to detract the possibility or cure ED. The preconceived searches were performed in Scopus and PubMed search engines. To search for different clinical applications and trials, the combined keywords [Prostaglandin/Alprostadil] + [X] + [erectile dysfunction] have been used (Table 1). These 3 components search results are amalgamated and classified in the results and discussion section. PubMed searches were restricted to advanced searches in titles and abstracts without using MeSH. Other scrutinization has been done based on the comprehensive focus of the context of each segment or on an ad hoc basis. The content's uniformity from a theoretical and literary point of view was then re-criticized and revised accordingly.

RESULTS AND DISCUSSION

Prostaglandins as a Topical Therapy for ED

Prostaglandins have shown significant positive effects in the treatment of ED. Unlike PDE5Is, this class of drugs exerts its effects directly. After binding to PGE1 receptors, Alprostadil activates the cyclic adenosine monophosphate pathway, inducing an erection into smooth muscle.[64,102] This pathway further leads to the activation of protein kinase A, which leads to the relaxation of smooth muscles by stopping the flow of intracellular potassium and calcium. Following smooth muscle relaxation, the cavernosal arteries dilate. Alprostadil can also achieve this goal by acting as a norepinephrine antagonist.[103] PGE1 increases intracellular cAMP after binding to E-prostaglandin receptors through adenylate cyclase activity bound to the cortex. Activation of Maxi K channels (neuronal calcium sensors) changes the flow of calcium ions, resulting in cell polarity, and finally inhibits noradrenaline and angiotensin II secretion.[43,104,105]

Although PDE5Is are the first line of treatment for ED, it is claimed that these drugs are not responsive in about half of patients. In addition, further problems of systemic side effects of these drugs are also troublesome, which has caused intolerance and dissatisfaction among patients and has led to the introduction of prostaglandins as a factor with proper response and low side effects.[102,106–108] Prostaglandins are used both through the penis and topically or transdermally.[109] Many companies are working on developing topical methods such as gels.[110] Researchers have focused on the topical use of agents such as nitrates, PGE1, papaverine, minoxidil, aminophylline, and codergocrine.[48,111–113]

Although not approved and not licensed, topical prostaglandins have been used in research due to their non-invasive and systemic efficacy. One of these localized prostaglandins was an analog of PGE called alprostadil.[111,114–123] Research on topical alprostadil in the United States is in clinical phase III.[124] A multicenter, open-label, long-term study of 1161 patients to ensure

the efficacy and safety of topical alprostadil confirmed this.[125] Foldvari and colleagues, in a survey of the extent and ways of skin absorption of PGE1, concluded that PGE1, along with a new biphasic delivery system, showed a significant increase in penetration and was more successful than other formulations. However, delivery via additional barrier layers such as tunica albuginea is required.[126] Extensive studies showed that combination therapy with alprostadil might be more effective if PDE5Is do not respond adequately.[127] In a similar survey by Moncada et al. for patients for whom monotherapy with PDE5Is did not respond well, a combination of PDE5I plus 300 micrograms of topical alprostadil cream was used 30 minutes before sexual intercourse. The results were promising enough. In total, except for 6 patients who were excluded from the study, 49 patients (78%) achieved a score of 3 or 4 Erectile Hardness Scale (EHS), but 19 patients (28%) did not receive a response. Patients were evaluated after 4, 8, and 12 weeks and a mean increase in the International Index of Erectile Function - Erectile Function score (IIEF-EF) from 17 to 22 was reported.[128]

Alprostadil is the only intracavernous drug approved in the USA. However, nitroglycerin cream or paste, a combination cream containing aminophylline, isosorbide dinitrate, and codergocrine mesylate or alprostadil cream, has been used in research studies.[129] However, topical alprostadil (cream) called Alprostadil NexACT has been approved in Canada, including alprostadil and a skin penetration enhancer called DDAIP. The double-blind, placebo-controlled experiments showed promising and significant effects in treating and controlling ED in a wide range of patients.[130] Despite the proven effects of PGE1 due to its aggressive use (medicated urethral system for erection (MUSE)), researchers are looking for an easier and more effective way to deliver the drug.[64] Despite its relatively good response rate (65%), this invasive method had disadvantages, one of which was developing a hypotensive episode. This hypothesis was tested by limiting the systemic uptake of prostaglandins by placing a compression band on the base vein of the penis. The results showed that none of the people who used the bandage had this complication (12 people). This statistic was the opposite in the group who did not use the pressure bandage (3 out of 3 people).[131] One suggested way to solve this problem is using topical prostaglandins.[64] Although topical prostaglandins alone may not be considered an effective monotherapy, they can be very effective in combination with oral drugs.[43] It seems that a drug in the form of a trimix combination of PGE1, papaverine, and phentolamine can work in 62% of men with low doses.[132] One of the suggested ways to solve this problem and increase the effectiveness and penetration of the drug into deep cavernosal bodies is to use better formulations for drug delivery, such as liposomal formulations. This proposal was tested on 5 patients double-blind and placebo-controlled. This experiment was performed using 3 different formulations. Liposome A formula containing soya phosphatidylcholine (15% wt / wt) and PGE1 (0.05% wt / wt) at pH 7. Formula B also contained soya phosphatidylcholine (15% wt / wt) and PGE1 (0.05% wt / wt) similarly, but with the difference that it was formulated in pH 8 with 1% wt / vol calcium thioglycolate as a skin penetration enhancer. The third formula (C) was similar to the first formulation in terms of soy phosphatidylcholine, PGE1, and pH. However, it contained 2% wt / vol methylsalicylate as a skin penetration enhancer, and the encapsulation efficiency was twelve percent lower than formula one (66%). Formulation A was used for placebo without PGE1. As a result, the lowest adsorption was reported for the second formulation, and the highest yield was reported for the third formulation. An increase in systolic flow velocity was observed in formulation C up to 7 times compared to the baseline state. Also, one of the conclusions of this study was that the dermal absorption of the drug in the non-liposomal state was so low that it was left to continue the study of that type of formulation, and the study was continued only with liposomal formulations.[69]

Another small study conducted in phase I, placebo-controlled, nonblinded investigation of safety and efficacy on 8 patients, showed that the mean cavernous artery diameter increased from 0.9 to 0.11 cm with topical prostaglandin-E1 and the mean peak systolic flow velocity from 15.4 to 22.8 cm.[133] In a limited study of 7 healthy individuals to evaluate cream retention and displacement, 100 mg of alprostadil cream contained 300 μg of the active ingredient in combination with nonabsorbable 99mTc-sulfur colloid and radiolabeled 99mTchexamethylpropylene amine oxime (HMPAO) was used 2 separate days. The results showed that the dose retention was about 99%, and the migrating dose ratio was about 1%. In one case, the results were different. The study was a 2-way crossover study in which neither researchers nor blind people were exposed.[134] A dose of 300 micrograms has shown an 83% effect in global studies, and that is the highest performance improvement recorded.[135–137] The maximum dose of PGE1 that can be used without side effects is 500 micrograms.[138] By adjusting the individual dose, erectile function improves in 73% of patients.[139] In an uncontrolled study performed using 0.4% alprostadil gel and skin penetration enhancers, the effects of 0.5 g of topical gel were shown to be comparable to intracavernosal injections.[64] There have been many studies on the effects of prostaglandins on ED. The results of these studies, in turn, have been significant. In one study, which was performed using 0.04% prostaglandin-El gel (weight-weight) based on lipophilic ethylene glycol ointment on ten men, 8 people went through all the phases, and one of the reasons for one person's withdrawal was the redness of the face after using the gel. Examinations were performed 45 minutes after gel application. In this study, the peak systolic velocity increased to over 25 cm/s in 50% of all test cases, and grade 4 and 5 erections were extended to 2. In all cases, an increase was observed in both the mean diameter of the cavernous artery and the mean peak systolic flow velocity. Patients showed good tolerance to this topical prostaglandin after topical use on the arm or genitals. It seems that this prostaglandin is well tolerated for topical use. In

general, as a result of this study, topical prostaglandin-El can be suggested as an effective drug therapy in the treatment of patients with spinal cord injury for further studies.[72,140] In a similar study on 48 men (single-blind, placebo controlled), using SEPA as a placebo, a mixture of 95+5 of alprostadil and SEPA was used for the experimental group (Topiglan topical gel). The 48 men used only a single dose of the half to one milligram of gel containing 0.1% and 0.5% PGE1, or placebo. The response received was different in all doses with placebo but did not differ significantly from the other doses. Between 67% and 75% of the experimental group responded to the drug, compared to only 17% in the control group. Apart from the skin discomfort caused to the majority, no other serious side effects were seen in this study, so the gel appears safe for topical use. The erection produced was significant, although many men needed visual and tactile stimuli to achieve an erection.[46,80,102,141–143] In a study using PGE1 + SEPA 5% cream (Topiglan, MacroChem Co., Lexington, MA) on the glans penis in a feline erection model, a triple intracavernosal injection combination consisting of 1.65 mg papaverine, 25 microgram phentolamine, and 0.5 microgram PGE1 was used as a reference and placebo cream was used for control. The result was reported that using a topical combination of PGE+SEPA could increase intracavernosal pressure without showing significant systemic effects.[144,145] Patients' tolerance to the drug was also evaluated in 35 men. The drug was taken 3 times a week for 4 weeks. Drug tolerance was satisfactory during this period. In the second phase, which was double-blind, placebo-controlled, single-institution, randomized, and in-clinic, the efficacy and safety of this drug were studied in 62 patients. 38.9% of the drug group and 6.9% of the placebo group showed an erectile response sufficient to penetrate the vagina. Common symptoms, such as heat or mild burning, were low and were more common in the drug group than in the placebo group. In one person, symptoms of hypotension were recorded after 90 minutes. The third phase was performed on 460 couples to find information about ED. The results showed that the combination of PGE1/SEPA (Topiglan) was not significantly different from the control group. Although the full results of this study have not yet been reported.[146] In a placebo-controlled, double-blind study of 60 patients with moderate to severe ED, Topiglan (Macrochem, Lexington, MA) was administered, and 39% of patients reported having enough erections to penetrate the vagina. Side effects, including heat and a mild burning sensation, were not significantly different from the placebo group.[147]

Extensive studies confirm the better efficacy of alprostadil in the presence of a modern skin enhancer.[148] In a study examining post-robot assisted radical prostatectomy (RARP) rehabilitation therapy in patients with ED, 72 patients were examined, and 68 patients came to the analysis stage. The exclusion of others from the study had nothing to do with treatment. In the first month after surgery, complete ED was observed in all patients, and treatment was started with Topical alprostadil (Vitaros). In the third month, positive SEP-Q2 in 60 patients (88.2%) and a positive SEP-Q3 for 51 patients (75%) were observed, and the effects of significant improvement appeared in all patients. No specific complications were reported, and only in 2 individuals painful erections were reported. This study, conducted by Della Camera et al., analyzed the parameters before the operation and was also examined in the sixth month after surgery.[149] Vitaros cream (alprostadil 0.33% with 2.5% w/w dodecyl-2-n,n dimethylaminopropionate hydrochloride) has been approved by the health organization of Canada as a first-line treatment, and its studies for the FDA approval are ongoing.[150] In an extensive survey, 2 placebo-controlled, multi-stage, randomized, double-blind, phase III experiments were performed on 1732 patients with moderate to severe ED at 3 doses of 100 (n = 434), 200 (n = 430), and 300 μg (n = 434), 24 separate doses were used for 12 weeks, and changes in the EF domain of the IIEF, vaginal penetration/attempt rate, and intercourse completion to ejaculation rate were assessed. At a dose of 300, the patients received an excellent response to the placebo with 32% greater success (52 vs 20). Although this result was weaker than previous studies, the researchers believe that this was because of the higher average age of the study group (60 years). Even in another relatively large study of 152 patients, 52% of people who had previously tried at least 2 treatments reported Vitaros/Virirec as effective.[135,151,152]

In a study conducted with patients in all mild, moderate, and severe ED categories, 50, 100, and 200 micrograms were prescribed for mild to moderate ED patients. Dosages of 100, 200, and 300 micrograms of alprostadil were used for severe patients. To measure the success rate of vaginal penetration, patients were divided into 2 categories: mild to moderate and severe. In the first group for doses of 50, 100, and 200 micrograms, the success rates were 69.4, 69.1, and 82.9, respectively. It was reported 55.3% in the placebo group. In the second group, 32.3, 36.2, and 38.6 percent were recorded for 100, 200, and 300 microgram doses against 15.6 percent for the placebo group. In this group, for no dose, the differences were not statistically significant.[153] These creams have no food or drug interactions, and their consumption is safe and well-tolerated. In addition, it has a rapid onset of action and good skin penetration (via the polar region of the phospholipid bilayer on the plasma membrane).[135] Overalls such as pain, erythema, and burning, as in other studies, were reported to be limited (4.4% and 12.2%), respectively.[154] However, due to its low side effects and proper skin absorption, it can be considered a promising option in treating ED.[150]

In a larger trial, tests were performed on 20 clinics in 2 studies in the United States. These studies were performed as double-blind, placebo-controlled. In the first trial, which included 12 research clinics (161 patients), patients were divided into one placebo and 3 cream groups. They used Alprostadil 0.05, 0.1, and 0.2 mg, formulated as a 100 mg cream with skin penetration enhancers like Alprox-TDs (NexMed Inc., Robbinsville, NJ). USA patients in this study had mild to moderate ED. In the second study, which was performed on 8 clinics involving 142 critically ill patients with the same method, the doses were changed

to 0.01, 0.2, and 0.3. In both studies, the drug's efficacy increased with increasing dose, and changes in the score of ED in both groups at the highest therapeutic dose compared to the plate showed a significant increase. Side effects were also carefully checked. Most of the complications were short-term and mild to moderate except in one case of near syncopal. The episode, which occurred in the first study following a dose of 0.2, lasted 10 minutes. Another severe side effect was urinary tract pain. This study was ongoing in Phase 3 at the time of writing.[155] Alprox-TD has completed its Phase I trials in the United States and continues its clinical trials in Argentina.[156] In a more extensive study of 1,732 patients with the double-blinded, parallel-group method, it was found that ED and sexual encounter profile scores progressed considerably using 200 and 300 micrograms of alprostadil as a cream formulation.[157]

According to a double-blind study performed with placebo-controlled 1% alprostadil gel, significant erythema was observed 15 minutes after, comparing with the placebo group. This effect peaked after 45 minutes and lasted up to 90 minutes.[102] In another study by Goldstein et al., Performed on a 1% alprostadil gel combined with the SEPA in a double-blind, placebo-controlled manner on 62 men, the maximum time to complain of side effects was 15 minutes after ingestion. This study also found the most remarkable difference in the intensity of action and performance of Topiglan gel compared to placebo between 45 and 60 minutes.[158] In a single-blind study by McWarry et al. with 3 concentrations of 0.5, 1, and 2.5 mg alprostadil with 5% SEPA (Topiglan; MacroChem, Lexington, MA) in 67, 75, and 67% of patients, respectively. There was a significant positive correlation between gel consumption and response and stimulation, which was more intense with the help of visual and tactile stimuli for the first 25 minutes.[64] Also, a mid-term study (12 weeks) reported significant therapeutic effects for Alprostadil compared with placebo.[130] Alprostadil combination therapies have also been studied to some extent. For example, combination therapy with prazosin is slightly more effective than monotherapy, but this slight increase seems significant.[159] The use of anesthetics in combination with alprostadil has also been suggested. One of these anesthetics is dyclonine. In the only double-blind crossover study that used this, the combination of 0.5% dyclonine / 0.4% alprostadil compared to 1% dyclonine alone or 0.4% alprostadil alone had a better effect. Mean Intravaginal Ejaculatory Latency Times (IELTs) was more than one minute higher than the placebo group (2.34 and 4.08 min), and 17.5% of men lasted up to an average of 18.2 minutes.[160,161] Another suggested solution to ED problems is Prostaglandin E1 ethyl ester (PGE1-EE). The use of PGE1 gel with SEPA or the use of PGE1-EE can have significant effects on improving transdermal penetration. Skin esterases degrade more than 99% of PGE1-EE, and this lipophilic ester releases PGE1. The length of penetration affects its therapeutic effect.[162] In a double-blind study to evaluate the impact of this substance, 4 doses of 125, 250, 500, and 1000 micrograms of PGE1-EE were used, and for placebo, a patch containing 5 micrograms of PGE1-EE was used. After a screening phase in which 4 patients were excluded, 34 remained in the study. At a dose of 500, about 26%, and at a dose of 1000 micrograms, 50% of patients received an adequate response. In addition, at a dose of 1000, an erection occurred faster, stronger, more severely, and had a longer duration of action or was very well announced. This shows that if studies continue to find the correct dose, this can be offered as a suitable treatment.[163] However, Ian Eardley and colleagues believe that topical compounds (including papaverine, minoxidil, nitroglycerin, and even topical alprostadil with skin penetration enhancers) are ineffective and find the clinical results disappointing; they did not elaborate.[164] The combination of 3 substances, PGE 1, minoxidil, and nitroglycerin in the form of cream and topically, is one of the recommended compounds for treatment that has been studied. In a study on rats, the response rate of topical cream was 30 to 40% compared to intracavernous injections.[165] In addition to rats, studies have been performed in cats, and proven effects have been obtained.[128,144,166]

Hatzimouratidis emphasizes that alprostadil cream is less effective than injectable treatment. Still, its ease of use can be an acceptable option.[157] Hatzimouratidis, except for 2 drugs, alprostadil with SEPA (Topiglan) and alprostadil with NexAct (Alprox-TD), which have undergone phase III clinical trials, described other topical treatments as unreliable and their effects unclear.[167] NEXMED tested the success rate of Alprox-TD on 56 mild to moderate patients and reported an efficacy of 75%. Also, for Topiglan in Phase II placebo-controlled double-blind study in 60 moderate to severe patients, in 12 of the 31 drug groups, adequate erections were recorded to penetrate the vagina. Nevertheless, this statistic was 2 out of 29 in the placebo group. Skin reactions such as burning or heat were observed in 44% and 30% of patients in each group, respectively, which is not a statistical difference (P=0.302).[168,169] A placebo-controlled study of Topiglan, topical prostaglandin-E1, and SEPA, found that up to 75 percent of patients responded to the compound, compared with 17 percent for placebo users.[170]

Alprox-TD (NexMed, Inc., Robbinsville, NJ) was used in an extensive study of more than 1,700 patients in 85 US clinics and provided significant improvement effects in patients.[147]

In a study adjusted for diabetic men, DDAIP-boosted topical alprostadil at 200 and 300 micrograms reported 44 and 36 percent efficacy in these 2 doses, respectively.[171]

Moreland et al. also believe that penile blood flow increases with topical therapies. Still, reports of adequate erections for vaginal penetration are underestimated and suggest that skin penetration enhancers may solve the problem.[172] In addition to penetration enhancers, unique formulations can also help increase skin penetration and transdermal absorption. For example, in a study performed on rat skin at normal pH, the formulation of 20% alcoholic hydrogel containing limonene or

Table 2. A detailed summary of trials and studies on topical PGE1 for ED treatment

Study	Formulation	Population	Dose (μg)	Supplementary	Efficacy	Side effects
Moncada et al.	Alprostadil Cream (Vitaros©/ Virirec©)	74	300	Oral PDEIs + DDAIP.HCl (skin penetration enhancer)	49 patients (78%) achieved an EHS score of 3 or 4, but 19 patients (28%) did not receive a response.	Mild and short-lasting genital pain, tenderness, and erythema.
Foldvari et al.	Liposomal PGE1 0.05%	5	-	Methylsalicylate (skin penetration enhancer)	7-fold elevation in systolic flow velocity.	Not reported.
Kim et al.	0.04% PGE1 Gel	8	-	Ethylene glycol ointment	Cavernous artery diameter increased from 0.9 to 0.11, and the mean peak systolic flow velocity from 15.4 to 22.8 cm.	Redness of the face lead to one person's withdrawal.
Yeager et al.	Alprostadil Cream	7	300	Nonabsorbable 99mTc-sulfur colloid and radiolabeled 99mTchexamethylpropylene amine oxime (HMPAO)	Migrating dose ratio was reported about 1%.	Not reported.
Yap et al.	0.4% Alprostadil Gel	Not reported.	200	-	The effects of 0.5 g of topical gel were shown to be comparable to intracavernosal injections.	Not reported.
McVary et al.	0.5% - 1% - 2.5% PGE1 Gel (Topiglan)	48	500	SEPA 5% (skin penetration enhancer)	Between 67% and 75% of the experimental group responded to the drug, compared to only 17% in the control group.	Skin discomfort.
Usta et al.	0.25% - 0.5% - 1% PGE1 Cream	8 (Cats)	250-500-1000	SEPA 5% (skin penetration enhancer)	Increased intracavernosal pressure.	No significant systemic effects.
McMahon	PGE1 gel (Topiglan)	Phase I: 35	-	SEPA 5% (skin penetration enhancer)	Phase I: Patients' tolerance was evaluated and was acceptable.	Drug tolerance was satisfactory during this period.
		Phase II: 62			Phase II: about 40% of the drug group reached sufficient erectile response.	Local heat or mild burning. Hypotension (rare).
		Phase III: 460			Phase III: outcome was not significantly different from the control group.	Not reported.
Camera et al.	0.33% Alprostadil Cream (Vitaros ©)	68	-	DDAIP.HCl 2.5% (skin penetration enhancer)	Positive SEP-Q2 for 60 patients (88.2%) and a positive SEP-Q3 for 51 patients (75%) were observed.	In 2 individuals, painful erections were reported
Padma-Nathan et al.	Alprostadil Cream (Alprox-TD)	1732	100- 200-300	NexACT (skin penetration enhancer)	At a dose of 300, the patients received an excellent response to the placebo with 32% greater success.	Penile burning, genital pain, and genital erythema. partner treatment-related adverse event (vaginal burning)
Rooney et al.	Alprostadil Cream	1161	100- 200-300	-	Most patients (74%) demonstrated an overall improvement in erectile function on most end-points.	Application site burning or erythema. Priapism. 5% of patients discontinued because of adverse effects.
Steidle et al.	Alprostadil Cream (Alprox-TD)	303	50- 100-200- 300	NexACT (skin penetration enhancer)	88% of patients in this study had some improvement in their overall erectile condition during the period of treatment, and greater than 80% of all patients entered into the Phase II program completed treatment.	genital pain, tenderness, and erythema.
Padma-Nathan et al.	Alprostadil Cream (Alprox-TD)	Mild: 161	50- 100-200	NexACT (skin penetration enhancer)	93% improvement in erections for the 0.2 mg treatment group.	A near-syncopal episode was reported as a severe adverse effect. Urogenital pain. Symptomatic and asymptomatic hypotension.
		Severe: 142	100- 200-300		83% improvement in erections for the 0.3 mg treatment group.	
Goldstein et al.	1% Alprostadil Gel (Topiglan)	62	-	SEPA 5% (skin penetration enhancer)	Among 31 treated patients, 12 (38.9%) gained a sufficient erection for vaginal penetration.	Penile erythema, warmth or burning, tingling, and coolness.
Gittleman et al.	0.4% Alprostadil Cream	Not reported	-	0.5% dyclonine	Mean IELTs were more than one minute higher than the placebo group (2.34 and 4.08 min), and 17.5% of men lasted up to an average of 18.2 minutes.	Not reported.
	PGE1-EE Patch	34		-		

(continued)

Table 2. Continued

Study	Formulation	Population	Dose (μg)	Supplementary	Efficacy	Side effects
Schanz et al.			125- 250- 500- 1000		At a dose of 500, about 26%, and at a dose of 1000 micrograms, 50% of patients received an adequate response.	Erythema, burning, and local pain. local side effects were generally mild
Hatzimouratidis et al.	0.33% Alprostadil Cream (Vitaros ©)	Not reported	200- 300	DDAIP.HCl 2.5% (skin penetration enhancer)	44% - 36% efficacy in these 2 doses, respectively.	Not reported.
Park et al.	PGE1-EE alcoholic hydrogel	Not reported	-	Limonene or Cineole	These formulations elevated the flux of PGE1-EE up to about 4-fold compared to control.	Not reported

cineole increased the drug flux by up to 4 times without other penetration enhancers. In the continuation of the study on a cat, the intracavernosal pressure was significantly increased compared to the control.[173] Some believe that topical therapy is effective only for people with organic impotence, and the appropriate group for topical treatment is patients whose impotence is psychological. The lack of absorption of topical agents through tunica albuginea can be considered another reason for these topical agents' low effectiveness compared to other more direct treatments.[65,174] After studying the efficacy of papaverine in ED, Ming Ming Wen and colleagues considered it a better option than prostaglandin E1, citing the lower stability of prostaglandin E1 at room temperature and its high price.[41]

However, Foldvari has a different opinion by examining the metabolism of PGE1 in topical conditions and formulations. He believes that transdermal delivery of PGE1 is not restricted by skin metabolism, and there will be no problem in this regard. William D Alexander states that the success rate of topical agents such as alprostadil, minoxidil, or even a combination of drugs is low and has limited success. It, therefore, claims that these drugs are not generally recommended in the UK.[175] The safety of alprostadil has been tested in trials. Concomitant administration of alprostadil cream with drugs from other categories such as anti-inflammatory drugs, anti-hypertensive drugs, etc., has also been studied, and no significant change in efficacy or safety has been observed. Alprostadil cream has good overall safety; however, besides the limited side effects that the user has for himself, it can also cause weight gain (4.4%) or itching (2.1%) in the sexual partner. This option is also not a good choice for people with severe nerve or circulatory damage or taking blood thinners. Due to the drug's potential toxicity to the fetus, this drug is prohibited in people whose sexual partner is pregnant or planning to become pregnant.[139,151] Its use is also limited and cautious in people with abnormal penile anatomy.[176] Another contraindication to the use of Alprostadil is in patients taking MAOIs. With all these descriptions, topical use of prostaglandin E1, such as alprostadil cream (Alprox-TD, NexMed, Inc.), is one of the most appropriate options considering all the influential factors and side effects for the treatment and control of ED if approved.[103,177,178] Topical PGE1 or intracavernosal injection therapy (with a combination of Trimix (phentolamine, papaverine, and PGE1) or a combination of Bimix (phentolamine and papaverine)) can be considered as a second-line treatment.[179] All the original studies reviewed in this project are summarized in Table 2.

CONCLUSION

ED is a prevalent problem often caused by a patient's medical condition. Despite being the first line of treatment for ED, phosphodiesterase inhibitors do not provide an acceptable response in half of their users and have numerous systemic side effects and contraindications. PDE5Is and other drugs, such as vasodilators

and testosterone, seem to be topically effective in individuals. In some people, topical prostaglandin increases cavernous artery diameter, which leads to effective intercourse when ED improves. Notably, prostaglandins' potential to improve ED diminishes as people get older. Topical prostaglandins are well tolerated, have few side effects, and have no drug-drug and food-drug interactions. Painful erections, urinary tract pain, syncope, erythema, and unusual partner side effects like weight gain and itching are all rare side effects.

Alprostadil formulations depend on penetration and would affect better when combined with penetration enhancers such as DDAIP and SEPA. Lipophile ethylene glycol and alcoholic hydrogel formulations with limonene or cineole, as well as liposomes, particularly liposomes from phosphatidylcholine with methyl salicylates, positively affect the penetration. Furthermore, a formulation including prostaglandin E1 ethyl ester enhances the penetration and action of prostaglandin E1. In general, the effectiveness of topical prostaglandins in the treatment of ED can be reported as moderate but acceptable. Prostaglandins are more efficacious than monotherapy when administered orally or topically alongside other medications such as minoxidil, nitroglycerin, phosphodiesterase inhibitors, prazosin, herbal medicines, etc. However, due to their expensive cost and lower stability at room temperature, several studies have preferred alternative medications such as papaverine over prostaglandins. To achieve this therapeutic goal, more research and new types of prostaglandin medication formulations will be required in the future. Also, some formulations are needed to be investigated in the future, including a combination of prostaglandins and herbal medicines that are useful in treating ED orally or topically.

ACKNOWLEDGMENT

We would like to thank the Pharmaceutical Sciences and Cosmetic Products Research Center, Kerman University of Medical Sciences, Kerman, Iran for their financial support.

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Conflicts of Interest: The authors declare that they have no competing interests.

Funding: This research was supported by a grant from Pharmaceutical Sciences and Cosmetic Products Research Center, Kerman University of Medical Sciences, Kerman, Iran.

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