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Review

Addressing unmet needs for patients with erectile dysfunction: a narrative review of topical therapies

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Abstract

Background: Treatment of patients with erectile dysfunction (ED) was revolutionized by the development and approval of phosphodiesterase type 5 inhibitors (PDE5is), which have been repeatedly shown to be safe and effective in men with this condition. However, some patients do not respond to these agents and others may prefer an alternative therapy.

Aim: The objective of this paper is to evaluate topical therapies for ED used in clinical studies, either as single agents or in combination with a PDE5i, and consequently determine which topical therapies meet the criteria of an 'ideal medication for ED.'

Methods: The PubMed database was searched to identify clinical studies of topical agents that have been evaluated in men with ED. This review was supplemented by a search of presentations at the 2024 annual meetings of the American Urological Association and Sexual Medicine Society of North America.

Results: The literature review and subsequent screening resulted in 39 clinical studies and 5 meeting abstracts for review. The studies demonstrated efficacy for intraurethral and topical alprostadil, topical prostaglandin E_1 ethyl ester, nitric oxide donors, testosterone (in selected patients), and a non-medicated hydro-alcoholic gel. The studies reviewed also demonstrated a significant benefit of adding topical alprostadil to therapy in patients with inadequate responses to PDE5is. An effective topical therapy delivered to its site of action with a rapid onset could improve patients' and partners' satisfaction with and acceptance of treatment. These actions have been demonstrated by a new over-the-counter agent, MED3000, authorized by the United States Food and Drug Administration, and for topical alprostadil, which is available with a prescription in the European Union.

Clinical Translation: The availability of safe and effective topical ED therapy is an important addition to current treatment options for men with this condition.

Strengths and Limitations: This study provides results from a comprehensive search strategy by including a wide range of search criteria. However, the heterogeneity of studies evaluated creates difficulties in directly comparing results from different studies.

Conclusion: The results of this analysis show that current topical therapies can provide statistically and clinically significant improvements in erectile function in men with ED and may provide an effective alternative to PDE5i in men who require or prefer an alternative therapy.

Keywords: erectile dysfunction; erectile function; etiology; psychological; sexual dysfunction; topical therapy.

Introduction

Erectile dysfunction (ED), the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse,[1] has a reported prevalence of around 24% in men between 40 and 80 years of age in the United States.[2,3] A report from Denmark indicated that 18% of sexually active men had ED,[4] and a study that included data from Brazil, China, France, Germany, Italy, Spain, the United Kingdom, and the United States indicated an ED prevalence of 49.7%.[5] While ED can occur at any age, incidence and prevalence are higher in older men.[3,6,7] Additionally, it has been suggested that the prevalence of ED is increasingly reported in men <40 years old,[8] and recent results have shown that the prevalence of ED in young men aged 18-24 years old is 17.9%, a value higher than that reported in prior studies.[3]

Multiple studies have documented the adverse effects of ED on quality of life for men with this condition, as well as their partners. ED is associated with anxiety, decreased self-confidence and self-esteem, anger, depression, frustration, guilt, and reduced intimacy.[9-13] Men with ED have a high risk for incident depression compared to those who do not.[14] Results from many studies have further shown that

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the adverse effects of ED extend to the partners of men with this condition.[12] These adverse effects include decreased intimacy, reduced sexual desire, and relationship dissatisfaction. In addition, decreased sexual satisfaction and frequency of orgasm in partners are significantly related to the man's self-reported severity of ED.[11,15] Partners of men with ED also develop a sense of hopelessness and frustration about their sex lives.[16] Partners may experience insults, suspicion and jealousy, violence, and even injury from men with ED.[17,18]

Both non-pharmacologic and pharmacologic interventions have been used effectively to treat ED, but they have significant limitations. Non-pharmacologic interventions include vacuum devices and penile implants, and both have been shown to be effective for the treatment of ED.[19] However, vacuum devices may be limited by lack of spontaneity, premature loss of penile tumescence and rigidity, and pain or discomfort either during application of suction or during intercourse.[20] Implants are a more invasive option that may be used for patients with ED who are refractory or intolerant to pharmacological or mechanical treatments.[19] Barriers to their use include high cost, lack of insurance coverage in some countries, device failure, and risk of surgical complications.[21] While non-pharmacological interventions remain important for some patients, phosphodiesterase type 5 inhibitors (PDE5is), a pharmacologic therapy, are the most widely used treatment for ED[22] with their use supported by a large body of clinical evidence.[23-26] However, results from multiple studies have indicated that between a quarter and one-third of men who achieve initial success with PDE5is ultimately discontinue these treatments[27,28] and that the overall dropout rate is around 50% after 1 year.[29] Side effects, partner-related issues, cost, reluctance to continue medication-dependent intercourse, and lack of efficacy and spontaneous sexual activity have all been cited as reasons for stopping PDE5i treatment.[28-31] Intracavernosal injection of vasoactive agents has also been used effectively for the treatment of ED,[32] but these treatments may be limited by lack of spontaneity as well as fear and anxiety surrounding self-injection.[33,34] About two-thirds of ED patients discontinue these treatments.[35,36]

Given the limitations of current treatments and their varying success rates, there has been ongoing effort to develop therapies that better meet the criteria for an ideal ED medication. It has been stated that an ideal medication for ED should be discreet, effective, suitable for on-demand use, have a rapid onset and sustained duration of action, support spontaneity. be safe; have no interactions with food, drink, or other drugs, and be accepted by the partner.[37] An efficacious and accessible topical treatment for ED has the potential to meet these goals and may also have advantages over systemic treatment. These include: (1) the ability to provide targeted treatment at the site of action with a rapid onset rather than systemic circulation, which may be associated with a slow onset and an increased risk for side effects and drug interactions; (2) avoidance of first-pass metabolism in the liver, which may require higher drug doses to achieve effective concentrations at the site of action and may produce toxic metabolites; and (3) easy non-invasive application.[38,39] Topical delivery of ED medication with a rapid onset of action also has the potential to facilitate spontaneity and increase partner acceptance by making application a part of foreplay. This paper reviews the clinical evidence for topical ED treatments, focusing on how well they align with the criteria for an ideal medication.

Methods

PubMed was searched using the search term "topical" OR "intraurethral" AND "erectile dysfunction." We included English language publications that specifically addressed ED and clinical studies or trials that included a clinical end point. No other limitations (eg, dates for the search, treatment population, specific aspects of study design, or outcome measures) were put in place. "Clinical Study" and "Clinical Trial" restrictions were placed on the PubMed search, then abstracts, and consequently full text, were hand-screened for suitability against the inclusion criteria. The review of studies evaluating topical ED therapies was supplemented by a search of abstracts for studies presented at the 2024 meetings of the American Urological Association (AUA) and Sexual Medicine Society of North America (SMSNA). The objective of these searches was to gain information about treatments for which data had been presented at major meetings but had not yet been published. Inclusion criteria remained the same for AUA and SMSNA searches. Studies from PubMed, AUA, and SMSNA were grouped and summarized by therapy type.

The PubMed search resulted in retrieval of 385 studies published over the period from 1968 to 2024. Applying "Clinical Study" and "Clinical Trial" filters to the search resulted in a total of 59 studies spanning 1989 to 2024. After screening and reviewing against inclusion criteria, 8 studies were written in a non-English language, 9 that addressed conditions other than ED, and 6 studies without at least 1 clinical endpoint were removed. Consequently, 36 studies were reviewed. Searches through the bibliographies of the papers reviewed resulted in retrieval of 3 additional relevant references. After applying the same search criteria, AUA abstracts resulted in retrieval of 39 citations, of which 1 provided clinical results for a topical therapy. Search of all sessions related to ED at the 2024 Fall SMSNA resulted in retrieval of 4 clinical studies focused on clinical evaluation of topical therapies for ED. Ultimately, 44 publications were evaluated in this review.

Results

Intraurethral, transurethral, or intra-meatal alprostadil

The search recovered 8 clinical studies focused on intraurethral, transurethral, or intra-meatal alprostadil.[40-47] These approaches to alprostadil delivery consistently demonstrated statistically significant, but not always clinically meaningful,[48] improvements in erectile function (EF) (Figure 1).[40,43-45] Clinical success comparable to systemic sildenafil was reported in 1 comparative study.[41] Intraurethral alprostadil has also been shown to be efficacious in 58% of men for whom intracavernosal therapy (alprostadil, papaverine, phentolamine, or a combination of these agents) was not effective.[47] Other studies have indicated limited efficacy for intraurethral alprostadil. In 1 trial, 34% of 212 patients with ED achieved clinical success with this treatment and only 31% of in-office responders were still using it after 9 months.[42] In another trial, only 18.6% of the 115 patients with ED who were tested in the office continued to use intraurethral alprostadil at home. The remainder discontinued treatment due to pain, insufficient erections for intercourse, and/or cost.[46] Intraurethral alprostadil may be limited by penile pain, which has been reported by up to 30% of patients,[34] and discomfort, which was reported by 41% of patients in another

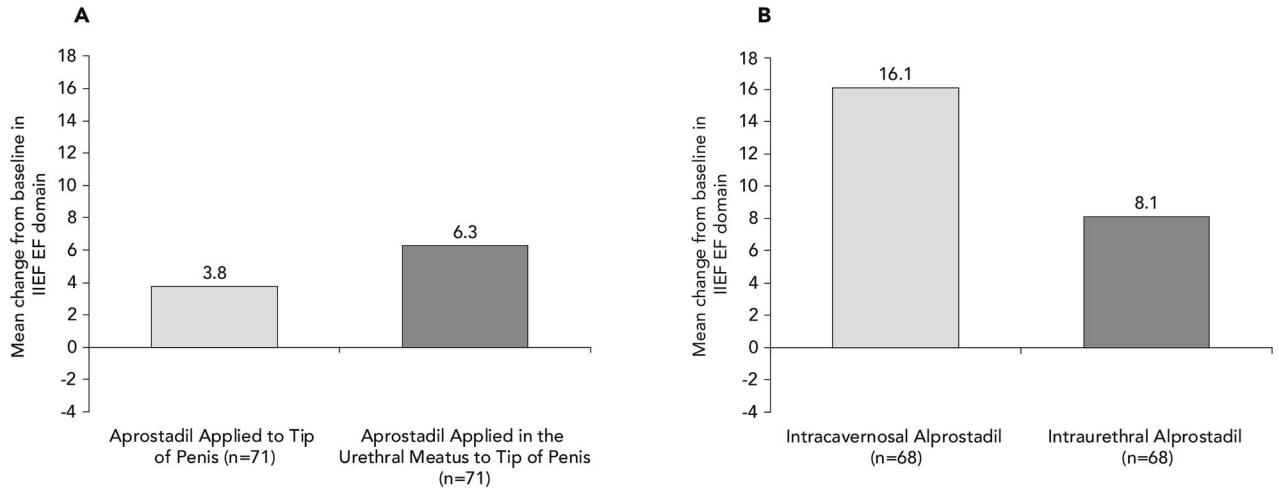

Figure 1. Changes from baseline in patients treated with alprostadil applied to the urethral meatus vs the tip of the penis (A)[40] or applied intraurethrally vs injected intracavernosally (B).[44]

trial.[46] However, it should be noted that results from 1 study indicated a low rate (7%) of urogenital pain with intraurethral alprostadil and that 90% of patients rated it as easy to use.[45] Intraurethral alprostadil (MUSE® system suppositories) is no longer available in the United States because the manufacturer, Viatris, discontinued the medication in June 2024.[49] It is important to note that this discontinuation was not related to any reports of adverse events (AEs).[50]

Consideration of efficacy results for intraurethral, transurethral, or intra-meatal alprostadil and all of the topical therapies summarized in the following section should be carried out in the context of that demonstrated for PDE5is. Results from representative studies of sildenafil, vardenafil, tadalafil, and avanafil are shown in Figure 2.[23-26] Improvements in International Index of Erectile Function (IIEF-EF) domain scores achieved with these PDE5is generally exceed those that have been shown for topical therapies.

Topical alprostadil

Alprostadil cream was evaluated in 6 of the clinical studies recovered in the literature search,[51-56] and results for those that assessed EF using the IIEF-EF domain are shown in Figure 3A-D. Two multicenter, double-blind, parallel-group studies formed an integrated analysis of clinical results from 1732 patients with a score of ≤25 on the EF domain of the IIEF questionnaire. These patients were treated with a placebo or 100, 200, or 300 μg alprostadil cream for 12 weeks.[53] The mean changes from baseline to end point in IIEF-EF domain scores were -0.7 for placebo and 1.6, 2.5, and 2.4 points for 100, 200, or 300 μg alprostadil cream, respectively ($P < .001$).[53] Scores on Sexual Encounter Profile (SEP) Questions 2 and 3 improved slightly and achieved statistical significance for all drug treatment groups compared with placebo ($P < .001$).[53] It is important to note that the mean changes from baseline for the IIEF-EF domain scores for all alprostadil cream doses were less than the minimal clinically important difference (≥4) established for this measure, suggesting an overpowered study.[48] This was also the case for the percentage changes from baseline in positive responses to SEP Questions 2 and 3 (≥23.0% and ≥21.4%, respectively).[57] The most common treatment-related AEs in this study were penile burning (6.0% for placebo vs 17.1%, 24.7%, and 23.0% for 100, 200, and 300 μg alprostadil cream, respectively) and penile erythema (2.1% for placebo vs 7.6%, 9.1%, and 11.3% for 100, 200, and 300 μg alprostadil cream, respectively).[53]

Alprostadil cream was also evaluated in a multicenter, open-label, long-term study that included 1161 men with ED. Patients self-administered 100, 200, or 300 μg for up to 9 months based on the response at 4 weeks (8 doses) of treatment with 200 μg.[52] In this trial, the changes from baseline in IIEF-EF domain scores for 100, 200, and 300 μg alprostadil cream were 13.0, 13.2, and 10.0, respectively.[52] The most frequently reported AEs in this study were application site reactions (24.0%, 11.3%, and 12.2% for 100, 200, and 300 μg alprostadil cream, respectively) and application site pain (24.0%, 6.5%, and 4.4% for 100, 200, and 300 μg alprostadil cream, respectively).[52] While alprostadil cream provided clinically meaningful efficacy in some studies, had an acceptable safety profile, and met many of the criteria for an ideal ED treatment, the United States Food and Drug Administration (FDA) stated that it could not move forward with the approval of alprostadil cream due to deficiencies related to chemistry, manufacturing, and control, as well as safety concerns about the product.[58] Alprostadil 3 mg/g cream, however, is approved for the treatment of ED in the European Union.[59]

Topical prostaglandin E_1 ethyl ester

Prostaglandin E_1 ethyl ester (EE) is a molecule very similar to alprostadil. The literature review identified 3 studies in which it was used to treat men with ED.[43,60,61] Prostaglandin E_1 EE was evaluated in a randomized, double-blind study that included 34 men with ED.[60] An improvement in EF was determined with the IIEF questionnaire, the mean total score of which improved from 28 at baseline to 34 at the end of the study. The mean score for the EF domain improved from 9 points at baseline to 11 points at the end of the study.[60] Application of prostaglandin E_1 EE resulted in marked or severe erythema in 19% of treated patients vs 12% for placebo. The respective values for marked or severe burning in treated patients compared with placebo were 6% and 4%, and those for marked or severe pain to touch were 5% and 4%.[60] A study of prostaglandin E_1 EE in 8 men with ED indicated that it was well tolerated, with "clinical" erections noted in

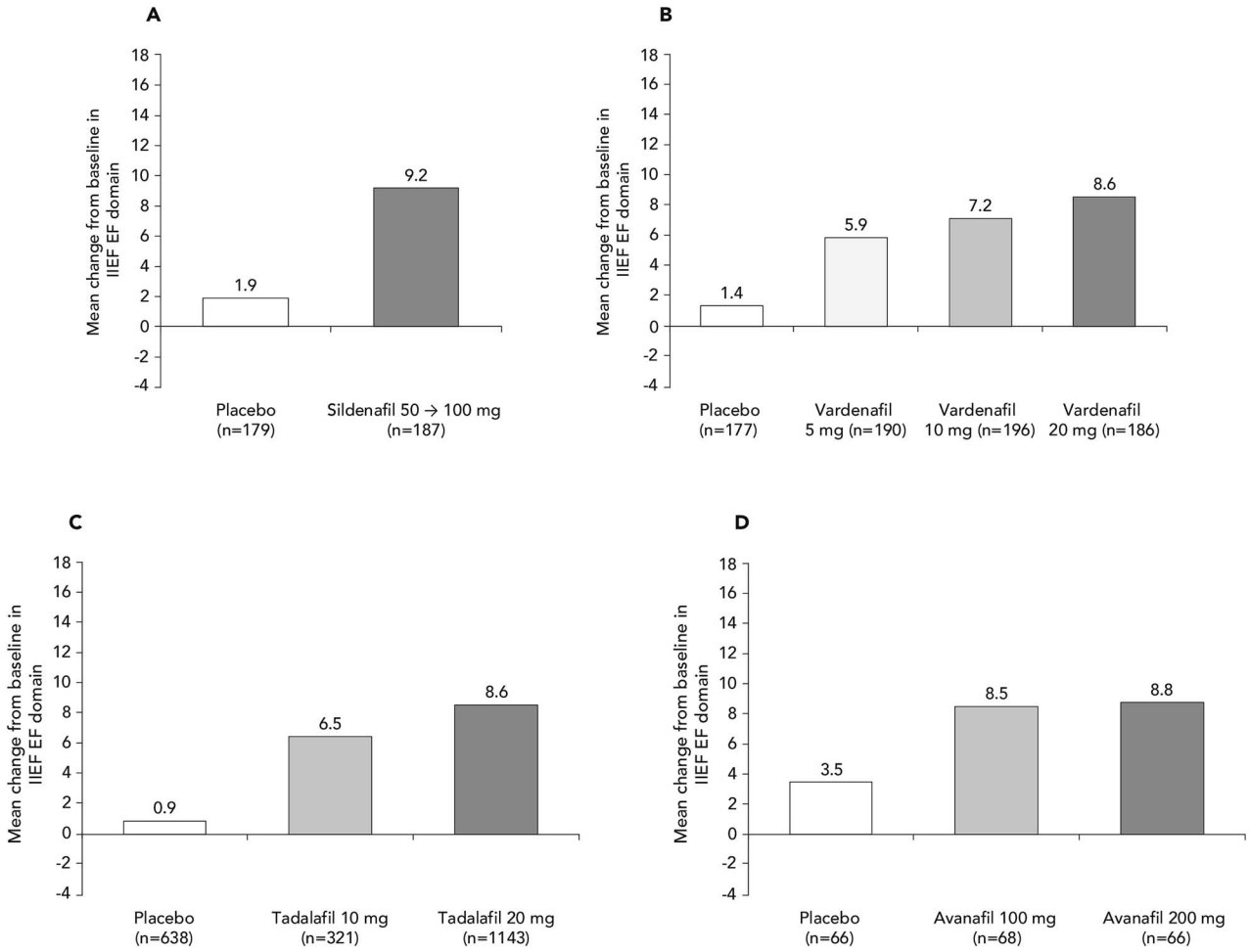

Figure 2. Representative results from studies in which the efficacy of sildenafil (A),[23] vardenafil (B),[24] tadalafil (C),[26] or avanafil (D)[25] was assessed using IIEF-EF domain scores.

2 patients.[43] Prostaglandin E_1 EE has been combined with SEPA (2-n-nonyl-1,3-dioxolane), a proprietary transdermal permeation enhancer, in a single-blind, non-randomized, rising-dose study.[61] Application of this preparation resulted in achievement of erections by 67%-75% of patients vs 17% of those who received SEPA alone ($P < .001$). Skin irritation occurred significantly more frequently with alprostadil combined with SEPA vs SEPA alone ($P < .0013$).[61]

Topical nitric oxide donors

Nitric oxide donors (glyceryl trinitrate, isosorbide dinitrate, nitroglycerin) were evaluated in 6 studies recovered by the literature searches.[62-67] Assessment of 2% nitroglycerin paste under laboratory conditions in 26 men with ED indicated that it increased the diameter and blood flow in the cavernous arteries in 18 patients. It also increased tumescence as determined with a strain gauge transducer.[65] A study of 14 patients with ED who had responded to intracorporeal injection therapy were randomized to a cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate or placebo. The active treatment achieved 3 "good" and 12 partial erections across 77 applications, compared with 4 "good" and 13 partial erections across 76 placebo cream applications.[66] A gel containing glyceryl trinitrate was compared with a non-medicated hydro-alcoholic gel in a randomized, double-blind, crossover trial of 232 men with ED. Each treatment was given for 4 weeks, separated by a 1-week washout interval. The mean baseline IIEF-EF score was 17.1, which increased to 19.6 with the glyceryl trinitrate gel vs 18.5 for the hydro-alcoholic gel ($P = .0132$). Overall, 23.1% of patients showed a clinically relevant (≥4-point) increase in IIEF-EF domain scores after treatment with glyceryl trinitrate gel vs 14.5% for the hydro-alcoholic gel ($P = .0272$). The most commonly reported AEs during treatment with the glyceryl trinitrate gel were headache (7.9%) and nasopharyngitis (5.7%).[62] A crossover study included 36 men with ED who were randomized to treatment with a cream containing aminophylline 3%, isosorbide dinitrate 0.25%, and co-dergocrine mesylate 0.05% for 1 week and placebo for another. A total of 21 patients reported full erections and satisfactory intercourse with the active cream. This was also the case for 3 men during placebo treatment. No "major" side effects were reported.[63] A similar randomized crossover trial, including 42 men with ED and low or slightly depressed testosterone levels, evaluated a cream containing testosterone 0.8%, isosorbide dinitrate 0.5%, and co-dergocrine mesylate 0.06% for 1 month and a cream containing only testosterone 0.8% for another, with no placebo arm. Altogether, 28 patients reported full erection and satisfactory intercourse with only polypharmacy cream and 13 patients reported the same with either cream. No marked side effects were reported after use of either cream.[64]

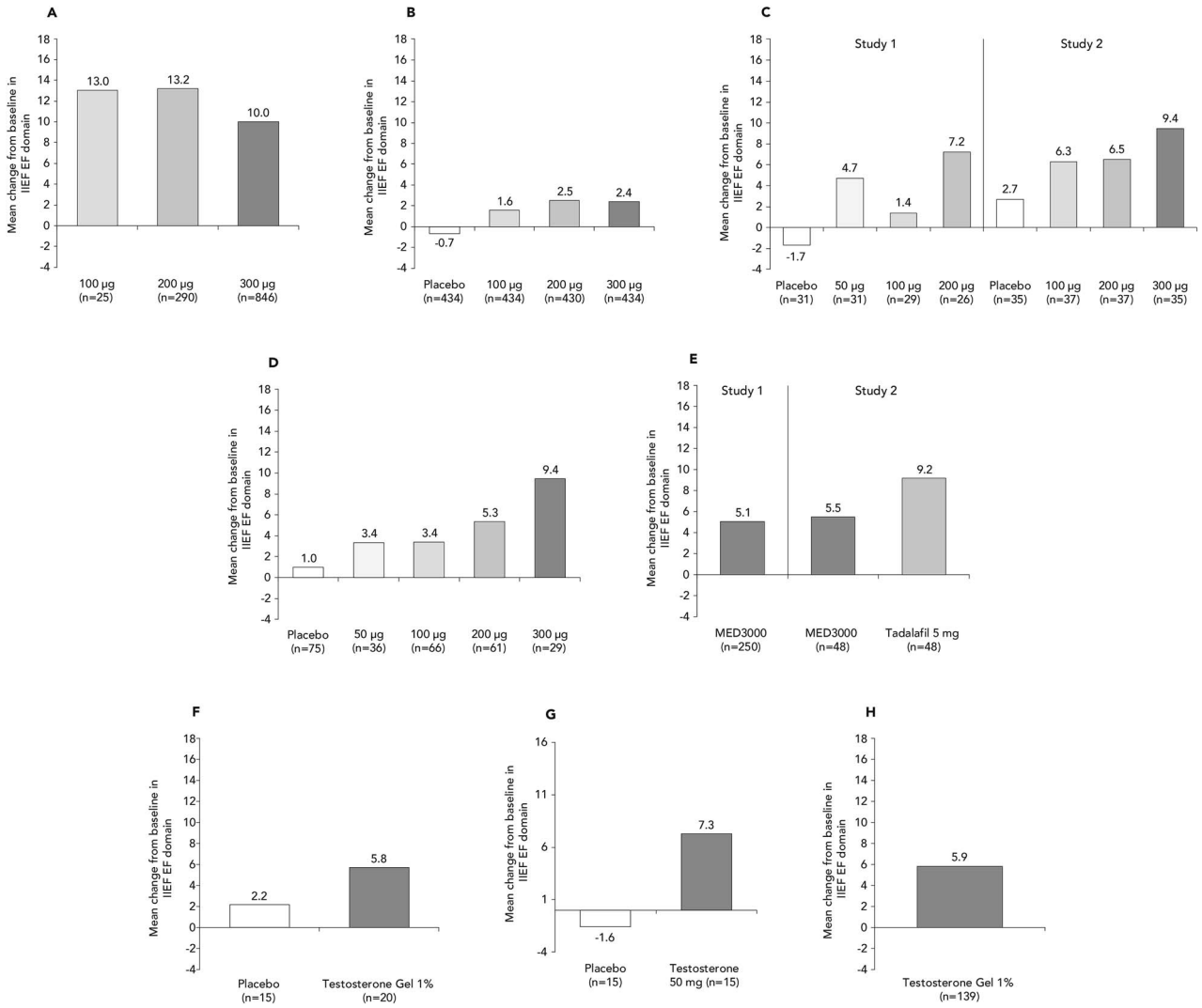

Figure 3. Results obtained in clinical studies of topical alprostadil (A-D),[45-48] MED3000 (E),[62,65] and topical testosterone (F-H)[73-75] where efficacy was assessed using IIEF-EF domain scores.

A double-blind comparison of nitroglycerin vs minoxidil in 33 patients with ED indicated greater activity and fewer side effects with the latter agent. Both were more effective in patients with neurogenic vs vascular ED.[65]

Non-medicated hydro-alcoholic gel (MED3000)

MED3000 was employed as the control arm in 1 of the studies described in the preceding section.[43] The unexpected response to this preparation prompted its evaluation in 2 additional studies summarized in 4 reports.[68-71] MED3000 was included as the control arm (n = 250 patients) and tested against glyceryl trinitrate in a 12-week, multicenter, randomized, double-blind, parallel-group study involving men with a clinical diagnosis of ED for >3 months. No placebo group was included. Study results showed that the use of MED3000 resulted in significant improvements in EF from baseline (Figure 3E). Changes exceeded the minimal clinically important difference (≥4 points) in the IIEF-EF domain, per the Rosen criteria,[48] in 63% of patients (Figure 4A). MED3000 also resulted in significant improvements from baseline in scores for the SEP Questionnaire and the Self-Esteem and Relationship Questionnaire. In this trial, noticeable erections within 10 minutes of treatment application were reported in 60.1% of intercourse attempts (Figure 4B). MED3000 has also been evaluated in a second multicenter, randomized, open-label, parallel-group study, in which it was compared with 5 mg oral tadalafil over 24 weeks, in 96 men with ED. Results from this study showed that 59% of patients using MED3000 achieved clinically meaningful improvements in IIEF-EF domain scores vs 83% of those treated with tadalafil. In addition, 44.9% of intercourse attempts resulted in noticeable erections in <10 minutes for men using MED3000 vs 30.0% in those taking tadalafil.[68]

A post hoc analysis of results from the first study of MED3000 underscored the benefit of a topical therapy that facilitated partner involvement in the application as part of foreplay. In this subgroup analysis, 209 patients treated with MED3000 were divided into 2 groups: those with partner involvement in the gel application and those without. Treatment responses (IIEF-EF domain, SEP Question 2, SEP Question 3) and time taken to achieve erection were compared in the 2 groups. Partner involvement in the application of MED3000 significantly increased the percentage of IIEF-EF domain responders (66.1% vs 52.0%, $P = .0373$), and those who responded positively to SEP Question 3 ($P = .006$). Partner involvement also increased the percentage of patients

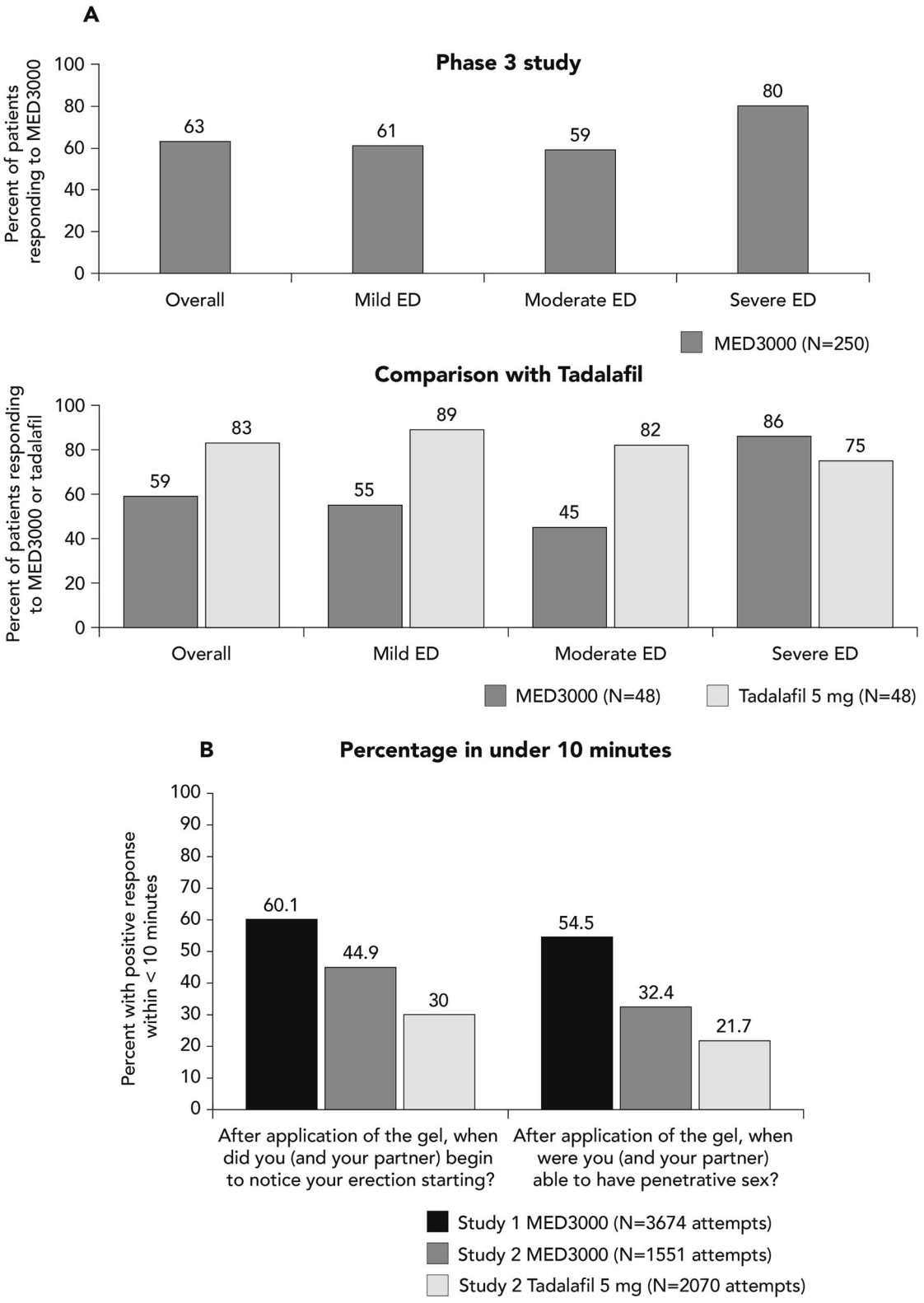

Figure 4. Responder* analysis demonstrating the proportion of patients reporting a meaningful improvement from baseline for IIEF-EF by ED type, based on the criteria from Rosen *et al*.[48] in the phase 3 study of MED3000 and a trial in which it was compared with tadalafil (A). Effectiveness analysis showing the proportion of intercourse attempts in which patients achieved an erection and/or felt able to have penetrative sex within 10 minutes of therapy from the 2 studies of MED3000 (B).[68] *Responders defined as having an increase of IIEF ≥4 from baseline ED (overall), and ≥ 2, ≥5, and ≥ 7 from baseline for the mild, moderate, and severe subjects, respectively (minimal clinically important difference according to Rosen *et al*.[48]).

who responded positively to SEP Question 2 (41.9% vs 33.0%) and those who first noticed an erection within 10 minutes (61.2% vs 50.4%), although neither of these trends achieved statistical significance.[68]

Safety results for MED3000, from the study where it served as a control for glyceryl trinitrate–containing formulations, indicated a low risk for either local (penile burning in 1.2% of patients) or systemic (headache in 2.8%) AEs. The corresponding values for MED3000, combined with 0.2% or 0.6% glyceryl trinitrate, were 1.2% vs 6.0% for penile burning and 10.8% vs 17.3% for headache, respectively.[68] The most common AE for tadalafil in the trial comparing it with MED3000 was headache (19.1%).[68] MED3000 was authorized for marketing by the FDA as a device for the treatment of ED in June 2023. The authorization of MED3000 marks the first over-the-counter gel designed to treat ED.[72]

Testosterone gel

Testosterone gel has been evaluated in 5 studies of men with hypogonadism and ED.[72-76] Results from those in which the response to treatment was assessed with IIEF-EF domain scores are shown in Figure 4F-H.[74-76] The Testim Registry in the United States included patients treated with 1% testosterone gel. The analysis included 271 patients who were treated for 12 months, with no placebo arm. Treatment significantly increased total testosterone, free testosterone, and Brief Male Sexual Function Inventory (BMSFI) scores from baseline (all $P < .001$). Significant improvements were observed for all BMSFI domains including EF.[73] A community-based 6-month, open-label, multinational, observational study included 799 hypogonadal men treated with a daily dose of 50, 75, or 100 mg 1% testosterone gel. The gel was applied to the skin of shoulders and upper arm, and/or abdomen. In this study, a responder was defined as a patient with ≥1 total testosterone measurement in the eugonadal range. Mean IIEF total scores increased significantly ($P < .0001$) in both responders and non-responders, with no significant difference in scores between the 2 groups. The mean increase in total IIEF score became statistically significant for all patients as early as 1 month after initiation of the treatment (+9.4, a 64.8% increase, $P < .0001$). This early improvement was also observed for each IIEF subscore (EF, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction). The IIEF-EF subscore showed the greatest increase over 6 months of all the subscales, with a mean increase of 124.5% at 1 month and 533.3% at 6 months.[77]

Other agents used as monotherapy

Other agents used as monotherapy for ED include saffron,[78] papaverine,[79] and capsaicin.[79] A randomized, parallel-group, double-blind, placebo-controlled trial evaluated the potential benefit of topical saffron (*Crocus sativus* L.) gel vs placebo in 50 men with diabetes and ED. Patients were assessed with the IIEF at baseline and after 1 month of treatment. The saffron gel increased IIEF-EF scores from 12.9 to 17.6, and placebo treatment increased scores from 13.6 to 13.9 ($P < .001$ for the difference between treatments).[78] Intraurethral administration of capsaicin (10^{-5}M) was compared with papaverine (8 mg) and saline placebo in 20 men with ED (5 patients for each active treatment and 10 for placebo). Both active treatments resulted in erections, whereas none were recorded with a placebo. No details were provided regarding safety or tolerability, but it was noted that capsaicin administration resulted in a "warm-to-burning" sensation.[79]

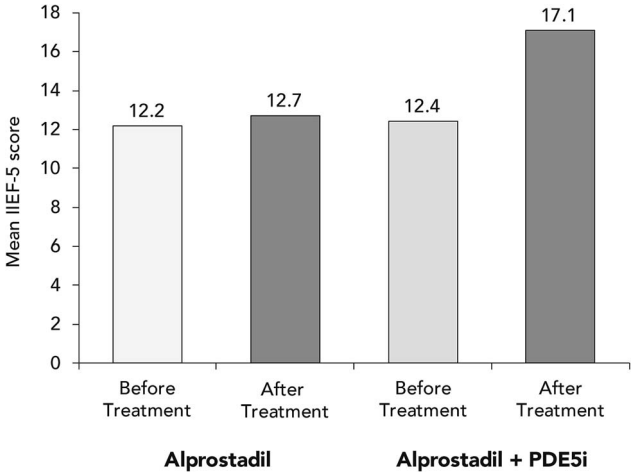

Figure 5. Effects of treatments on the IIEF-5 score (baseline vs after treatment).[79]

Use of topical agents as part of combination therapy

Several studies have combined a topical agent with a PDE5i. A 3-month, prospective, 2-arm, open-label, non-randomized study assessed the effects of topical alprostadil 300 μg/100 mg alone vs combining alprostadil with PDE5i in 170 men with inadequate responses to PDE5i monotherapy.[80] Mean scores for the 5-item version of the IIEF Questionnaire increased from 12.4 to 17.1 with combination therapy (Figure 5) ($P < .001$). There was no significant increase in scores in the patients who received alprostadil monotherapy (baseline mean = 12.2, mean at 3 months = 12.7, $P = .148$). The number of affirmative responses to SEP Question 2 significantly increased from baseline in the combination therapy group, although this effect was not seen with monotherapy treatment (57 increased to 78; $P < .001$ vs 48 increased to 49, $P = .894$). However, there were significant increases in positive responses to SEP Question 3 in both groups (1 increased to 50 vs 0 increased to 10, $P < .001$ for each group). Facial flushing was the only AE that occurred more frequently with combination therapy vs alprostadil alone (7.1% vs 0%, $P = .021$).[80]

Combination therapy was also evaluated in a study of 28 men who had undergone radical prostatectomy and 11 who had a diagnosis of organic ED, all of whom had failed treatment with 100 mg of sildenafil citrate and/or 1000 μg of intraurethral alprostadil. Combination therapy was initiated with 100 mg of sildenafil citrate orally, 60 minutes prior to intercourse, and 500 μg of intraurethral alprostadil immediately before intercourse. At 30 months, all 28 patients reported erections sufficient for vaginal penetration, with 3.6 intercourse episodes per month, although no placebo arm was included in this trial. No AEs were reported.[81]

The combination of intraurethral alprostadil and sildenafil vs each agent alone were compared in 120 men with ED, who were being managed in routine clinical practice and followed up to 18 months.[82] The mean IIEF-EF domain score at the end of follow-up was 24.1 (a 123% improvement from baseline) for combined therapy, 19.8 (83% improvement) for sildenafil, and 15.2 (41% improvement) for alprostadil ($P < .05$ for

comparison between combination therapy and each single agent).[82]

The TADTEST study (Testosterone Gel in the Treatment of Erectile Dysfunction) was a multicenter, multinational, double-blind, placebo-controlled trial that included 173 men with ED and low or low-normal testosterone levels (≤4 ng/mL or bioavailable testosterone ≤1 ng/mL) who did not respond to a PDE5i.[82] Patients were initially treated with tadalafil 10 mg once daily for 4 weeks. Non-responders were randomized to receive add-on placebo or a 1% hydroalcoholic testosterone gel (50 mg/5 g gel), with titration to 10 mg if results were clinically unsatisfactory. EF progressively improved over 12 weeks in both groups. In the overall population, with a mean baseline testosterone level of 3.37 ng/mL, there was no additional effect of testosterone administration. However, the addition of testosterone in men with baseline levels ≤3 ng/mL was significantly superior to placebo for improving IIEF-EF domain scores ($P = .027$) and the percentage of patients with positive responses to SEP Question 3 ($P = .038$).[83]

A retrospective chart review assessed the efficacy of adding intraurethral Bimix gel (papaverine and phentolamine) to oral treatment in 56 patients with ED who had inadequate responses to PDE5i.[84] Efficacy was assessed by comparing the Sexual Health Inventory for Men (SHIM) scores before and after treatment. The mean SHIM score increased from 9.62 to 11.93 after adding intraurethral Bimix gel to oral therapy ($P < .001$). The most common AE was a mild burning sensation at the administration site during the application and absorption period. There were no other AEs.[84]

Discussion

Efficacy of topical therapies

The summarized papers indicate that a variety of topical therapies have been studied for the treatment of ED, with varying benefits and limitations. However, approved treatments are limited to MED3000 and alprostadil cream only. The latter is yet to be approved in the United States due to manufacturing considerations. Efficacy and safety of MED3000 are supported by 2 studies with active comparators, topical glyceryl trinitrate and tadalafil.[62,68,71] It has only been evaluated as monotherapy. Results from the 2 studies of MED3000 indicated that it improved IIEF-EF domain scores by 5.1 and 5.5 points, respectively.[62,68,71] Alprostadil cream has been shown to be effective for the treatment of ED when used as monotherapy[51-56] and in combination with a PDE5i.[80] Changes from baseline in IIEF-EF domain scores for alprostadil monotherapy ranged from 2.4 to 10.0 for the highest dose tested (300 μg).[52-55] There is also support for the efficacy of testosterone gel as treatment for men with ED and hypogonadism.[73,77] Changes from baseline for IIEF-EF domain scores for 1% testosterone gel ranged from 5.8 to 7.3 points.[74-76] These agents met the above-stated criteria for an ideal ED treatment: delivery to the site of action with a rapid onset, avoidance of first-pass metabolism in the liver, and easy non-invasive application.[38,39] They may provide benefits for patients who are not suitable candidates for PDE5i or prefer not to use 1 of these medications. In considering this issue, it is important to emphasize that there is no evidence of a topical therapy demonstrating superiority over a PDE5i in a head-to-head comparison. In addition, representative studies for PDE5is indicated that the highest doses evaluated resulted in improvements from baseline in IIEF-EF domain scores ranging from 8.8 to 9.2 points.[23-26]

Can topical therapies lower barriers to treatment for men with ED?

While topical therapies might be expected to lower some barriers to ED treatment (eg, aversion to injected agents or intolerance to PDE5is), there is no evidence that this is the case. Alprostadil cream is available in Europe as a prescription medication and so requires interaction with a healthcare professional;[85] - its use does not overcome this potential barrier to treatment.[3] In contrast, MED3000 is available both over the counter and online and does not require interaction with a healthcare professional.[85] Results from the United Kingdom provide some insight regarding the effects of lowering this barrier to ED medication. In November 2017, the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom formally reclassified sildenafil citrate 50 mg tablets as a pharmacy medicine (sildenafil-P) for adult men with ED.[86] While this eliminated the requirement of a physician's prescription, some interaction with a pharmacist was still required.[87] A causal relationship cannot be inferred; however, results from 1 study reported a 5.8% increase in sildenafil prescriptions between 2017 and 2018.[88]

There is a possibility that availability of ED treatment that does not require a physician's prescription (sildenafil-P in the United Kingdom) or much initial interaction with a healthcare professional (MED3000) might result in patients actually overcoming the initial embarrassment of contacting their physician. While no information is available for MED3000, there are data for sildenafil-P. A 1-year prospective real-world observational study assessed the behavior of 1132 men with ED before and after the availability of sildenafil-P.[89] Results indicated mean physician/nurse practitioner ($P = .003$) and pharmacist visits ($P < .001$) for any reason were significantly higher among sildenafil-P users than those who never used sildenafil.[89] Results from a second survey of 297 men with ED who had purchased at least 1 supply of sildenafil-P indicated that 19.2% had visited a physician and received advice regarding their ED treatment and that 45.8% planned to do so.[90] These results suggest that removing the initial barrier to treatment of patient-healthcare professional interaction may encourage interaction in the future. However, determination of whether this is actually the case would require a well-controlled prospective study that would be difficult to design and carry out.

The future of topical ED treatment

The range of topical ED therapies may expand in the future as additional agents are currently in phase 2 or 3 clinical development. TR399 is a topical formulation of 5% vardenafil currently being evaluated in a single-arm, open-label trial. This trial focuses on the safety, pharmacokinetics, and efficacy of TR399 in healthy volunteers and in patients with ED.[91] A topical formulation of sildenafil (5% cream) has been evaluated in a phase 2 study of men with ED, although results from this study have not been published, presented, or posted on the ClinicalTrials.gov website.[92] BZ371A is described as a first-in-class peptide that enhances the activity of nitric oxide synthase. Topical application of BZ371A results in vasodilation and increased local blood flow, independent of

any stimulus, facilitating penile erection.[93] It is currently being evaluated in a phase 2 study of men with ED following radical prostatectomy.[94] While topical agents currently in development may become important additions to the treatment armamentarium for ED, they will not be available for several years, pending success in phase 2 and subsequent phase 3 trials.

Technology may also increase communication between men with ED and their physicians, helping to lower this barrier to treatment. Telemedicine has the potential to facilitate interaction between a healthcare professional and men with ED. The SMSNA has noted that telemedicine provides privacy for discussing sensitive issues, which is particularly important for conditions associated with stigma and for individuals who must travel substantial distances for an office visit.[95]

Limitations of this review

There are several limitations in the present narrative review evaluating published studies on topical ED therapies. First, the searches carried out may have missed studies that were not abstracted in PubMed or not published and presented at meetings other than the 2024 AUA and SMSNA conferences. Second, the designs and measures used to assess efficacy employed in the trials reviewed were heterogeneous. Many of them were not blinded or randomized and included a placebo control and/or statistical power calculations for determination of statistical significance. While data presented focused on trials that employed the IIEF-EF domain as an outcome measure, results from trials of a given agent (eg, alprostadil cream) were variable and this may have been due to any of a wide range of factors (eg, baseline ED etiology and severity, instructions regarding application of the topical agent, and partner involvement). As all of these factors preclude any conclusions regarding the efficacy of 1 topical therapy vs another, such comparisons were avoided in presentation of the results.

Conclusions

An effective and authorized topical therapy, such as MED3000 or alprostadil cream (available in the European Union but not the United States), delivered to its site of action with a rapid onset, has the potential to increase spontaneity, partner acceptance, and involvement in treatment for those not suitable for PDE5i therapy. However, determination of whether or not this is the case requires large-scale well-controlled prospective studies. The availability of these interventions without a prescription might increase the chance of initiation of therapy for men with ED. This possibility should also be addressed in clinical studies.

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Conflict of interest

G.B.B. has served as an advisor for Futura Medicine and Haleon.
W.J.G.H. has served as an advisor/consultant for Boston Scientific, Coloplast, and Jazz Pharmaceuticals; a consultant/advisor, investigator, and lecturer for Endo; an advisory board member for Gilead/Galapagos, Futura Medicine/Haleon, Maximus, and Promescent; and a board member, officer, and trustee for Theralogix.
A.G. has served as a lecturer/consultant for Eli Lilly; a lecturer/advisory board member for Pfizer/Viatris, FREYA, and Futura Medicine/Eroxon; an advisory board member for Sandoz; a lecturer for Astellas and Lundbeck; and a lecturer and stockholder for Novo Nordisk.
S.H. serves as an advisory board member for Haleon and a consultant for Coloplast.

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