



## INDUSTRY EDUCATION

### Topical Options for ED



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Erectile dysfunction (ED) is a common patient concern, and its prevalence is strongly associated with age. Data from the US National Health and Nutrition Examination Survey suggests that 8.2% of men between ages 40-49 years and 77.5% of men greater than 75 years old suffer from erectile dysfunction.<sup>1</sup> The prevalence of ED was also associated with other conditions such as diabetes mellitus, smoking, cardiovascular disease, hypertension, and obesity.<sup>1</sup> ED is most commonly managed with prescription phosphodiesterase-5 (PDE5) inhibitors used orally such as sildenafil, tadalafil, or vardenafil.<sup>1</sup> Commercially available injectables for ED such as alprostadil or phentolamine mesylate injections are also sometimes used. Compounded options for ED often include combination injectable products such as phentolamine mesylate/papaverine HCl/alprostadil combinations, commonly referred to as “Tri-mix”. Tri-mix injections can be associated with serious side effects. One study evaluating trimix use and reasons for dropout in 189 patients noted that 30% of patients discontinued Tri-mix due to lack of efficacy, 5.2% experienced fibrosis or scarring, and 3.7% reported priapism.<sup>2</sup> While Tri-mix works well for many patients, adverse effects make this route inappropriate for some patients creating a need for alternatives. In this newsletter, we will discuss existing evidence for the use of topically administered treatments, for the management of ED.

Alprostadil is available in the United States as an injectable for ED as well as an intraurethral suppository, but in other countries, there are alternatives such as intraurethral alprostadil. Vitaros is an intraurethral cream available in some European countries as well as Canada. It is 3mg/g alprostadil and is packaged in single dose syringes carrying 100mg of cream, equivalent to 300mcg alprostadil. Phase II and III trials demonstrated up to 83% efficacy with this product with only 3% of the treated population reporting systemic adverse effects.<sup>3</sup> In addition to intraurethral administration, some studies have also evaluated topical/transdermal use. One study of alprostadil 1% had patients apply 0.25ml of alprostadil 1% or placebo gel to the glans penis. The study

reported better responses to the alprostadil treatment at all timepoints, with greatest differences noted at 45 and 60 minutes after application. The study noted that of the tested patients 38.9% in the treatment group and 6.9% in the placebo group achieved an erection deemed sufficient for penetration.<sup>4</sup>

Some studies have also evaluated papaverine HCl for transdermal use. One study of drug release of papaverine HCl in a gel vehicle found an alcohol-containing penetration enhancer resulted in drug penetration both in vitro and in vivo in rabbits. The study suggested that their results supported the use of penetration enhancer to deliver papaverine HCl transdermally.<sup>5</sup> Another study evaluated 15% and 20% papaverine HCl gel applied to the scrotum, perineum, and penis. Patient response was evaluated 45 minutes after treatment. The treatment was well tolerated and papaverine HCl was minimally systemically absorbed, the researchers hypothesized that effects seen, mainly increase in duration of erection compared to placebo, were a result of local rather than systemic absorption.<sup>6</sup> Phentolamine mesylate, while sometimes included in transdermal erectile dysfunction combination products, has not currently been studied in well controlled trials for its potentially efficacy via the transdermal route.

Sildenafil is a PDE5 Inhibitor commercially available for oral use for ED, but there is some information to suggest that it may be efficacious transdermally as well. One placebo-controlled study compared sildenafil 1% gel to sildenafil 100mg tablets. The topical gel group applied 0.5g of sildenafil 1% gel to the glans of the penis approximately 5 minutes before sexual activity and the tablet group took a 100mg tablet 1 hour before sexual activity. In the gel group, 25% of patients achieved complete or moderate erections compared to 75% of the tablet group. Though oral tablets demonstrated increased likelihood of complete or moderate erection, both groups did see benefit and onset of erection in the patients who applied sildenafil gel was  $7.4 \pm 3.6$  minutes, but was  $37.8 \pm 14.9$  minutes in the group who used oral tablets.<sup>7</sup> Though there aren't many other studies on sildenafil cream topical for erectile dysfunction, other studies for conditions such as Raynaud's have demonstrated benefit and increased blood flow as a result of local administration of sildenafil 5% cream, further suggesting that sildenafil may be absorbed from topical administration.<sup>8</sup> Though currently information regarding other in vivo studies on other PDE5 inhibitors topically for erectile dysfunction are not available, some studies have found benefit for tadalafil used topically for Raynaud's, suggesting transdermal penetration and potential local efficacy.<sup>9</sup> Future studies are needed to confirm the potential of tadalafil as a topical treatment for erectile dysfunction.

Other active ingredients used transdermally to increase blood flow are sometimes also considered for combination topical ED mediations. Arginine, sometimes used at 3-6% in female sexual dysfunction creams, was found in a study of diabetic patients to improve blood flow. These patients applied transdermal arginine 12.5% cream to the feet and noted improved blood flow with a doppler flow meter and with an infrared thermometer 30 minutes after application.<sup>10</sup> Despite this promising information, not enough data yet exists to suggest that arginine transdermal is appropriate for the management of ED.

Though there is limited information to support transdermal application of medication for ED, some data exists to suggest efficacy. The transdermal route could be considered for patients who prefer not to use oral or injectable medications. Check out the Fagron Academy site for related formulas. If you have further questions, feel free to reach out to Fagron Academy Technical Support Services!

## Sources:

1. Mulhall J, Luo X, Zou K, Stecher V, Galaznik A. Relationship between age and erectile dysfunction diagnosis or treatment using real-world observational data in the United States. *Int J Clin Pract*. 2016; 70(12):1012-1018. doi: [10.1111/ijcp.12908](https://doi.org/10.1111/ijcp.12908).
2. Casabe A, Bachra A, Cheliz G, Romano S, Rey H, Fredotovich. Drop-out reasons and complications in self-injection triple vasoactive drug mixture in sexual erectile dysfunction. *International Journal of Impotence Research*. 1998; 10:5-9.
3. Cuzin B. Alprostadil cream in the treatment of erectile dysfunction: clinical evidence and experience. *Ther Adv Urol*. 2016; 8(4):249-256.

4. Goldstein I, Payton T, Schechter P. A double-blind, placebo-controlled, efficacy and safety study of topical gel formulation of 1% alprostadil (Topiglan) for the in-office treatment of erectile dysfunction. *Adult urology*. 2001;57(2):301-305. DOI:[https://doi.org/10.1016/S0090-4295\(00\)00936-5](https://doi.org/10.1016/S0090-4295(00)00936-5).
5. Ming Wen M El-Kamel A, Khalil S. Systemic enhancement of papaverine transdermal gel for erectile dysfunction. *Drug Dev Ind Pharm*. 2012; 38(8): 912-922. doi: 10.3109/03639045.2011.633262.
6. Kim E, el-Rashidy R, McVary K. Papaverine topical gel for treatment of erectile dysfunction. *J Urol*. 1995; 153(2):361-5. doi: 10.1097/00005392-199502000-00019.
7. Yonessi M, Saeedi M. A double-blind placebo-controlled evaluation of the effect of topical sildenafil on erectile dysfunction. *The Journal of Applied Research*. 2005;5(2):289-294.
8. Research Letter. Nifedipine cream versus sildenafil cream for patients with secondary Raynaud phenomenon: a randomized double-blind, controlled pilot study. *J Am Acad Dermatol*:78(1):189
9. Fernández-Codina, A., Kazem, M. & Pope, J.E. Possible benefit of tadalafil cream for the treatment of Raynaud's phenomenon and digital ulcers in systemic sclerosis. *Clin Rheumatol* 39, 963–965 (2020). <https://doi.org/10.1007/s10067-020-04966-z>
10. Fossel E. Improvement of temperature and flow in feet of subjects with diabetes with use of a transdermal preparation of L-arginine: a pilot study. *Diabetes Care*. 2004; 27(1): 284-285. <https://doi.org/10.2337/diacare.27.1.284>.

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