Summary Report

Alprostadil

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

December 2020

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

Table of Tables

Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
AUA	American Urological Association
EMA	European Medicines Agency
ED	Erectile dysfunction
EU	European Union
FDA	Food and Drug Administration
FSAD	Female sexual arousal disorder
ICI	Intracavernosal injection
IRB	Institutional Review Board
OTC	Over-the-counter
PDE5I	Phosphodiesterase type 5 inhibitor
PGE1	Prostaglandin E1
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of alprostadil (UNII code: F5TD010360), also known as prostaglandin E1 (PGE1), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how alprostadil is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how alprostadil has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of alprostadil and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Alprostadil was nominated for inclusion on the 503B Bulks List by Fagron, the Outsourcing Facilities Association (OFA), and Specialty Sterile Pharmaceutical Society (SSPS). Alprostadil was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Alprostadil was nominated for erectile dysfunction (ED) and female sexual arousal disorder (FSAD) via topical creams, lotions, gels, solutions, and a 2.5-5000 mcg/mL injection. One nominator specified the injection form to be via the intravenous route while another specified via the intracavernosal route.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of alprostadil.[6-18]

Reasons provided for nomination to the 503B Bulks List included:

- In the US, an estimated 30 million men suffer from ED; 10-15% of the 30 million fail the current available therapies. The current orally available ED medications "have an overall 50-60% effectiveness in diabetic patients." Injectable options have a 60-80% effectiveness rate. The available Caverject® (alprostadil) injection is limited in dosing and affects only one aspect of ED. By adding 2 more ingredients such as phentolamine and papaverine (the most common additions) to make a Trimix formulation, multiple ED factors can be targeted. This can help create a preparation that can fill therapy gaps.
- The strengths at which the FDA-approved medications (Caverject® and edex®) are available in are not appropriate for reconstitution into a Trimix formulation. Too much volume would be included in the finished preparation making it impossible to add the other two ingredients while still obtaining a usable volume for injection. Places such as the corpus cavernosum have limited space for volumes of medication. Doses greater than 1 mL usually leak out into the surrounding tissues. Hence, the majority of the Trimix dosing is designed to be obtained in 0.2-0.4 mL. The reconstituted volume of Caverject® and edex® are 10-40 mcg/mL while the amount of alprostadil in Trimix ranges from 12-40 mcg/dose. Lower injection volumes can lead to greater compliance.
- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength that is not available commercially.

- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- According to SSPS, in order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of alprostadil products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for alprostadil; name variations of alprostadil were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing alprostadil. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed two comprehensive search strategies for both Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe two concepts: alprostadil and topical administration or form. The second search strategy

used a combination of controlled vocabulary terms and keywords to describe three concepts: alprostadil, injectable administration, and papaverine or phentolamine (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategies because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on April 4, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on April 4, 2020 for clinical practice guidelines that recommended the use of alprostadil and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which alprostadil was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if alprostadil was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which alprostadil was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of alprostadil; setting; total number of patients; number of patients who received alprostadil; patient population; indication for use of alprostadil; dosage form and strength; dose; ROA; frequency and duration of therapy; use of alprostadil in a combination product; use and formulation of alprostadil in a compounded product; use of alprostadil compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances alprostadil was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use alprostadil: endocrinology, naturopathy, obstetrics and gynecology, and urology. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities

were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of alprostadil in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Alprostadil is available as an FDA-approved product in the nominated dosage form and ROA.
- Alprostadil is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for alprostadil.
- Alprostadil is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK. An EMA pharmacovigilance risk assessment report concluded that there is an increased risk of myocardial ischemia and cerebrovascular accidents associated with alprostadil in patients with risk factors for ischemic heart disease and cerebrovascular accidents.[19] Based on this, the report proposed a warning label for intracavernous alprostadil products for ED to be used with caution in patients with cardiovascular and cerebrovascular risk factors.[19] In addition, another EMA report concluded that gastrointestinal hemorrhage should be listed as an adverse drug reaction for all alprostadil products indicated for peripheral arterial occlusive disease.[20]

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Alprostadil	0.5 mg/mL; 0.01-0.04 mg/vial	Injectable	Injection	Prescription	05/19/1997

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Alprostadil	10-500 mcg/mL; 20 mcg/vial	Liquid, powder for solution, kit, solution	Intra-arterial, intracavernosal, infusion, injection, intravenous	Abu Dhabi	Active	–
				Australia	Prescription	4/11/1994
				Belgium	Prescription	11/9/1983
				Canada	Prescription	12/31/1982
				Hong Kong	Prescription	6/30/1984
				Ireland	Prescription	3/13/1995
				Latvia	Prescription	7/11/2003
				Namibia	–	2/14/1983
				New Zealand	Prescription	3/11/1982
				Saudi Arabia	Prescription	–
				UK	Prescription	07/23/1981
Alprostadil	2-3 mg/g	Cream	Topical	Abu Dhabi	Active	–
				Belgium	Prescription	06/15/2015
				Ireland	Prescription	10/09/2015
				UK	Prescription	08/2/2013

Abbreviation: "– ", not mentioned.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format.

Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 1300 references; 4 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 890 titles and abstracts were screened. After screening, the full text of 243 articles was reviewed. Finally, 26 studies were included. Two hundred seventeen studies were excluded for the following reasons: wrong study design (170 studies); wrong dosage form or ROA (16); alprostadil used as brand or proprietary product (12); alprostadil not used clinically (10); duplicate study (4); alprostadil only mentioned briefly (3); unable to obtain (1); wrong substance (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 26 included studies were published between 1991 and 2020. There were 10 experimental studies, 10 observational studies, 5 descriptive studies, and 1 clinical practice guideline. The 26 studies were conducted in the following countries: Brazil, China, Egypt, and US.

A total of 3803 patients participated in the 26 included studies. The number of patients in each study ranged from 1 to 1089.

Outcome measures differed among the included studies and included: erection rigidity strength, erectile function, duration of erection, percent tumescence, Doppler assessment, sexual satisfaction, side effects such as presence of intracorporeal fibrosis, plaque formation, or priapism, intracavernosal injection (ICI) compliance rating, patient-reported experience, frequency of injection use, resumption of unaided erection, change in arousal success rate.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of alprostadil

One thousand seven hundred eleven patients received alprostadil alone as a topical formulation in doses ranging from 0.1 g to 1.5 g, or in combination with papaverine and phentolamine as a Trimix injection as a treatment for ED, administered via the intracavernosal and intracorporeal routes in doses ranging from 0.05 mL to 2 mL In three studies of injectable alprostadil either alone or in combination with papaverine and phentolamine for treatment of ED, the number of patients who received treatment was not specified.[21-23] Duration of treatment for intracavernosal and intracorporeal administration ranged from once to 81 months. The duration of treatment was not specified for topical administration.

Three hundred seventy-nine patients received alprostadil as a treatment for FSAD, administered topically in doses ranging from 100 mcg to 900 mcg. Duration of treatment lasted for 8 weeks.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Alprostadil was used as a compounded product and it was used in a combination product (refer to Tables 8 and 9).

In 16 studies, the authors' concluding statement recommended the use of Trimix for the treatment of ED.[22-37] In 3 studies, the authors' concluding statement recommended the use of topical alprostadil

for ED[38,39] and FSAD.[40] In 3 studies, the authors' concluded that the use of Trimix was not recommended or further studies were necessary for the treatment of ED[21,41] and FSAD.[42] In 3 studies, the authors' concluding statements were not specific to alprostadil.[43-45] A clinical practice guideline from the American Urological Association (AUA) recommended the use of alprostadil ICI alone or in combination with other substances like papaverine, phentolamine, and atropine for men who have contraindications to phosphodiesterase type 5 inhibitor (PDE5I) for the treatment of ED.[46] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 26 included studies, 12 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of alprostadil.

ED is "an inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[47] According to the AUA, oral PDE5Is are first line of treatment for men with ED unless contraindicated.[46] For patients who have contraindications to using PDE5I, prefer to not take an oral medication, or are getting an inadequate response from PDE5I, they may consider using the ICI approach for ED.[46] Alprostadil is the only FDA-approved medication for ICI therapy, and is the only medication that tends to be used as a single agent.[46] Papaverine, phentolamine, and atropine are three other medications with established efficacy for ED that are used in various combinations with one another and alprostadil.[46]

Vasoactive ICI agents were first introduced in 1982.[7] Papaverine and phentolamine were the first to be used widely for ED treatment but "these unlicensed agents sometimes had significant side effects such as priapism and cavernosal fibrosis."[10] In 1986, the use of alprostadil for ED treatment and diagnosis was first reported, and in 1996, the FDA approved Caverject®, an alprostadil sterile powder formulation for injection.[7,10] The recommended dose range of alprostadil injection is 2.5 to 40 mcg, with 2.5 mcg as the recommended starting dose.[10]

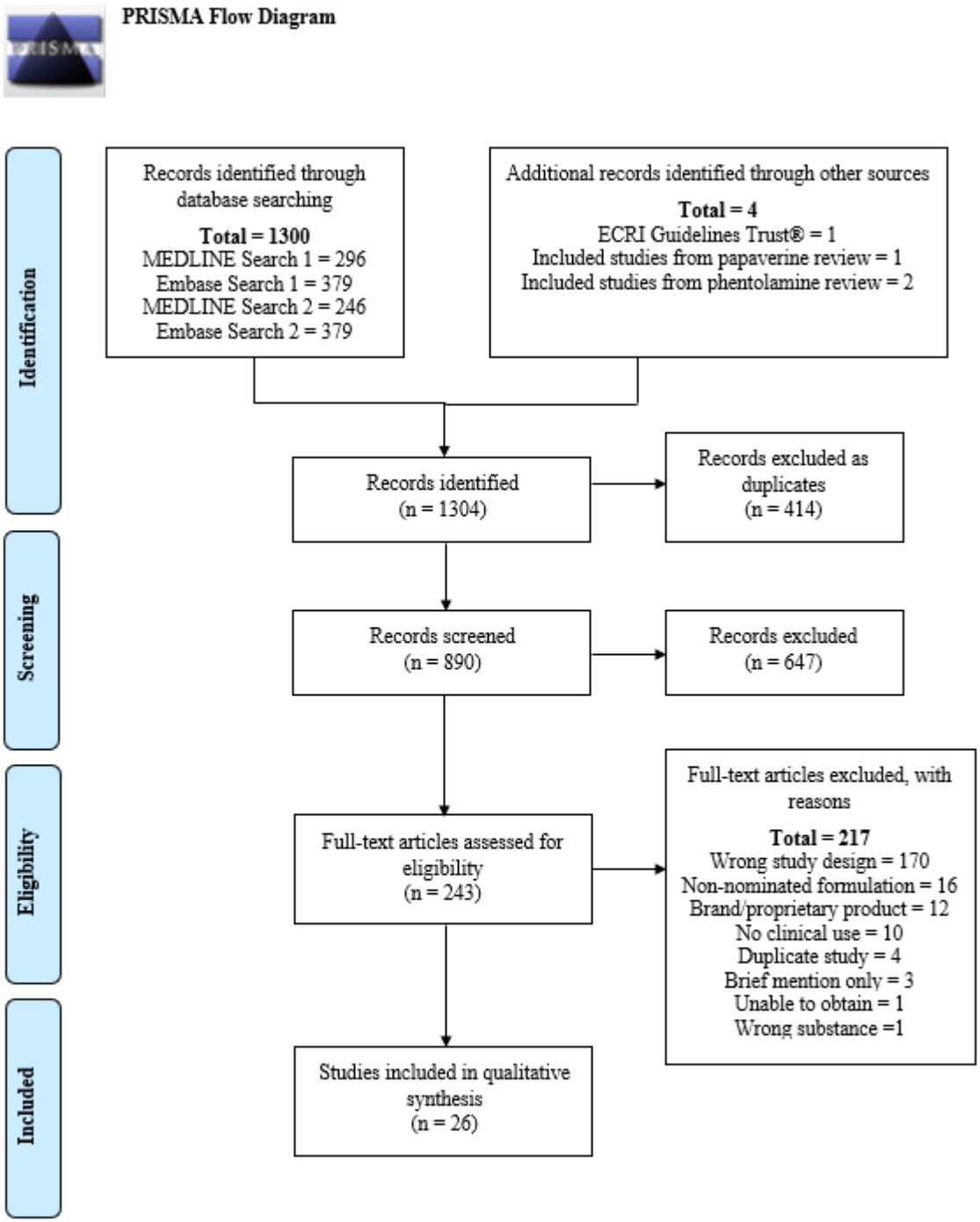
In 1990, Trimix, a mix of papaverine, phentolamine, and alprostadil, was popularized by Goldstein as an effective regimen of self-injection therapy.[48] Trimix is recommended to those who fail ICI monotherapy.[10] This combination allows for lower doses to be used, thus reducing frequency of undesirable side effects, and enhances efficacy by acting synergistically.[15] Although ICIs have good clinical efficacy rates, "dropout rates [are] as high as 40-50% due to pain, priapism, penile fibrosis, hematoma, ecchymosis, or fear of the needle."[49,50] There is currently no combination therapy that is globally approved, many of the combinations are formulated by compounding pharmacies leading to "variations in constituents and consistencies among such therapies."[50] The compound also must be refrigerated and used within 30 days because of the rapid degradation of alprostadil.[48] Cost may be another factor for consideration in the treatment of ED. The compounded injectable agents can be less costly than FDA-approved products, but insurance does not always cover compounded products.[22,24]

FSAD is when a "woman experiences distress due to the inability to attain or maintain adequate vaginal lubrication."[9] It "may manifest as diminished vaginal lubrication, decreased labial and clitoral sensation, decreased labial and clitoral engorgement, or a lack of vaginal smooth muscle relaxation."[12] According to a 2010 review, FSAD is a common problem among women, but it is not routinely diagnosed or treated.[9] This could be because there is currently no FDA-approved drug and no "gold standard" for treatment.[9] There are some potential medications available that are still under investigation that could help promote the arousal response in women.[9] Alprostadil could be a potential treatment because it is a potent vasodilator so it "naturally regulates blood flow through the

reproductive tract."[9] Prostaglandins also improve sensation and facilitate the central nerve stimulation that occurs during arousal by enhancing the activity of sensory afferent nerves.[9] Currently, alprostadil has an off-label use in women and can be compounded into a cream.[9] In a 2003 trial, 94 women with FSAD were randomized to receive 1 of 3 strengths (500, 1000, or 1500 mcg) of an alprostadil cream called Femprox® by NexMed, Inc or a placebo cream.[12] Padma-Nathan et al found that alprostadil topical cream improved the sexual arousal rate of women, but it was not statistically significant when compared to placebo.[12] No serious adverse events were observed during the study.[12]

The topical cream by NexMed, Inc has also been studied in men with ED in a 2009 trial with 1161 patients.[14] Patients used 200 mcg of alprostadil for the first 4 weeks and then depending on response to the dose, patients could choose to administer 100 mcg (if hyper-responsive), 200 mcg (if no change in response), or 300 mcg (if hypo-responsive) doses for up to 9 months with a maximum of 2 doses per week.[14] Most patients and their partners consider the topical alprostadil cream to be effective and safe.[14] The 300 mcg dose "facilitated the greatest improvement in erectile function in the majority of patients."[14] According to a 2016 review, "topical alprostadil cream has proven to be an effective and well-tolerated treatment for ED and can be safely used in men undergoing therapy with alpha-blockers, antihypertensive agents, and/or nitrates."[49]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	Number of Studies
Descriptive[25-27,32,34]	5
Experimental[21,23,30,35,38-40,42-44]	10
Observational[22,24,28,29,31,33,35-37,41,45]	10
Clinical practice guidelines[46]	1

Table 4. Number of studies by country

Country	Number of Studies
China[40]	1
Egypt[30,44]	2
US[21-29,31-39,41-43,46]	22
Multiple Countries • Brazil and US[45]	1
	Total US[a]: 23 Total Non-US Countries[a]: 4

[a]Study 45 counted in both US and non-US total.

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Indication 1: Erectile dysfunction (ED)					
Albaugh and Ferrans, 2010, US[24]	One-group, pretest/posttest design	20 Men who had prostatectomy for prostate cancer (100%, mean 58 y ± 8.8)	• Papaverine/phentolamine (2) • Trimix (11) • Edex/PGE1 (7)	Erection rigidity strength, erectile function via the International Index of Erectile Function (IIEF), self-esteem and relationship questionnaire, erectile dysfunction inventory of treatment satisfaction, injection self-efficacy scale – all before, 1 month, and 3 months after initiation of ICI therapy	Penile injections for ED after radical prostatectomy were an effective treatment option and associated with improved satisfaction with the sexual relationship and improved sexual confidence and self-esteem.
Allen *et al*, 1992, US[21]	Double-blind, crossover study	7 Men with organic impotence (100%, age not mentioned)	• Papaverine/phentolamine (7*) • Trimix (not specified) • Papaverine/PGE1 (not specified) *Each patient received 2 injections per test date. All were given papaverine/phentolamine and then given either papaverine/PGE1 or Trimix	Duration of erection, maximum rigidity	The combination of papaverine with PGE1 produces longer duration erections than papaverine with phentolamine. There is no additional benefit gained by adding phentolamine to papaverine with PGE1.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Bennett *et al*, 1991, US[25]	Case series	116 Impotent patients (100%, range 30-75 y)	• Trimix (116)	Percent tumescence, Doppler assessment	The Trimix combination of papaverine, phentolamine, and PGE1 is effective and safe for a self-administered pharmacological treatment program.
Bernie *et al*, 2017, US[22]	Prospective	175 Patients enrolled in the ICI program Group 1 empiric (100%, mean 61.9 y ± standard error of the mean 1.4) Group 2 risk-based (100%, mean 61.3 y ± standard error of the mean 0.7)	• Group 1 empiric* (57) • Group 2 risk-based**(118) *Patients treated irrespective of ED etiology or severity. Initial is PGE1 only then PGE1/phentolamine or a low dose Trimix. **Patients treated with papaverine and phentolamine, low dose Trimix or a high dose Trimix using an algorithm factoring ED etiology and risk factors.	IIEF-erectile function domain, quality of erection questionnaire, sexual quality of life, erectile dysfunction inventory of treatment satisfaction at baseline, 3, and 6 months after initiation of therapy	Both treatment strategies resulted in significant improvements across multiple domains of sexual function. The complication rates, satisfaction, and efficacy overall were similar in both.
Burnett *et al*, 2018, US[46]	Guideline	Males with erectile dysfunction	Not applicable	Not applicable	The option of alprostadil ICI has a moderate recommendation, evidence level grade C. Men who have contraindications to PDE5I, prefer to not take an oral medication, or find PDE5I medications ineffective, may choose the ICI route to treating ED. Alprostadil is typically used as a single agent but is also typically used in combination with others such as papaverine, phentolamine, and atropine.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Chao and Clowers, 1994, US[26]	Case series	35 Patients with neurogenic ED (100%, range 22-59 y)	• Trimix (35)	Presence of intracorporeal fibrosis or plaque formation, rigid erection lasting 1-2 hours	Trimix ICI therapy is a "satisfactory, cost-effective method to [achieve] erection without significant side effects."
Davis *et al*, 2009, US[43]	Randomized, phase II open label study	107 Patients with prostate cancer recommended for unilateral nerve-sparing radical prostatectomy Control group (100%, mean 55.3 y ± 6.1) Sural nerve graft group (100%, mean 57.3 y ± 4.8)	• Control group (41) • Sural nerve graft (66) At postoperative week 6, all patients had a treatment plan that included sildenafil, a vacuum erection device, and ICI therapy with Trimix.	Patient completed quality of life questionnaires, assessment of penile rehabilitation compliance, side effects, intracavernous injection compliance rating (good, poor, or none)	Unilateral sural nerve graft with radical prostatectomy compared to unilateral sural nerve graft alone did not increase potency rate at 2 year following surgery. "Secondary endpoints also did not show an improvement in time to potency or urinary function at 1 [year]. Based upon the power of this study, we cannot exclude a smaller benefit."
Govier *et al*, 1993, US[27]	Case series	Part 1: 170 Patients with ED (100%, age not specified) Part 2: 146 Patients with ED (100%, range 24-85 y) Part 1: Patients learn how to perform injection and to establish the effective dose for the patient. Part 2: Of the original 170, only 146 patients want to continue the treatment program.	• Trimix (170)	Functional erection and side effects	"In summary, while the perfect injectable agent for a pharmacological erection program does not exist, triple-drug therapy has many positive features. Its superior smooth muscle relaxation and dose response, low incidence of pain and low incidence of scarring make it a viable first line agent for patients in a pharmacological erection program."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Gupta *et al*, 1997, US[28]	Retrospective chart review	1089 ED patients Active group (100%, range 21-91 y) Inactive group (100%, range 22-94 y)	• PGE1 (636) • Papaverine/PGE1 (21) • Papaverine/phentolamine (143) • Trimix (222)	Patient-reported experience, physical exam, and frequency of injection use	There was a high satisfaction rate for the use of PGE1. "Failure with [PGE1] and triple drug therapy is a likely predictor of failure of intracavernous injection. Remaining in the program past a critical period of approximately 2 months is a probable predictor of long-term success, confirming intracavernous injection as an effective long-term option."
Hsiao *et al*, 2011, US[31]	Cohort	122 Patients who were prescribed ICI for ED treatment for at least 6 months (100%, mean 68 y ± 32)	• Trimix (122)	Change in scores in satisfaction domains of IIEF; type of injection used; predictors of satisfaction	"While over a third of patients had stopped ICI at the time of follow-up, those that continued to inject had high levels of satisfaction as measured by the IIEF, the gold standard for the evaluation of erectile function."
Katlowitz *et al*, 1993, US[32]	Case series	25 Patients with suspected vasculogenic impotence (100%, range 36-72 y)	• PGE1 (11) • Trimix (14)	Arterial diameter, peak systolic flow and end-diastolic flow on Doppler ultrasound, and grade of erection	"Our data indicate that a patient who fails intracavernosal injection in the office setting should not be immediately excluded from a pharmacologic erection program because adequate erection may be achieved after injection by the addition of audiovisual sexual stimulation."
Kim *et al*, 1995, US[38]	Phase I, placebo controlled, nonblinded study	10 Patients with ED (100%, range 19-50 y)	• PGE1 (10)	Mean cavernous artery diameter, vital signs, mean peak systolic, diastolic flow velocity, side effects, grade and duration of erection	Topical application of PGE1 to the genitalia seems to be safe and well tolerated, and significantly increases blood flow to the penis.
Lauer, 2018, US[23]	–	21 Patients with spinal cord injury and ED (100%, age not mentioned)	• Trimix • PGE1 Number of patients not specified for either intervention	Sexual satisfaction score and Sexual Health Inventory of Men questionnaire	Both ED and sexual satisfaction in spinal cord injured males were improved via penile injections. Penile injections are a clinically effective intervention.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Maniam *et al*, 2001, US[41]	Retrospective study	19 Patients with organic ED (100%, mean 53.47 y ± 9.96)	• PGE1 (7) • Trimix (12)	Nocturnal penile tumescence testing parameters via number of erectile episodes, base and tip tumescence, percent of time with rigidity greater than 70% at the penile base and tip	The data implies that there is subjective improvement that develops in some men after long-term ICI, but there is no objective improvement in spontaneous erectile function as measured by nocturnal penile tumescence testing.
Marshall *et al*, 1994, US[33]	–	45 Patients (100%, mean 58.7 y ± 8)	• PGE1 (21) • Trimix (14) • Control (10)	Doppler ultrasound study (cavernous artery diameter and peak flow) before and after long-term ICI therapy	"In this study, we have shown that long-term intracavernous therapy with vasoactive substances leads to significantly improved blood flow in the cavernous artery. This may represent a medication induced improvement in the efficiency of the sinusoidal and arteriolar smooth muscle."
McCullough *et al*, 2020, US[34]	Case report	1 ED patient (100%, 52 y)	• Trimix (1)	Erection hardness	"[Computed tomography] cavernosography is useful in determining the site of venous leak in mean with ED and aids in the therapeutic decision making and patient education."
Miranda *et al*, 2015, Brazil and US[45]	Cohort	476 Patients who had radical prostatectomy and on penile injection therapy (100%, mean 62 y ± 14)	• Trimix (476)	Rate of priapism	There was no difference in rate of priapism between tadalafil and sildenafil users. For men on tadalafil, the mean Trimix dose was higher and a higher proportion of those on tadalafil experienced a prolonged erection not requiring an emergency room visit. Both strategies with tadalafil and sildenafil appear to be safe in the penile injection population, but excellent patient counseling is required especially for those using tadalafil.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Mullhall *et al*, 2005, US[35]	Nonrandomized study	132 Patients with clinically organ-confined prostate cancer, who had fully functional erection by self-report and who were scheduled to undergo radio prostatectomy surgery (100%, mean 59 y ± 10.6)	• Rehabilitation* group (58) • No rehabilitation group - no erectogenic medication treatments (74) *Pursued pharmacologic penile rehabilitation-protocol is initial challenge with sildenafil. If sildenafil fails, then Trimix ICI therapy used	Capability of having medication-unassisted intercourse, mean erectile rigidity, mean IIEF erectile function domain scores, percentage of patients responding to sildenafil, the time to become a sildenafil responder and the percentage of patients responding to ICI therapy	A pharmacologic penile rehabilitation protocol results in higher rates of spontaneous functional erections and erectogenic drug response after radical prostatectomy.
Nandipati *et al*, 2006, US[36]	Non-randomized prospective study	22 Patients who underwent bilateral nerve-sparing radical prostatectomy (100%, mean 58.3 y ± 6.9)	• PGE1 (18) • Low dose Trimix (4)	Sexual activity, abridged version of IIEF questionnaire, penile doppler studies at 3 and 6 months	"Early injections facilitate early sexual intercourse, patient satisfaction and potentially early return of spontaneous erections. Combination therapy with sildenafil allows lower dose of intracavernous injections, which decreases the discomfort."
Raina *et al*, 2003, US[29]	Retrospective study	102 Patients who had radical prostatectomy (100%, mean 60.4 y ± 6.3)	• PGE1 (62) • Low dose Trimix (21) • High dose Trimix (19)	Sexual Health Inventory of Men scores, IIEF scores, treatment effect, frequency of use, duration of erection	"This study suggests that intracorporeal injections are an excellent salvage option in nerve sparing patients who fail oral therapy and a first option in patients with non-nerve sparing procedures."
Salem and Mostafa, 2012, Egypt[30]	–	176 Patients with organic erectile dysfunction (100%, age not specified)	• Trimix (56) • Sildenafil (55) • Vacuum constrictive device (54)	Resumption of unaided erection, mean peak systolic velocity, mean cavernosal artery diameter	"It is concluded that repeated regular use of ICI, sildenafil or [vacuum constrictive device] by patients with organic ED has a positive impact on their cavernous blood flow and erectile activity."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Shamloul *et al*, 2004, Egypt[44]	Double-blind comparative study	50 Patients with ED (100%, mean 47.2 y ± 3.4)	• Group A – in-office Bimix (papaverine and phentolamine) ICI, 1-week later papaverine and chlorpromazine ICI (20) • Group B – in-office Trimix ICI, 1-week later papaverine, PGE1, and chlorpromazine (20) • Group C – various chlorpromazine ICI (10)	Erectile response	Chlorpromazine is similar to phentolamine's efficacy and short-term side effect profile. It can be used as an intracavernous vasoactive agent.
Steidle *et al*, 2002, US[39]	Randomized, multicenter, parallel-group, double-blind, placebo-controlled studies	303 Patients with ED of at least 3 months (100%, age provided by group) Placebo (100%, 59.1 y ± 6.5) Alprostadil 50 mcg (100%, mean 54.1 y ± 8.2) Alprostadil 100 mcg (100%, mean 55.7 y ± 8.9) Alprostadil 200 mcg (100%, mean 58.8 y ± 8) Alprostadil 300 mcg (100%, mean 62.8 y ± 5.6)	• Placebo (73) • Alprostadil 50 mcg (36) • Alprostadil 100 mcg (66) • Alprostadil 200 mcg (61) • Alprostadil 300 mcg (29)	Change in erectile function domain score	Topical alprostadil cream when combined with a novel dermal permeation-enhancer could be a potentially useful agent for ED treatment.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)[b,c]	Primary Outcome Measure	Authors' Conclusions
Von Heyden *et al*, 1993, US[37]	Retrospective analysis	101 Patients who received ICI as primary therapy for vasculogenic impotence (100%, range 22-80 y)	• PGE1 (70) • Trimix (31)	Ultrasound of the penis, quality of erection on graded scale	"We believe that an erection longer than 30 to 60 minutes carries an increased risk of priapism. By diminishing the dose of intracavernous agent necessary for home injection, the combined intracavernous injection and self-stimulation test markedly decreases this risk. Although occasionally a patient may find a request for genital self-stimulation to be embarrassing, in our experience most patients cooperate fully once the rationale for self-stimulation is explained to them. That rationale is to initiate and maintain a natural erection adequate for sexual satisfaction without adverse effects. This is the preferred outcome of our self-injection program."
Indication 2: Female sexual arousal disorder (FSAD)					
Heiman *et al*, 2006, US[42]	Prospective, randomized, multicenter, double-blind, crossover-design study	79 Patients with naturally or surgically post-menopausal and FSAD (0%, range 40-70 y)	• Alprostadil 100 mcg and placebo (40) • Alprostadil 400 mcg and placebo (39)	Investigator assessments of genital vasocongestion, patient assessments of physical and emotional sexual arousal, and sexual satisfaction	"These data suggest topical alprostadil should be further researched as a potentially appropriate on-demand therapeutic choice for women experiencing FSAD."
Liao *et al*, 2008, China[40]	Double-blind, placebo-controlled study	400 Patients with FSAD (0%, range 22-62 y)	• Placebo (100) • PGE1 500 mcg (100) • PGE1 700 mcg (100) • PGE1 900 mcg (100)	Change in arousal success rate	Applying topical alprostadil before vaginal intercourse in patients with FSAD significantly improved the sexual arousal rate.

Abbreviations: "–", not mentioned; ED, erectile dysfunction; FSAD, female sexual arousal disorder; ICI, intracavernosal injection; IIEF, International Index of Erectile Function; PGE1, prostaglandin E1.

[a]As defined by authors.

[b]Alprostadil is also known as prostaglandin 1 (PGE1); for accuracy, the substance name that the study authors used is presented in this table.

[c]Trimix is a combination of alprostadil, papaverine, and phentolamine.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Erectile dysfunction[21-29,31-39,41,43,45,46]	0.05-1 mL	5-500 mcg/mL	Solution	Intracavernosal, intracorporeal	Twice – 81 months
	1-1.5 g	0.04%	Gel	Topical	–
	Approximately 100 mg in weight and 0.1 mL in volume	50-300 mcg	Cream	Topical	–
Female sexual arousal disorder[42]	100-400 mcg	–	Solution	Topical	–

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Erectile dysfunction[30,44,45]	0.5-2 mL	10 mcg/mL	Solution	Intracavernosal	Once – 3 months
Female sexual arousal disorder[40]	500-900 mcg	–	Cream	Topical	8 weeks

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Alprostadil 5 mcg/mL – 500 mg/mL / Papaverine 17.65 mcg/mL – 30 mg/mL / Phentolamine 0.59 mcg/mL – 5 mg/mL – injection[21-37,41,43-46]	22

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Erectile dysfunction[31,36]	2006-2011	Purchased from a compounding pharmacy[31]	Solution	–
		Not mentioned, "this mixture is purchased from the hospital pharmacy."[36]		Alprostadil 5.88 mcg/mL / Papaverine 17.65 mg/mL / Phentolamine 0.59 mg/mL

Abbreviation: "–", not mentioned.

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Eight SMEs discussed alprostadil. Amongst these 8 SMEs, there were 5 medical doctors, 1 clinical psychologist, 1 sexuality educator, and 1 regulatory specialist. The SMEs specialized and/or were board-certified in andrology, psychology, sexual/reproductive health, and urology, working in academic medical centers, pharmacy/pharma companies, and private practice/clinics. The SMEs had been in practice for 8 to 45 years.

For the treatment of ED, the patient is usually first given a PDE5I such as Cialis® (tadalafil), Levitra® (vardenafil), Stendra® (avanafil), or Viagra® (sildenafil citrate) unless they are unable to take PDE5Is due to contraindications or are unable to tolerate the side effects. If a PDE5I fails, then most patients will go on Trimix (alprostadil/papaverine/phentolamine) ICI therapy. Although Trimix is typically the go to, there are also other variations such as Bimix and Quadmix. One SME added that PDE5Is usually do not work in patient populations who have more severe ED due to a severe corpus venous leak such as: severe diabetics with a very high hemoglobin A1c; patients who are 3-6 months post-vasectomy; post-radical cystectomy; or a history of any pelvic surgery with neurogenic ED as the underlying cause. However, a trial of PDE5Is should still be given. If the injections do not work, then a penile implant would be the next option. One SME also provided some background about the ED drugs, stating that Trimix has been used since the early 1990s, before PDE5Is. Sildenafil citrate and tadalafil were approved in 1998.

All the SMEs who specialized in urology used Trimix. Trimix is a "staple of treatment for severe ED," and is in the AUA guidelines for ED. Caverject® and edex®, alprostadil products for injection, are FDA-approved drugs that use a higher volume for injection, but they do not work as well as Trimix. Several SMEs commented that injecting alprostadil alone can cause pain and/or burning, especially when used at higher doses. The Trimix combination works synergistically and the side effects such as pain and burning are lessened because of the lower alprostadil dose. One SME stated the only time they used the commercially available alprostadil injection is when they have a patient who travels a lot and they are unable to keep Trimix refrigerated. The SME prefered to start with Trimix, and scale back with dose adjustments or other mixes as needed because patients who have failed oral PDE5Is usually have severe ED. For patients in which a PDE5I is efficacious but intolerable due to side effects, Bimix can be considered. If the patient is started on a single agent ICI with an associated side effect and fail that, then "[the patient's] confidence [for] using any other injection [therapy] goes down dramatically." There is one SME who expressed that most people do not want to use an injection, especially in a sensitive area. One SME added that 65-70% of patients will respond to the injections, which is the same response rate as PDE5Is. The reason patients do not respond to PDE5Is is usually because their disease is severe.

A few SMEs also commented about the cost of these ED drugs. One stated that until 2 years ago when sildenafil citrate and tadalafil became generic, compounded ICIs were less expensive than PDE5Is so there were some patients who used compounded ICI for financial reasons. An SME also commented that they think the commercially available injection products are expensive.

All the SMEs used compounded ICIs; some SMEs specified that they obtain them from a 503A compounding pharmacy. There was also a 503B who stated that they have compounded Trimix. One SME mentioned that they do stock Trimix in their office to use when conducting penile Dopplers to evaluate blood flow. For patient specific prescriptions, one SME stated that the injection is ordered, compounded, and then shipped to that patient's house. The patient then brings the compounded product to their office to teach the patient how to use the injection and to monitor the patient's response. The patient is also given specific instructions on the dose to use at home and how to increase the dose. The potential concerns with a patient using the injection incorrectly include priapism, nerve damage, bleeding,

and hematomas; however, this SME has not encountered these issues because they have shown the patients the proper administration technique.

Several SMEs also discussed female sexual arousal. An SME explained that arousal can be categorized as both genital and subjective. "Genital is the physiologic sensation of sexual pleasure during sexual activity, the feeling of the nerves endings. If your body [were] to lubricate, we could increase blood flow to the vulva to create enough sensation during sexual activity." Subjective arousal is experiencing pleasure during sexual activity. On the other hand, "desire is about wanting and anticipating." For genital arousal disorders, treatment depends on the etiology because it could be due to other disease states such as type II diabetes or lupus. If trying to increase sensation, then sometimes increasing blood flow might be useful. One SME mentioned that arousal disorder is often a secondary issue with pain, interest, or another factor typically the primary issue. Another SME commented that there is an FDA-approved device called Eros but there are no FDA-approved treatments for genital arousal disorders yet. This SME had not used Eros before because insurance does not cover it, making it expensive and there are other options they would try first, such as a vibrator. Off-label use of PDE5Is make sense for increasing blood flow to the vulva and clitoris since they are already used for infertility to create a better lining for the uterus. Another option for increasing sensitivity and sensation is alprostadil, which has the most data available for arousal problems. Although there are no good phase III FDA trials in the US for alprostadil, there is "enough data that it would make sense to use that off-label." For alprostadil, one SME thought that a topical product would make sense in terms of patient administration. Another SME stated that there has been a study using alprostadil cream to increase blood flow;[51] in their practice, they use the cream in patients who want a therapy, but they have not seen a great response rate. There are currently two approved medications for desire disorder (bremelanotide and flibanserin) but nothing for arousal or orgasm. There is also Zestra®, an OTC product, that is "trying to show efficacy and [there is] nothing in it [that is] particularly harmful. Some women swear by it…but very few have found it effective." One SME hopes there will be more FDA-approved treatments for women.

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

A separate survey was distributed by the Nurse Practitioners in Women's Health (NPWH) organization; 96 people responded to this survey (refer to Table 11 for respondent characteristics and Appendix 2.2 for survey instrument).

Among respondents, 1 (1%) used compounded alprostadil as a single-ingredient product and 1 (1%) used compounded alprostadil in combination with papaverine and phentolamine. Respondents did not use either single-ingredient or combination alprostadil as a topical cream, lotion, gel, or solution. Respondents did not provide the conditions or diseases for which they used either single-ingredient or combination alprostadil (refer to Table 12).

Respondents used compounded single-ingredient or combination alprostadil due to lack of commercial products in an appropriate dosage form, strength, or combination (50% of 2 total responses), patient allergies (0%), other patient conditions preventing use of commercial products (0%), no commercially available products with alprostadil (0%), or other with no explanation (50%) (refer to Table 13).

The majority of respondents who used compounded single-ingredient or combination alprostadil (2, 100%) did stock non-patient-specific compounded alprostadil products at their practice. Respondents that did stock non-patient-specific aminophylline compounded the products themselves at their practice (2, 100% of respondents). Refer to Table 14 for how respondents obtained compounded alprostadil.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=96)
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Master of Science (MS)	1
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	95
Physician Assistant (PA)	0
Practice Setting	**Responses, n (N=96)[a]**
Physician office or private practice	47
Outpatient clinic	29
Hospital or health system	9
Academic medical center	7
Emergency room	0
Operating room	1
Other[b]	3

[a]Some respondents reported more than one practice setting.
[b]Responses to other: retired from research; Graduate Education Program faculty; "recently moved to FL."

Table 12. Conditions for which single-ingredient or combination alprostadil prescribed or administered

Condition	Responses, n (N=2)[a]
Female sexual arousal disorder	0
Other	1
None of the above	1

[a]Out of 96 respondents, 2 reported prescribing or using compounded single-ingredient or combination alprostadil.

Table 13. Reasons for using compounded single-ingredient or combination alprostadil

Reason	Responses, n (N=2)[a]
Commercial product not available in desired dosage form, strength, or combination	1
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	0
No commercial products	0
Other – no explanation provided	1

[a]Out of 96 respondents, 2 reported prescribing or using compounded single-ingredient or combination alprostadil.

Table 14. Use of non-patient-specific compounded single-ingredient or combination alprostadil

Do you stock non-patient-specific compounded single-ingredient or combination alprostadil at your practice?	**Responses, n (N=2)[a]**
Yes	2
No	0
Not sure	0
How do you obtain your stock of non-patient-specific compounded single-ingredient or combination alprostadil?	
Compound yourself at practice	2
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	0
Purchase from outsourcing facility	0
Other	0

[a]Out of 96 respondents, 2 reported prescribing or using compounded single-ingredient or combination alprostadil.

CONCLUSION

Alprostadil was nominated for inclusion on the 503B Bulks List for ED and FSAD via topical creams, lotions, gels, solutions, and a 2.5-5000 mcg/mL injection. Alprostadil is available in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, US, and UK. An EMA pharmacovigilance risk assessment report concluded that there is an increased risk of myocardial ischemia and cerebrovascular accidents associated with alprostadil in patients with risk factors for ischemic heart disease and cerebrovascular accidents.[19] Another EMA report also concluded that gastrointestinal hemorrhage should be listed as an adverse drug reaction for all alprostadil products indicated for peripheral arterial occlusive disease.[20]

From the literature review and interviews conducted, alprostadil is used for ED and FSAD. In the included literature review studies, topical alprostadil alone has been used for the treatment of ED and FSAD, and the Trimix injection has been used for the treatment for ED. The current treatment for ED includes a PDE5I, Trimix injection, or a penile implant. For treatment of genital arousal disorders, there is an FDA-approved device called Eros but no FDA-approved medications. Other potential treatments for genital arousal disorders include a vibrator, PDE5Is, and alprostadil.

All the SMEs who specialized in urology used Trimix. Trimix is a "staple of treatment for severe ED," and is in the AUA guidelines for ED. Several SMEs commented that injecting alprostadil alone can cause pain and/or burning, especially when used at higher doses. The Trimix combination works synergistically and the side effects such as pain and burning are lessened because of the lower alprostadil dose. One SME stated the only time they used the commercially available alprostadil injection is when they have a patient who travels a lot and is unable to keep Trimix refrigerated. All the SMEs use compounded ICIs; some SMEs specified that they obtain it from a 503A compounding pharmacy, and one mentioned that they stock Trimix in their office to use when conducting penile Dopplers. Patients are taught in office how to use the ICI therapy. There was also a 503B who stated that they have compounded Trimix. One SME thought that a topical alprostadil product would make sense in terms of patient administration while another SME stated there has not been a great response rate seen with the cream formulation.

Among respondents to the NPWH survey, 1 out of 96 respondents used compounded alprostadil as a single-ingredient product and 1 used compounded alprostadil in combination with papaverine and phentolamine. Respondents did not use either single-ingredient or combination alprostadil as a topical cream, lotion, gel, or solution. Lack of commercial products in the dosage form, strength, or combination that the respondent needed and other with no explanation were the reasons for using compounded alprostadil products over an FDA-approved product. Respondents reported stocking compounded alprostadil at their practice.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.
6. Al-Adl AM, Abdel-Wahab O, El-Karamany T, Aal AA. Combined intracavernous vasoactive drugs and sildenafil citrate in treatment of severe erectile dysfunction not responding to on-demand monotherapy. *Arab Journal of Urology Print.* 2011;9(2):153-158.
7. Choi HK, Adimoelja A, Kim SC, Soebadi DM, Seong DH, Garceau RJ. A dose-response study of alprostadil sterile powder (S.Po.) (Caverject) for the treatment of erectile dysfunction in Korean and Indonesian men. *International journal of impotence research.* 1997;9(1):47-51.
8. Coker C, Bettocchi C, Pryor J. Caverject, a new licensed prostaglandin preparation for use in erectile dysfunction. *Journal of Andrology.* 1994;15(6 SUPPL.):71S.
9. Feldhaus-Dahir M. Treatment options for female sexual arousal disorder: part II. *Urol Nurs.* 2010;30(4):247-251.
10. Hanchanale V, Eardley I. Alprostadil for the treatment of impotence. *Expert opinion on pharmacotherapy.* 2014;15(3):421-428.
11. Hatzimouratidis K, Hatzichristou D. How to treat erectile dysfunction in men with diabetes: from pathophysiology to treatment. *Curr Diab Rep.* 2014;14(11):545-545.
12. Padma-Nathan H, Brown C, Fendl J, Salem S, Yeager J, Harningr R. Efficacy and safety of topical alprostadil cream for the treatment of female sexual arousal disorder (FSAD): a double-blind, multicenter, randomized, and placebo-controlled clinical trial. *Journal of sex & marital therapy.* 2003;29(5):329-344.
13. Ribé N, Rajmil O, Bassas L, Jurado C, Pomerol JM. Response to intracavernosal administration of three different drugs in the same group of patients with erectile dysfunction. *Archivos Espanoles de Urologia.* 2001;54(4):355-359.
14. Rooney M, Pfister W, Mahoney M, Nelson M, Yeager J, Steidle C. Long-term, multicenter study of the safety and efficacy of topical alprostadil cream in male patients with erectile dysfunction. *J Sex Med.* 2009;6(2):520-534.
15. Seyam R, Mohamed K, Akhras AA, Rashwan H. A prospective randomized study to optimize the dosage of trimix ingredients and compare its efficacy and safety with prostaglandin E1. *International Journal of Impotence Research.* 2005;17(4):346-353.
16. Steers WD. Pharmacologic treatment of erectile dysfunction. *Rev Urol.* 2002;4 Suppl 3(Suppl 3):S17-S25.

17. Trissel LA, Zhang Y. Long-term stability of Trimix: a three-drug injection used to treat erectile dysfunction. *Int J Pharm Compd.* 2004;8(3):231-235.

18. Uebel RA, Wium CA, Schmidt AC. Stability evaluation of a prostaglandin E1 saline solution packed in insulin syringes. *International journal of impotence research.* 2001;13(1):16-17.

19. Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD-h). *Alprostadil (erectile dysfunction): CMDh Scientific conclusions and grounds for variation, amendments to the Product Information and timetable for the implementation.* Langen, Germany: Heads of Medicines Agencies;2016. PSUSA/00000110/201601.

20. Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD-h). *Alprostadil (indicated in peripheral arterial occlusive diseases): CMDh Scientific conclusions and grounds for variation, amendments to the Product Information and timetable for the implementation.* Langen, Germany: Heads of Medicines Agencies;2018. PSUSA/00000111/201707.

21. Allen RP, Engel RM, Smolev JK, Brendler CB. Objective double-blind evaluation of erectile function with intracorporeal papaverine in combination with phentolamine and/or prostaglandin E1. *Journal of Urology.* 1992;148(4):1181-1183.

22. Bernie HL, Segal R, Le B, Burnett A, Bivalacqua TJ. An empirical vs risk-based approach algorithm to intracavernosal injection therapy: A prospective study. *Sexual Medicine.* 2017;5(1):e31-e36.

23. Lauer P. Effectiveness of penile injection therapy in spinal cord injured males. *Journal of Spinal Cord Medicine.* 2018;41(5):582.

24. Albaugh JA, Ferrans CE. Impact of penile injections on men with erectile dysfunction after prostatectomy. *Urol Nurs.* 2010;30(1):64-77.

25. Bennett AH, Carpenter AJ, Barada JH. An improved vasoactive drug combination for a pharmacological erection program. *Journal of Urology.* 1991;146(6):1564-1565.

26. Chao R, Clowers DE. Experience with intracavernosal tri-mixture for the management of neurogenic erectile dysfunction. *Archives of Physical Medicine & Rehabilitation.* 1994;75(3):276-278.

27. Govier FE, McClure RD, Weissman RM, Gibbons RP, Pritchett TR, Kramer-Levien D. Experience with triple-drug therapy in a pharmacological erection program. *Journal of Urology.* 1993;150(6):1822-1824.

28. Gupta R, Kirschen J, Barrow RC, 2nd, Eid JF. Predictors of success and risk factors for attrition in the use of intracavernous injection. *Journal of Urology.* 1997;157(5):1681-1686.

29. Raina R, Lakin MM, Thukral M, et al. Long-term efficacy and compliance of intracorporeal (IC) injection for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. *International Journal of Impotence Research.* 2003;15(5):318-322.

30. Salem H, Mostafa T. Rehabilitation of the cavernous smooth muscle in patients with organic erectile dysfunction. *Andrologia.* 2012;44(2):125-129.

31. Hsiao W, Bennett N, Guhring P, Narus J, Mulhall JP. Satisfaction profiles in men using intracavernosal injection therapy. *Journal of Sexual Medicine.* 2011;8(2):512-517.

32. Katlowitz NM, Albano GJ, Morales P, Golimbu M. Potentiation of drug-induced erection with audiovisual sexual stimulation. *Urology.* 1993;41(5):431-434.

33. Marshall GA, Breza J, Lue TF. Improved hemodynamic response after long-term intracavernous injection for impotence. *Urology.* 1994;43(6):844-848.

34. McCullough A, Trussler J, Flacke S, Alnammi M. 369 pressure necrosis of proximal corpora in elite ironman resulting in massive venous leak. *Journal of Sexual Medicine.* 2020;17(1):S101-S102.

35. Mulhall JP, Land S, Parker M, et al. The use of an erectogenic pharmacotheraphy regimen following radical prostatectomy improves recovery of spontaneous erectile function. *Journal of Sexual Medicine.* 2005;2(4):532-542.

36. Nandipati KC, Raina R, Agarwal A, Zippe CD. Erectile dysfunction following radical retropubic prostatectomy: Epidemiology, pathophysiology and pharmacological management. *Drugs and Aging.* 2006;23(2):101-117.

37. Von Heyden B, Donatucci CF, Kaula N, Lue TF. Intracavernous pharmacotherapy for impotence: Selection of appropriate agent and dose. *Journal of Urology.* 1993;149(5 SUPPL.):1288-1290.

38. Kim ED, McVary KT. Topical prostaglandin-E1 for the treatment of erectile dysfunction. *Journal of Urology.* 1995;153(6):1828-1830.

39. Steidle C, Padma-Nathan H, Salem S, et al. Topical alprostadil cream for the treatment of erectile dysfunction: a combined analysis of the phase II program. *Urology.* 2002;60(6):1077-1082.

40. Liao Q, Zhang M, Geng L, et al. Efficacy and safety of alprostadil cream for the treatment of female sexual arousal disorder: a double-blind, placebo-controlled study in chinese population. *Journal of Sexual Medicine.* 2008;5(8):1923-1931.

41. Maniam P, Seftel AD, Corty EW, Rutchik SD, Hampel N, Althof SE. Nocturnal penile tumescence activity unchanged after long-term intracavernous injection therapy. *Journal of Urology.* 2001;165(3):830-832; discussion 832.

42. Heiman JR, Gittelman M, Costabile R, et al. Topical alprostadil (PGE1) for the treatment of female sexual arousal disorder: in-clinic evaluation of safety and efficacy. *Journal of Psychosomatic Obstetrics & Gynecology.* 2006;27(1):31-41.

43. Davis JW, Chang DW, Chevray P, et al. Randomized phase II trial evaluation of erectile function after attempted unilateral cavernous nerve-sparing retropubic radical prostatectomy with versus without unilateral sural nerve grafting for clinically localized prostate cancer. *European Urology.* 2009;55(5):1135-1144.

44. Shamloul R, El-Dakhly M, Ghanem H, Gadallah A, Mokhtar H. Intracavernous chlorpromazine versus phentolamine: a double-blind clinical comparative study. *Journal of Sexual Medicine.* 2004;1(3):310-313.

45. Miranda E, Deveci S, Jenkins L, Narus J, Mulhall J. Daily tadalafil does not increase priapism rates in an intracavernosal injection (ICI) rehabilitation program, after radical prostatectomy (RP). *Journal of Urology.* 2015;193(4):e774-e775.

46. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA guideline. *J Urol.* 2018;200(3):633-641.

47. Rew KT, Heidelbaugh JJ. Erectile dysfunction. *Am Fam Physician.* 2016;94(10):820-827.

48. Pinsky MR, Chawla A, Hellstrom WJ. Intracavernosal therapy and vacuum devices to treat erectile dysfunction. *Archivos Espanoles de Urologia.* 2010;63(8):717-725.

49. Anaissie J, Hellstrom WJ. Clinical use of alprostadil topical cream in patients with erectile dysfunction: a review. *Research & Reports in Urology.* 2016;8:123-131.

50. Duncan C, Omran GJ, Teh J, Davis NF, Bolton DM, Lawrentschuk N. Erectile dysfunction: a global review of intracavernosal injectables. *World Journal of Urology*. 2019;37(6):1007-1014.

51. Goldstein SW, Gonzalez JR, Gagnon C, Goldstein I. Peripheral female genital arousal as assessed by thermography following topical genital application of alprostadil vs placebo arousal gel: A proof-of-principle study without visual sexual stimulation. *Sexual Medicine.* 2016;4(3):e166-175.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to April 3, 2020
- Date last searched: April 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 296

1	alprostadil/	6905
2	al?prostadil$.tw.	674
3	pge 1.tw.	649
4	pge1.tw.	5488
5	pge1alpha.tw.	1
6	prostaglandin$ e 1.tw.	792
7	prostaglandin$ e1.tw.	7153
8	prostaglandin$ e1alpha.tw.	5
9	or/1-8	13388
10	administration, topical/	38106
11	administration, cutaneous/	21834
12	topical$.tw.	103235
13	cutaneous$.tw.	148988
14	transdermal$.tw.	14298
15	exp gels/	50857
16	liniments/	123
17	ointments/	12745
18	skin cream/	985
19	gel?.tw.	304409
20	liniment?.tw.	143

21	ointment?.tw.	11675
22	salve?.tw.	338
23	paste?.tw.	12184
24	unguent$.tw.	112
25	lotion?.tw.	2264
26	cream?.tw.	18553
27	or/10-26	629315
28	and/9,27	535
29	exp animals/ not humans/	4686014
30	28 not 29	341
31	limit 30 to english language	296

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to April 3, 2020
- Date last searched: April 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 246

1	alprostadil/	6905
2	al?prostadil$.tw.	674
3	pge 1.tw.	649
4	pge1.tw.	5488
5	pge1alpha.tw.	1
6	prostaglandin$ e 1.tw.	792
7	prostaglandin$ e1.tw.	7153
8	prostaglandin$ e1alpha.tw.	5
9	or/1-8	13388
10	exp administration, intravenous/	142112

11	infusions, parenteral/	26205
12	injections/	42275
13	inject$.tw.	730933
14	infusion$.tw.	242365
15	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12047
16	intravenous$.tw.	336090
17	intra venous$.tw.	571
18	intravascular$.tw.	47075
19	intra vascular$.tw.	297
20	intracaverno?s$.tw.	3599
21	intra caverno?s$.tw.	88
22	intraspongiosal$.tw.	5
23	intra spongiosal$.tw.	0
24	or/10-23	1261854
25	papaverine/	5870
26	phentolamine/	9012
27	drug combinations/	72459
28	papaverin$.tw.	5169
29	fentolamin$.tw.	16
30	pentholamin$.tw.	2
31	pentolamin$.tw.	6
32	phentolamin$.tw.	9401
33	trimix.tw.	129
34	tri mix.tw.	5
35	(triple adj2 (therap$ or treat$)).tw.	9368
36	bimix.tw.	14

37	bi mix.tw.	2
38	or/25-37	102237
39	and/9,24,38	389
40	exp animals/ not humans/	4686014
41	39 not 40	327
42	limit 41 to english language	246

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 379

1	prostaglandin e1'/mj	11674
2	al$prostadil*':ti,ab,tn	1359
3	pge 1':ti,ab,tn	193
4	pge1':ti,ab,tn	1973
5	pge 1alpha':ti,ab,tn	1
6	prostaglandin* e 1':ti,ab,tn	234
7	prostaglandin* e1':ti,ab,tn	2850
8	prostaglandin* e1alpha':ti,ab,tn	0
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	15250
10	topical drug administration'/de	81608
11	cutaneous drug administration'/de	620
12	transdermal drug administration'/de	8894
13	topical treatment'/de	12462
14	topical*':ti,ab	146566
15	transdermal*':ti,ab	20865
16	cutaneous*':ti,ab	213902
17	cream'/de	9201
18	gel'/exp	73810
19	liniment'/de	248
20	lotion'/de	2810
21	ointment'/exp	18393
22	paste'/de	2490

23	salve'/de	165
24	cream$':ti,ab	29070
25	liniment$':ti,ab	231
26	lotion$':ti,ab	3945
27	ointment$':ti,ab	21306
28	paste$':ti,ab	14665
29	salve$':ti,ab	470
30	unguent*':ti,ab	239
31	gel$':ti,ab	357854
32	emulgel$':ti,ab	310
33	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	851182
34	#9 AND #33	671
35	[animals]/lim NOT [humans]/lim	6013410
36	#34 NOT #35	456
37	#34 NOT #35 AND [english]/lim	379

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 379

1	prostaglandin e1'/mj	11674
2	al$prostadil*':ti,ab,tn	1359
3	pge 1':ti,ab,tn	193
4	pge1':ti,ab,tn	1973
5	pge 1alpha':ti,ab,tn	1

6	prostaglandin* e 1':ti,ab,tn	234
7	prostaglandin* e1':ti,ab,tn	2850
8	prostaglandin* e1alpha':ti,ab,tn	0
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	15250
10	parenteral drug administration'/de	2118
11	intravenous drug administration'/exp	392156
12	intracavernous drug administration'/de	728
13	injection'/exp	247460
14	inject*':ti,ab	1085123
15	infusion*':ti,ab	353320
16	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18137
17	intravenous*':ti,ab	483246
18	intra venous*':ti,ab	1437
19	intravascular*':ti,ab	67223
20	intra vascular*':ti,ab	678
21	intracaverno$s*':ti,ab	5055
22	intra caverno$s*':ti,ab	189
23	intraspongiosal*':ti,ab	13
24	intra spongiosal*':ti,ab	1
25	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	1994120
26	papaverine'/de	14439
27	phentolamine'/de	25191
28	drug combination'/de	145988
29	papaverin*':ti,ab,tn	7356
30	fentolamin*':ti,ab,tn	17
31	pentholamin*':ti,ab,tn	2

32	pentolamin*':ti,ab,tn	17
33	phentolamin*':ti,ab,tn	11357
34	trimix':ti,ab	218
35	tri mix':ti,ab	15
36	(triple NEAR/2 (therap* OR treat*)):ti,ab	16260
37	bimix':ti,ab	29
38	bi mix':ti,ab	3
39	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	201019
40	#9 AND #25 AND #39	573
41	[animals]/lim NOT [humans]/lim	6013410
42	#40 NOT #41	498
43	#40 NOT #41 AND [english]/lim	379

Appendix 2.1. Survey instrument for use of alprostadil as solo product

Welcome. We want to understand your clinical use of compounded alprostadil. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer alprostadil to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer alprostadil by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Topical cream
   - o Topical gel
   - o Topical lotion
   - o Topical solution
   - o None of the above

4. I prescribe or administer alprostadil for the following conditions or diseases: (check all that apply)

   - o Erectile dysfunction
   - o Female sexual arousal
   - o Other (please explain) _____

5. I use compounded alprostadil because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing alprostadil.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded alprostadil at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded alprostadil from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 2.2. Survey instrument for use of alprostadil in combination product

Welcome. We want to understand your clinical use of compounded alprostadil / papaverine HCl / phentolamine. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer alprostadil / papaverine HCl / phentolamine to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer alprostadil / papaverine HCl / phentolamine by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Topical cream
   - o Topical gel
   - o Topical lotion
   - o Topical solution
   - o None of the above

4. I prescribe or administer alprostadil / papaverine HCl / phentolamine for the following conditions or diseases: (check all that apply)

   - o Erectile dysfunction
   - o Other (please explain) _____

5. I use compounded alprostadil / papaverine HCl / phentolamine because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing alprostadil / papaverine HCl / phentolamine.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded alprostadil / papaverine HCl / phentolamine at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded alprostadil / papaverine HCl / phentolamine from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 2.3. Survey instrument for Nurse Practitioners in Women's Health

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?
   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Which of the following compounded drugs do you prescribe or administer to your patients? (please check all that apply)
   - o Alprostadil as a solo product
   - o Alprostadil/Papaverine/Phentolamine as a combination product
   - o Aminophylline
   - o Anastrozole as a solo product
   - o Anastrozole/Testosterone as a combination product
   - o Oxytocin in combination with sildenafil citrate or tadalafil
   - o None of the above

4. Do you prescribe or administer alprostadil as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
   - o Topical cream, lotion, gel and/or solution
   - o Other (please explain) _____
   - o None of the above

5. I prescribe or administer alprostadil as a single agent product for the following conditions or diseases: (please check all that apply)
   - o Female sexual arousal disorder
   - o Other (please explain) _____
   - o None of the above

6. I use compounded alprostadil as a single agent product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing alprostadil.
    - o Other (please explain) _____
7. Do you stock non-patient-specific compounded alprostadil as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure
8. I obtain compounded alprostadil as a single agent product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
9. Do you prescribe or administer alprostadil / papaverine / phentolamine as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Topical cream, lotion, gel and/or solution
    - o Other (please explain) _____
    - o None of the above
10. I prescribe or administer alprostadil / papaverine / phentolamine as a combination product for the following conditions or diseases: (please check all that apply)
    - o Female sexual arousal disorder
    - o Other (please explain) _____
    - o None of the above
11. I use compounded alprostadil / papaverine / phentolamine as a combination product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing alprostadil / papaverine / phentolamine.
    - o Other (please explain) _____

12. Do you stock non-patient-specific compounded alprostadil / papaverine / phentolamine as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure

13. I obtain compounded alprostadil / papaverine / phentolamine as a combination product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

14. Do you prescribe or administer aminophylline as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o IV injection
    - o Oral liquid
    - o Oral capsules
    - o Topical cream, gel and/or ointments
    - o Other (please explain) _____
    - o None of the above

15. I prescribe or administer aminophylline as a single agent product for the following conditions or diseases: (please check all that apply)
    - o Orgasmic dysfunction
    - o Other (please explain) _____
    - o None of the above

16. I use compounded aminophylline as a single agent product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing aminophylline.
    - o Other (please explain) _____

17. Do you stock non-patient-specific compounded aminophylline as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure

18. I obtain compounded aminophylline as a single agent product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
19. Do you prescribe or administer anastrozole as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Subcutaneous or subdermal pellet
    - o Other (please explain) _____
    - o None of the above
20. I prescribe or administer anastrozole as a single agent product for the following conditions or diseases: (please check all that apply)
    - o Hormone replacement
    - o Other (please explain) _____
    - o None of the above
21. I use compounded anastrozole as a single agent product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing anastrozole.
    - o Other (please explain) _____
22. Do you stock non-patient-specific compounded anastrozole as a single agent product at your practice?
    - o Yes
    - o No
    - o I'm not sure
23. I obtain compounded anastrozole as a single agent product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
24. Do you prescribe or administer anastrozole / testosterone as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Subcutaneous or subdermal pellet
    - o Other (please explain) _____
    - o None of the above

25. I prescribe or administer anastrozole / testosterone as a combination product for the following conditions or diseases: (please check all that apply)
    - o Hormone replacement
    - o Other (please explain) _____
    - o None of the above

26. I use compounded anastrozole / testosterone as a combination product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing anastrozole / testosterone.
    - o Other (please explain) _____

27. Do you stock non-patient-specific compounded anastrozole / testosterone as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure

28. I obtain compounded anastrozole / testosterone as a combination product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

29. Do you prescribe or administer oxytocin with sildenafil or tadalafil as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
    - o Oral or sublingual troche
    - o Intravenous or intramuscular injection
    - o Other (please explain) _____

30. I prescribe or administer oxytocin with sildenafil or tadalafil as a combination product for the following conditions or diseases: (please check all that apply)
    - o Increase female orgasm intensity
    - o Induction of labor
    - o Postpartum hemorrhage
    - o Adjunct for induced abortion
    - o Other (please explain) _____

31. I use compounded oxytocin with sildenafil or tadalafil as a combination product because: (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing oxytocin with sildenafil or tadalafil.
    - o Other (please explain) _____
32. Do you stock non-patient-specific compounded oxytocin with sildenafil or tadalafil as a combination product at your practice?
    - o Yes
    - o No
    - o I'm not sure
33. I obtain compounded oxytocin with sildenafil or tadalafil as a combination product from the following: (please check all that apply)
    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____
34. What is your practice setting? (please check all that apply)
    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please explain) _____
35. What degree do you hold? (please check all that apply)
    - o Nurse Practitioner (NP)
    - o Other (please explain) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.