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Current status of intracavernosal injection therapy in erectile dysfunction

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Abstract

Introduction: Erectile dysfunction (ED) is defined as the inability to attain and/or maintain a penile erection. The first introduction of intracavernosal injection (ICI) for the treatment of erectile failure was in 1982 by Virag who reported the positive effects of papaverine on erectile tissue, followed by Brindley concurrently conducting research on ICI therapy with alpha-blockade. ICI remains a viable option for the treatment of ED, even after FDA approval of phosphodiesterase type 5 inhibitors in 1998. The American Urological Association (AUA) and the European Association of Urology (EAU) both recommend ICI as a second-line therapy for the treatment of ED. We herein provide an overview of the current state of ICI therapy for the treatment of ED.

Areas covered: We performed a literature review from 1977-2022, using PubMed and the current AUA and EAU guidelines to discuss the current state of ICI for the treatment of ED.

Expert opinion: Although other oral agents are considered first line for the treatment of ED, the current guidelines and literature demonstrate that ICI is a safe and effective option for patients; however, careful patient selection and counseling should be performed to maximize the effectiveness and safety of this ED treatment.

Keywords: Erectile dysfunction, intracavernosal injection, alprostadil, papaverine, phentolamine, Bimix, Trimix, Quadmix

Article highlights

- ED is defined as the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance.
- We have performed a literature review from 1977-2022, using PubMed and the current AUA and EAU guidelines to discuss the current state of the use of ICI for the treatment of ED.
- The AUA and EAU both recommend ICI as a second-line therapy for the treatment of ED after the use of PDE5 inhibitors. Of note, alprostadil is the only ICI therapy currently FDA approved for ED.
- Although combination therapy with Bimix, Trimix, and Quadmix have proven their efficacy, there is currently no FDA approval for any of these agents, making dosing and standardization of treatment difficult. Despite this, after review of the guidelines and literature regarding treatment for ED, it is clear that ICI is an effective treatment option for patients experiencing significant ED.
- Future directions for these agents are the FDA approval and standardization of dosing.

1. Introduction

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance [1]. The incidence of ED in the general population increases with age, and it is estimated that approximately 52% of men over the age of 40 experience some degree of ED [2]. There are a multitude of etiologies for ED, including vasculogenic, neurogenic, psychogenic, endocrinologic,

and medication-induced ED. The treatment of ED largely consisted of surgery, vacuum erection devices, and psychosocial interventions prior to the introduction of pharmacologic agents [3].

The first introduction of intracavernosal injection (ICI) for the treatment of erectile failure was in 1982 by Dr. Ronald Virag, a cardiovascular surgeon, who reported the positive effects of papaverine on erectile tissue [4]. Dr. Giles Brindley was concurrently conducting research on the effectiveness of phenoxybenzamine as an ICI therapy for ED [5]. His findings were published shortly after Virag; however, Brindley is most famous for his personal demonstration of ICI therapy's efficacy while at the 1983 American Urological Association's (AUA) Annual Meeting in Las Vegas, where he performed ICI on himself, using various vasoactive agents prior to his speech to give visual proof to his hypothesis.

During a normal erection after sexual stimulation, parasympathetic nerve endings release nitric oxide, which activates guanylate cyclase (GC) in the smooth muscle (SM) cell. In turn, GC converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP), which decreases the amount of intracellular calcium by activating protein kinase G, leading to the phosphorylation of potassium and calcium channels. This causes dilation of arterioles and relaxes the trabecular SMs, leading to an erection [Figure 1]. The increased pressure within the sinusoidal spaces in the cavernosal tissues presses against the tunica albuginea and prevents venous outflow of blood, allowing for the erection to be maintained. Phosphodiesterase (PDE), especially PDE type 5 (PDE5), is in high concentration within the cavernosal tissues and decreases the levels of cGMP, thus causing the contraction of the SM needed for detumescence. PDE5 inhibitors impede this pathology, thereby promoting the erectile response. Pharmacotherapies used in the treatment of ED take advantage of these physiologic pathways [6].

ICI remains a viable option for the treatment of ED, even after the introduction and FDA approval of oral PDE5 inhibitors in 1998 [7]. The AUA and the European Association of Urology (EAU) both recommend ICI as a second-line therapy for the treatment of ED after the use of PDE5 inhibitors or if PDE5 inhibitors are contraindicated. We herein provide an overview of the current state of ICI for the treatment of ED [1,8].

2. Overview of the Market

The therapeutic agents that are currently available for the treatment of ED include those administered orally, transurethrally, and by ICI. Of these agents, PDE5 inhibitors are consistently used as first-line agents, followed by those administered transurethrally and by ICI. The agents discussed in this review can be used as a single agent; however, they are often used in combination for a synergistic effect. The main concerns regarding ICI therapies are the unwanted side effects, such as prolonged erection/priapism, pain, hematoma, and cavernosal fibrosis. Further research on improving efficacy of these agents, via clinical trials, is needed in addition to FDA approval and dosage standardization to limit side effects.

3. Introduction of compounds

There are a multitude of therapeutic agents and combinations that are currently available for the treatment of ED via ICI. In this section, we provide a brief introduction of these available agents, which will be discussed further throughout this manuscript [16-30] [Table 1].

4. Pharmacodynamics

4.1.1 Alprostadil- Alprostadil is a prostaglandin E1 (PGE1) synthetic analog that binds as an agonist to prostaglandin (PG) receptors, activating AC and thus leading to

accumulation of cAMP. This increase in cAMP leads to a reduction in the influx of calcium, which is responsible for the pharmacologic effects, including SM relaxation, vasodilation, bronchodilation, and inhibition of platelet aggregation [9]. Alprostadil induces erection by relaxation of trabecular SM and by dilation of cavernous arteries. This leads to the expansion of lacunar spaces and entrapment of blood by compressing venules against the tunica albuginea. Alprostadil has also demonstrated to act at presynaptic α-adrenergic receptors (ARs) to decrease the release of noradrenaline release and thus decreasing the sympathetic response that normally leads to detumescence [10].

4.1.2 Papaverine- Papaverine is a benzylisoquinoline alkaloid of opium that acts as a nonspecific PDE inhibitor in SM cells, thereby causing an increase in intracellular cAMP and cGMP. This pathway induces SM relaxation with a subsequent increase in arterial flow into the corpora cavernosa and a decrease in venous outflow, leading to penile erection [11].

4.1.3 Phentolamine- Phentolamine mesylate is an α1- and α2-selective AR antagonist, thus causing vasodilation via SM relaxation. Phentolamine, through α-adrenergic inhibition, blocks the sympathetic pathway to detumescence, but, as a monotherapy, it does not induce an erection [12].

4.1.4 Aviptadil- Aviptadil is a synthetic vasoactive intestinal polypeptide that increases the activity of AC, leading to cavernosal SM relaxation with subsequent filling of the cavernous sinuses [13].

4.1.5 Bimix- Bimix is the result of the combined properties of both papaverine and phentolamine. Phentolamine supplements the action of papaverine by decreasing

arterial resistance and promoting vasodilation through both pathways in congruence [14].

4.1.6 **Trimix-** Trimix consists of a combination of papaverine, phentolamine, and alprostadil. Mechanistically, Trimix is like Bimix with the addition of alprostadil's accumulation of cAMP and reduction in the influx of intracellular calcium. This leads to greater SM relaxation and vasodilation [14].

4.1.7 **Quadmix-** Quadmix consists of a combination of papaverine, phentolamine, alprostadil, and atropine. Atropine sulfate, at high doses, is hypothesized to assist in the release of endothelium-derived relaxing factor, which is formed from L-arginine in endothelial cells. Acting through soluble GC in the vascular SM cells with the production of cGMP, Quadmix causes vasodilation and inhibits platelet adhesion and aggregation [15].

5. Pharmacokinetics

The pharmacokinetic principles of these agents, including absorption, distribution, metabolism, and excretion, are briefly listed in Tables 2 and 3 [16-30]. Due to the limited literature on the pharmacokinetics of these combination agents, further investigation into these agents is needed.

6. Clinical Efficacy

6.1.1 Alprostadil- Alprostadil is currently the only FDA-approved injectable medication for ED and is available in two formulations (alprostadil-alfadex and alprostadil sterile powder) [31]. At dosages of 10-20 mcg, alprostadil produces full erections in 70-80% of patients with ED [24,32]. Linet et al. performed three separate multi-institutional, prospective studies evaluating the efficacy and tolerability of alprostadil [33]. In one of the studies, the causes of ED were multifactorial in nature, and the assessment of satisfactory sexual activity was ascertained by both the study participant and the partner. Of the 13762 injections given to the 683 men enrolled, 11924 resulted in satisfactory sexual activity. Porst also demonstrated a response rate of over 70% in 4577 men who used intracavernosal alprostadil [34]. Of note, combination therapies have been found to be about twice as effective as PGE1 alone, more cost efficient, and usually without the discomfort associated with intracavernosal PGE1 injections; thus, the use of combination therapy is increasing when compared to alprostadil monotherapy.

6.1.2 Papaverine- Papaverine, as an intracavernosal monotherapy, is approximately 60% effective in promoting penile erection [32]. In a study by Yasumoto et al., a

total of 6 patients were injected with 40 mg/ml of papaverine hydrochloride monotherapy, with 4 of the patients having nonfunctional expansion. The monotherapy of papaverine was compared to PGE1, which was given to the same 6 patients. All patients demonstrated incomplete functional erections [35]. Papaverine is not approved for monotherapy by the FDA and is typically injected in combination formulations, as the risk for adverse events were demonstrated to be worse when administered alone. However, papaverine is administered alone in developing countries.

6.1.3 Phentolamine- Phentolamine is often administered in combination with other medications, such as alprostadil or papaverine, due to its weak efficacy as a monotherapy and its lack of FDA approval [36]. As a competitive antagonist at both α1- and α2-ARs, phentolamine's erectogenic effect is mediated by blocking the (antierectile) postsynaptic α1-AR [37]. Because of its potential for inhibition of the prejunctional α2-AR, which interferes with norepinephrine reuptake, the drug's erectogenic effect is believed to be antagonized [38]. This dual effect of the drug probably accounts for its limited success when administered intracavernosally as a sole agent [39]. Oral phentolamine at doses of 40 or 80 mg has demonstrated improvement in erectile function when evaluated with the International Index of Erectile Function (IIEF-5). Approximately 59% of men were able to achieve vaginal penetration in a randomized controlled trial [36]. Due to these positive results, oral phentolamine is available in many South American countries.

6.1.4 Aviptadil- Aviptadil has had disappointing effects when administered alone; however, when separately combined with other drugs, such as papaverine and phentolamine, erectile responses were elicited [13,40]. Aviptadil, in combination with phentolamine, is currently being sought for regulatory approval in the United States; however, it has been approved in Europe since 2000 [30]. In an open, multicenter, randomized crossover study comparing the efficacy and preference of alprostadil to aviptadil/phentolamine, 187 men were enrolled, and both agents were found to elicit comparable penile erections satisfactory for penetration [41]. A favorable side-effect profile with this combination was reported, as the incidence of priapism, pain, and fibrosis was low at 0.06, 0.5, and 0%, respectively, after a 12-month follow-up. Aviptadil/phentolamine is also effective in patients who do not respond to other single monotherapy injections, with efficacy rates of 67–73% [30]. Aviptadil/phentolamine has been clinically approved in the United Kingdom, in Denmark, and in New Zealand.

6.1.5 Bimix- Zorgniotti and Lefleur established the popularity of Bimix with the results of their study in 1986. During in-office testing, they observed an increased average response rate of 60-70% [42] when compared with monotherapy injections of alprostadil. In a recent multicenter study evaluating Bimix in 157 men, Bernie et al. noted a 94% efficacy rate, with a 0.9% to 2.6% side-effect incidence of priapism, pain, or hematoma [43]. The combination of phentolamine and papaverine, though not FDA approved in the United States, is approved and available for use in many European countries.

6.1.6 **Trimix-** Bernie et al., in a prospective study with 175 men enrolled, compared Trimix to PGE1 monotherapy. Trimix produced a longer-lasting, satisfactory erection but also increased the risk of priapism [43]. The study participants were evaluated via the IIEF-5, Quality of Erection Questionnaire, Sexual Quality of Life, and Erectile Dysfunction Inventory of Treatment Satisfaction, which indicated that combination therapy was noninferior to PGE1 alone. Interestingly, the group, who was treated with the higher dosage of Trimix, exhibited the largest risk of priapism [43]. Kulaksizoglu et al. noted that patients obtained comparable satisfactory penile erections with Trimix, when compared to PGE1, but patients preferred Trimix therapy [43]. A clinical double-blind study by Shenfeld et al. recorded that Trimix was superior to Bimix when administered to 20 impotent patients [45]. Bennet et al. described rigid erections in 50 to 62% of nonresponders to oral medications, suggesting that Trimix can offer treatment benefit for individuals who failed to respond to monotherapy with alprostadil or combination therapy with Bimix [46].

6.1.7 **Quadmix-** Hatzimourtidis reported that 95% to 100% of patients with ED achieved sustained rigidity after dose titration with Quadmix [47]. Montorsi et al. demonstrated that 96% of their patients with vasculogenic ED reported sustained erections suitable for penetration. Montorsi et al., who administered Quadmix to 56 patients with corporal veno-occlusive ED, also noted that 95% of their patients achieved rigid and sustained erections. [12]. One study observed less impressive results, with no statistically significant difference between pharmacologic injections enriched with or without atropine [15]. The hypothesis is that the

addition of atropine increases the synergism of the Trimix combination, continuing to enhance SM relaxation within the cavernous sinusoids and helicine arteries. As demonstrated by Baniel et al., the addition of atropine resulted in the improvement of several measurable hemodynamic events during an erection, including arterial dilation, venous compression, and sinusoidal relaxation [48].

7. Safety and Tolerability

7.1.1 Alprostadil- The use of ICI of alprostadil can cause a variety of adverse reactions, with penile pain as the most commonly reported. This was noted in 37% of patients who underwent treatment for up to 18 months [49, 50]. Other adverse reactions include priapism, penile fibrosis, injection-site hematoma, ecchymosis, penile rash, and penile edema [33]. These reactions were reported by 4% or less of patients who underwent treatment. Other noted symptoms include penile numbness, irritation, sensitivity, pruritus, erythema, skin tearing, and discoloration. Patients also experienced systemic adverse reactions, including hypotension, dizziness, and headache. Contraindications include sickle cell anemia or trait, multiple myeloma, and leukemia, conditions that would increase the risk of priapism. Other contraindications include those with fibrotic penile conditions, such as anatomical deformation, angulation, cavernosal fibrosis, Peyronie's disease, or penile implants [24].

7.1.2 Papaverine- As demonstrated by Moemen et al., priapism and corporal fibrosis were more commonly observed with papaverine when compared to PGE1 and

Trimix [51]. However, a noted risk to consider with ICI of papaverine is hepatotoxicity. A study analyzing the incidence of hepatotoxicity with ICIs of papaverine revealed that 2 out of 71 patients developed elevated liver function tests (LFTs) during treatment. This study recommended monitoring LFTs every 6 months [52].

7.1.3 **Phentolamine-** Due to similar mechanistic outcomes including SM relaxation and vasodilation, adverse reactions of phentolamine are similar to those of alprostadil [40]. Common side effects associated with this drug include systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset when given both orally and intracavernosally [30].

7.1.4 **Aviptadil-** In addition to having similar adverse reactions to the abovementioned medications, aviptadil injections can also cause transient facial flushing. This adverse effect was reported by 33.9% of patients in a study evaluating the side-effect profile and efficacy of aviptadil injections [53].

7.1.5 **Bimix-** Adverse reactions to Bimix injections are similar to those of the abovementioned medications. Short-term effects include priapism and penile pain, while a long-term side effect is cavernosal fibrosis. As Bimix is a combination of papaverine and phentolamine, hepatotoxicity is an adverse reaction to consider [54].

7.1.6 **Trimix-** Trimix has adverse reactions similar to the abovementioned adverse reactions. The prevalence of penile pain is reduced relative to alprostadil injections, as there are decreased levels of PG. Trimix also requires more complicated storage as well as preparation, which is important to consider [55].

While having similar side effects to alprostadil monotherapy, Trimix has a lower incidence of penile pain in part due to the lower dose of alprostadil [24]. One of the disadvantages is the increased incidence of fibrosis due to papaverine when compared with alprostadil monotherapy [40].

7.1.7 Quadmix- Adverse reactions are similar to Trimix. Additionally, Quadmix also requires relatively more complex preparation and storage similar to Trimix. Other adverse effects more specifically attributed to Quadmix include dizziness, plaque formation (7%), and subcutaneous hemorrhage (4%) [12]. In one study, small nodules were also reported in 57% of patients after more than 12 months of use [56,57].

8. Conclusion

ED is a condition that affects a multitude of men and is multifactorial in its etiology. There are numerous treatments for ED, including conservative lifestyle measures, medicinal agents, and surgical therapy. A thorough history, physical exam, laboratory workup, and an overall health assessment should be performed to provide the best treatment options. Although conservative measures are considered a viable treatment option per the AUA and EAU guidelines, there is a lack of sufficient evidence to support any one lifestyle modification as a definitive treatment option [1]. If conservative measures fail to improve erectile failure, then medical therapy is indicated.

Of the therapeutic agents used in the treatment of ED, oral PDE5 inhibitors are considered first-line therapy in both the AUA and EAU guidelines. In men who continue to experience ED after the use of oral agents or who have contraindications to the use of PDE5

inhibitors (eg, nitrates), ICI is considered second-line therapy, with penile prosthesis placement considered a third-line option. Of the agents used for ICI, alprostadil is the only FDA-approved agent for the treatment of ED. As discussed, combination therapies have demonstrated even greater efficacy than alprostadil alone. Specifically, Trimix has demonstrated a success rate of 92% and has a lower incidence of penile pain than alprostadil alone [8]. Although combination therapies have proven their efficacy, there is currently no FDA approval for any of these agents, making dosing and standardization of treatment difficult. ICI therapy has also demonstrated a high treatment withdrawal rate up to 79.9 percent. Reasons for withdrawal include poor treatment response, adverse event(s), and inconvenience of use [58]. Despite this, after review of the guidelines and literature regarding treatment for ED, it is clear that ICI can be an effective treatment option for patients experiencing significant ED.

9. Expert Opinion

In regard to ICI therapy in the treatment of ED, we believe that the key areas of improvement, including future directions of research, should concern the obtainment of FDA approval and the dosage standardization of these agents. To date, alprostadil is the only FDA-approved agent. In addition, the only ongoing trials involving ICI therapy for ED include experimental agents, such as platelet-rich plasma, umbilical cord mesenchymal cells, stem cells (SCs), and botulinum toxin. Further research into this field would expand the use of this therapy and potentially improve the efficacy of these agents by optimizing the current drug combinations and minimizing any side effects. Oral PDE5 inhibitors, unless contraindicated, are considered first-line therapy for ED. However, in a substantial proportion of patients (30%), the effectiveness of PDE5 inhibitors is unsatisfactory, with 46% of patients quitting oral medication

largely due to the lack of efficacy [2]. This demonstrates a need for ICI therapy to aid patients who are refractory to oral agents.

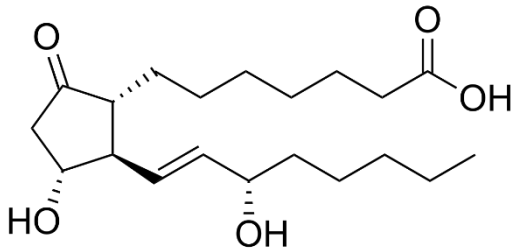
Of the agents currently under investigation, the use of SCs injected intracavernosally to improve erectile function is of particular interest. Although the exact mechanism of how SCs promote improvement is unclear, the current theory is that SCs have a paracrine effect on the cavernosal tissues, thereby promoting the differentiation of cells into SM cells, vascular endothelial cells, and even neurons, all of which are needed to obtain spontaneous erections. To investigate the effects of SC therapy for ED, Mirzaei et al. performed a single-blinded clinical trial with 20 diabetic patients. A sample of oral mucosa, which was collected from each patient in the experimental group, underwent incubation, and researchers carefully separated the SCs from the rest of the sample. These patients were injected once intracavernosally and evaluated with the IIEF-5 before and after the therapy. The patients in the control group, who underwent ICI of normal saline alone, were also evaluated with the IIEF-5 before and after the injections. While this was a small-scale study, the results demonstrated a positive trend in peak systolic velocity, resistance index, and IIEF-5 scores in the experimental group as compared to the control group, without any noted adverse events or side effects [59].

Although the findings of this study indicate a promising modality for ED, there are limitations in the use of SC therapies. More specifically, in this study, the process of collecting and shipping the sample to the lab was time consuming, with a total processing time of 10 days [59]. If this therapy were to acquire FDA approval for this indication, it could be inaccessible and unrealistic for many patients due to the time commitment and the shipping expenses associated with this type of collection. However, this study demonstrates the concept that ICI of SCs, even after a single dose, could potentially circumvent the need for surgery. This finding is

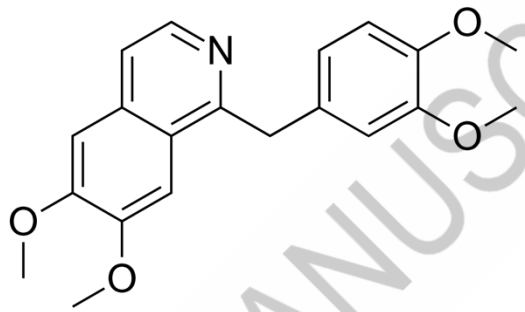
equally promising, as the current medical treatment of ED involves the use of on-demand administration to achieve desired effects. If SC therapies were to become widely available to patients, it could change the landscape of the treatment of ED by reducing the frequency of treatments.

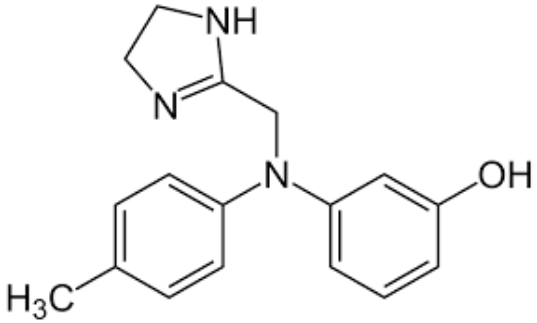
Our position is that the treatment of ED with ICI will continue to expand and improve over the course of the next decade. As demonstrated in our review, these agents are a safe and effective option for the appropriately selected patient and provide a unique niche in the treatment of ED. As discussed, the ICI of SCs is a promising novel therapy and may become more widely available for the treatment of ED, especially as technologies continue to improve. However, prior to incorporating the ICI of SCs into the algorithm of ED treatment, further studies regarding their mechanism of action are needed. The future of this area of pharmacology is encouraging, and continued research may significantly impact the treatment of ED by providing another medical modality, reducing the need for surgical options, and decreasing the need for on-demand agents to achieve spontaneous erections.

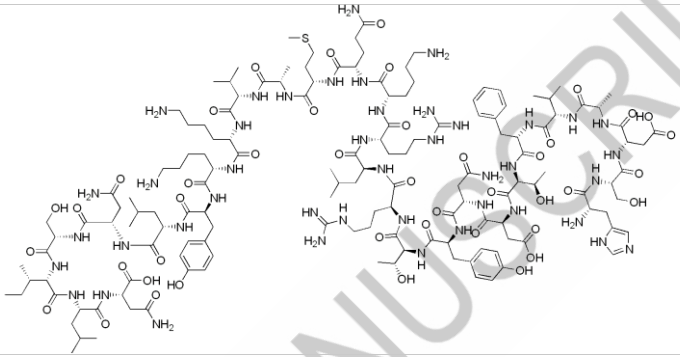
Drug Summary Boxes

Drug Name	**Alprostadil**
Phase	FDA approved
Indication	ED
Pharmacologic description	Prostaglandin analog
Chemical structure	
Pivotal paper	Lea et al. [9]

Route of administration	Intracavernosal

Drug Name	**Papaverine**
Phase	Off-label
Indication	ED
Pharmacologic description	Opioid alkaloid
Chemical structure	
Pivotal paper	Le et al. [14]
Route of administration	Intracavernosal

Drug Name	**Phentolamine**
Phase	Off-label
Indication	ED
Pharmacologic description	α1- and α2-adrenergic antagonist
Chemical structure	
Pivotal paper	Goldstein [36]
Route of administration	Intracavernosal

Drug Name	Aviptadil
Phase	Off-label, Approved in some European countries
Indication	ED
Pharmacologic description	Synthetic vasoactive intestinal polypeptide analog
Chemical structure	
Pivotal paper	Dinsmore and Wyllie [13]
Route of administration	Intracavernosal

Drug Name	Bimix
Phase	Off-label, Approved in some European countries
Indication	ED
Pharmacologic description	Phentolamine, Papaverine
Chemical structure	See above
Pivotal paper	Zorgniotti and Lefleur [42]
Route of administration	Intracavernosal

Drug Name	Trimix
Phase	Off-label
Indication	ED

Pharmacologic description	Phentolamine, papaverine, alprostadil
Chemical structure	See above
Pivotal paper	Bernie et al. [43]
Route of administration	Intracavernosal

Drug Name	**Quadmix**
Phase	Off-label
Indication	ED
Pharmacologic description	Phentolamine, papaverine, alprostadil, atropine
Chemical structure	See above
Pivotal paper	Montorsi et al. [12]
Route of administration	Intracavernosal

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Declaration of interest

W J G Hellstrom reports being a Consultant for Acerus Pharma, Boston Scientific, Coloplast, Endo, and Jazz Pharmaceuticals; and an Advisory Board Member for Gilead, Maximus, Promescent, and Theralogix. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Table 1: Therapeutic intracavernosal injection agents for the treatment of erectile dysfunction.

Drug Name	Chemical Name	MW[3]	MOA[4]	Uses
Alprostadil (PGE1)[1]	7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl] heptanoic acid	354.5 g/mol	Agonist of prostaglandin receptors activating AC[5]	ED[7], maintain patency of patent ductus arteriosus
Papaverine	1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline;hydrochloride	375.8 g/mol	Nonspecific PDE[6] inhibitor	Arterial vasospasm
Phentolamine	3-[N-(4,5-dihydro-1H-imidazol-2-ylmethyl)-4-methylanilino]phenol	281.4 g/mol	Competitive α-1 and α-2 adrenergic antagonist	Hypertensive crisis, diagnosis and treatment of pheochromocytoma episodes, prevention of dermal necrosis following norepinephrine administration
Aviptadil	IUPAC name[2]	3326.8 g/mol	Synthetic vasoactive intestinal peptide analog increasing activity of AC	Off-label: COVID-19, ARDS
Bimix	See chemical name for papaverine and phentolamine	See MW of papaverine and phentolamine	See MOA of papaverine and phentolamine	See uses of papaverine and phentolamine
Trimix	See chemical name for papaverine, phentolamine, and alprostadil	See MW of papaverine, phentolamine, and alprostadil	See MOA of papaverine, phentolamine, and alprostadil	See uses of papaverine, phentolamine, and alprostadil
Quadmix	α-(hydroxymethyl)-, 8-methyl-8-azabicyclo[3.2.1.]oct-3-yl ester, endo –(±)-, sulfate (2:1) (salt), monohydrate. See chemical name for papaverine, phentolamine, and alprostadil	Atropine: 289.4 g/mol See MW of papaverine, phentolamine, and alprostadil	Atropine: antimuscarinic, releases endothelial-derived relaxing factor See MOA of papaverine, phentolamine, and alprostadil	Atropine: temporary blockade of severe muscarinic effects, treatment of poisoning by organophosphates, mydriasis, and cycloplegia See uses of papaverine, phentolamine, and alprostadil

[1]**Misoprostol is another analog of prostaglandin E1 (PGE1) used to prevent nonsteroidal anti-inflammatory drug-induced peptic ulcers and to promote uterine contractions. Alprostadil can also be administered intraurethrally to induce erections.**
[2](2*S*)-4-amino-2-[[(2*S*)-2-[[(2*S*,3*S*)-2-[[(2*S*)-2-[[(2*S*)-4-amino-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-6-amino-2-[[(2*S*)-6-amino-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-5-amino-2-[[(2*S*)-6-amino-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*,3*R*)-2-[[(2*S*)-2-[[(2*S*)-4-amino-2-[[(2*S*)-2-[[(2*S*,3*R*)-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-amino-3-(1*H*-imidazol-5-yl)propanoyl]amino]-3-hydroxypropanoyl]amino]-3-carboxypropanoyl]amino]propanoyl]amino]-3-methylbutanoyl]amino]-3-phenylpropanoyl]amino]-3-hydroxybutanoyl]amino]-3-carboxypropanoyl]amino]-4-oxobutanoyl]amino]-3-(4-hydroxyphenyl)propanoyl]amino]-3-hydroxybutanoyl]amino]-5-carbamimidamidopentanoyl]amino]-4-methylpentanoyl]amino]-5-carbamimidamidopentanoyl]amino]hexanoyl]amino]-5-oxopentanoyl]amino]-4-methylsulfanylbutanoyl]amino]propanoyl]amino]-3-methylbutanoyl]amino]hexanoyl]amino]hexanoyl]amino]-3-(4-hydroxyphenyl)propanoyl]amino]-4-methylpentanoyl]amino]-4-oxobutanoyl]amino]-3-hydroxypropanoyl]amino]-3-methylpentanoyl]amino]-4-methylpentanoyl]amino]-4-oxobutanoic acid
[3]MW: Molecular Weight.
[4]MOA: Mechanism of Action.
[5]AC: Adenylate cyclase.
[6]Phosphodiesterase.
[7]ED: Erectile Dysfunction.

Table 2: Pharmacokinetics of intracavernosal injection agents used for the treatment of erectile dysfunction.

Drug	Dosage	AUC[1]	Cmax[2]	Half-life	VOD[3]
Alprostadil	Individualized dose by titration; Titrate by 2.5 mcg, then by 5-10 mcg intervals until erection of <1 hr maintained; not to exceed 40 mcg or 60 mcg depending on formulation used Neurogenic ED: Initial 1.25mcg, then titrate 1.25-2.5mcg, then by 2.5-5mcg until erection of <1hr	173 ± 115 pg·min/mL	16.8 ± 18.9 pg/mL (20 mcg edex)	9-11 minutes	N/A
Papaverine	20-80 mg/injection; injections given with a minimum of 24hrs between doses no more than 3 doses/week	21.46 ± 5.71 (h·mg/L)	N/A	1-2hrs	15% of body weight
Phentolamine	0.5-1 mg/injection; limit to one dose/day and no more than 3 doses/week [11]	Limited literature[4]		30 minutes	Limited literature[4]

Aviptadil	As monotherapy, no dose has induced a useful erection Invicorp: combination therapy consisting of 25µg aviptadil, 2mg phentolamine mesilate	Limited literature[4]	1-2 minutes	14ml/kg
Bimix	0.25-1.5 mg phentolamine, 7.5-45 mg papaverine [11]	Limited literature[4]		
Trimix	0.2-0.4 mg phentolamine, 8-16 mg papaverine, 10-20 mcg alprostadil [11]	Limited literature[4]		
Quadmix	50 mg papaverine hydrochloride, 10 mcg alprostadil, 0.2 mg phentolamine mesylate, 0.075 mg of atropine sulfate [15]	Limited literature[4]		

[1]AUC: Area under the curve. The AUC for alprostadil is for intracavernosal injection (ICI). The AUC for papaverine is for intravenous administration. There is little data on the AUC for ICI for many of these agents.
[2]Cmax: Maximum concentration.
[3]VOD: Volume of distribution.
[4]Information was not obtained.

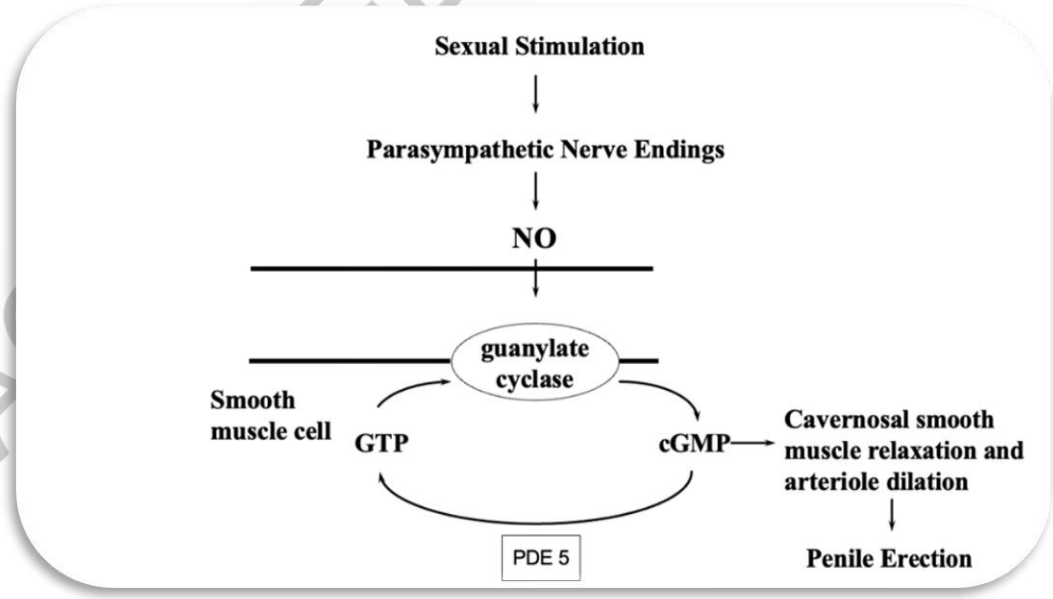
Table 3: Metabolization of intracavernosal injection agents used for the treatment of erectile dysfunction.

Drug	Metabolization	Metabolites	Excretion
Alprostadil	Locally or via the lung via β- and ω-oxidation after being absorbed systemically	13,14-dihydro-15-oxo-PGE_1*	Kidney (90%), feces (10%)
Papaverine	Liver	4'-desmethylpapaverine, 6-desmethylpapaverine, 7'-desmethylpapaverine, 4í,6-didesmethylpapaverine and 3í-	Kidney

		desmethylpapaverine	
Phentolamine	Liver	[3-[N-(4,5-dihydro-1H-imidazol-2-ylmethyl)-4-methylanilino]phenyl] hydrogen sulfate	Kidney (80%), feces (20%)
Aviptadil	Lungs	N/A	Kidney
Bimix	See above	See above	See above
Trimix	See above	See above	See above
Quadmix	Atropine: Liver (~50%), rest of dose remains unchanged until excretion	Atropine: unchanged atropine (50%), Noratropine (24%), atropine-N-oxide (15%), tropine (2%), tropic acid (3%)	Atropine: Kidney

*Prostaglandin E1.

Figure 1: This schematic demonstrates the mechanism of a penile erection. There is crosstalk from another mechanism involving the activation of adenylate cyclase (AC), which leads to the intracellular accumulation of cyclic adenosine monophosphate (cAMP). Both alprostadil and aviptadil exploit the cAMP pathway to induce their effects.



Abbreviations (in order of use):

1. erectile dysfunction – ED
2. intracavernosal injection – ICI
3. American Urological Association – AUA
4. guanylate cyclase – GC
5. smooth muscle – SM
6. cyclic guanosine monophosphate – cGMP
7. phosphodiesterase – PDE
8. phosphodiesterase type 5 – PDE5
9. European Association of Urology – EAU
10. adenylate cyclase – AC
11. cyclic adenosine monophosphate – cAMP
12. prostaglandin E1 - PGE1
13. molecular weight – MW
14. mechanism of action – MOA
15. prostaglandin – PG
16. adrenergic receptor – AR
17. area under the curve – AUC
18. maximum concentration – Cmax
19. volume of distribution – VOD
20. International Index of Erectile Function – IIEF-5
21. liver function tests – LFTs
22. stem cell – SC