Contemporary intracavernous pharmacotherapy for erectile dysfunction in the aging male

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With the introduction of phosphodiesterase type-5 inhibitors as a first-line, oral treatment for erectile dysfunction, intracavernous injection of vasoactive agents is regarded as a secondary therapy for most patients. However, clinicians evaluating the aging male must be aware of this important group of safe and effective therapies, since patients may be more appropriately treated for their erectile dysfunction with intracavernous prostaglandin E-1, papaverine or phentolamine (alone or in combination) owing to the presence of absolute contraindications to phosphodiesterase type-5 use, a failure to respond to these agents or patient preference. Ongoing research continues to define new options for the intracavernous treatment of erectile dysfunction, including gene transfer therapy. These efforts will probably result in the introduction of novel therapies with greater efficacy, tolerability and a more rapid onset of action, as an ever-expanding number and combination of agents is investigated. Until then, contemporary intracavernous vasoactive treatments will continue to successfully restore erectile function among patients with diverse erectile dysfunction etiologies and a variety of comorbidities.

The prevalence of erectile dysfunction (ED) is increasing and is expected to double over the next 20 years, effecting 300 million men worldwide by the year 2025 [1]. The combination of a rapid increase in the age of the world population, growing prevalence of comorbid conditions, such as diabetes and cardiovascular disease, and a better understanding of ED by patients has resulted in men seeking primary and specialty care for sexual concerns in ever-increasing numbers [2]. Advances in pharmacologic therapy, including the introduction of the oral phosphodiesterase type-5 (PDE-5) inhibitors sildenafil (Viagra®, Pfizer, NY, USA), tadalafil (Cialis®, Lilly-ICOS, IN, USA) and vardenafil (Levitra®, Bayer AG, Germany), coupled with an enhanced understanding of the physiology and pathophysiology of penile erection and causes of ED have contributed to a growing awareness by physicians and their patients of the importance of satisfactory sexual function [3].

Clinical experience indicates ED is commonly associated with aging; current estimates suggest that over half of men aged 40–70 years are unable to attain or maintain a penile erection sufficient for satisfactory sexual performance, with the prevalence of ED climbing to more than 75% in men aged over 70 years. [4–6] However, approximately 60% of the elderly population expresses an interest in maintaining sexual activity [7]. Therefore, it is not surprising that 68% of men and 60% of women are ‘in favor’ of older individuals using medical treatments to aid in sexual activity [8]. However, although ED has been shown to negatively affect quality of life in approximately a third of sexually active men and strained personal relationships for another 40%, it remains surprising that only a quarter of these men had discussed their problem with a healthcare professional. In an era of widespread media coverage, and the term ‘ED’ recognizable and more socially acceptable, it is essential to understand that 80% of men who had not consulted their medical practitioner expressed a willingness to discuss their problem if the topic was raised by their clinician [9]. Clearly, we have yet to completely overcome the reluctance of patients and/or their physician to explore ED as part of the general medical evaluation of the aging male.

In this report, pharmacologic and clinical information for the intracavernous agents used commonly in the treatment of ED is reviewed, with a special focus on the aging male, including indications for use and injection technique.

The role of intracavernous injection therapy in the treatment of ED Worldwide, oral PDE-5 inhibitors have emerged as the preferred first-line treatment of erectile dysfunction, owing to their safety, efficacy and ease of use [10]. For most men, current treatment algorithms emphasizing a minimally invasive and patient self-directed approach for the evaluation and treatment of ED are entirely appropriate [11].

Keywords: aging, impotence, injections, penile erection, pharmacotherapy

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Approaches such as this are time and cost effective, allowing for the majority of patients to achieve an effective result using these oral agents, without the need for extensive or specialized testing. Details outlining diagnosis, evaluation and treatment approaches for ED in the aging male fall outside the scope of this report; reviews by Morales, Rosen and Montague and colleagues are suggested for interested readers [3,12,13].

Intracavernous injection (ICI) of vasoactive agents remains the first-line therapy for select patients and a valuable treatment option for nonresponders to PDE-5 inhibitors or those that cannot tolerate the side effects of oral agents [14,15]. Although ICI therapy produces a predictable clinical effect with minimal systemic absorption and side effects, the need for needle delivery and the effectiveness of oral agents has resulted in only 14% of clinicians using ICI as their primary modality for treatment of ED [16]. Clinically, prostaglandin E-1 (PGE-1), papaverine and phentolamine, are the most commonly used injectable vasoactive agents for the diagnosis and treatment of ED. ICI remains a mainstay of ED management as local single-agent or combination vasoactive therapy offers several potential advantages to the patient, including a rapid onset of action, reduced incidence of systemic complications and drug interactions compared with systemic treatment and dependable efficacy for vascular and nonvascular (hormonal, neurogenic or psychogenic) forms of ED [17]. Patients who have failed first-line oral pharmacotherapy constitute the largest group of men considering ICI, with a significant erectile response rate of greater than 85% demonstrated among PDE-5 inhibitor nonresponders, indicating that progression to second-line injection therapy is appropriate [18–20]. Difficult to treat groups, including men with ED and severe forms of diabetes, vascular insufficiency, pelvic trauma, spinal cord injury and early post-radical prostatectomy, are often treated most reliably for their ED with ICI [21–24].

Owing to the underlying simplicity of agent and delivery, ICI has proven to be a robust means of treating ED, as evidenced by a recent study of 300 aging men (average age 67 years) in whom a full erection was observed in 75% of those treated with ICI [25]. The response rate of ICI is not affected by age [26]. In our view, for patients who fail, cannot tolerate or are contraindicated to first-line oral treatments, this nerve-independent form of reversible therapy represents an important, and often under-used, treatment option (Boxes 1 & 2). Not only has ICI gained worldwide acceptance as a safe and effective treatment for ED, but many of the treatment advances over the past 20 years can be traced to research in erectile physiology, ignited by the landmark discovery that direct injection of a vasoactive agent into the corpora cavernosa created an erection [27–30].

Review of clinical intracavernous vasoactive agents

Prostaglandin E-1

Prostaglandin E-1, the most widely used injectable vasoactive agent, is commonly prescribed for patients who fail first-line oral pharmacotherapy [15]. Since its introduction nearly 20 years ago, a vast body of evidence has accumulated describing efficacy and safety of PGE-1 and, in 1996, it became the first and only US FDA-approved injectable intracavernous drug for the management of ED [31,32]. PGE-1 modulates adenyl cyclase, upregulating cyclic adenosine monophosphate (cAMP) and leading to decreased free calcium concentrations in the penis. PGE-1 also modulates noradrenaline release, inhibiting sympathetic activity and further enhancing erectile function [33]. A plasma half-life of less than 1 min is observed, since PGE-1 is metabolized through rapid pulmonary clearance of up to 90% during first passage through the lung. The liver, kidney and local metabolism within the penis also contribute to the conversion of PGE-1 to inactive metabolites [34].

Our current protocol for PGE-1 therapy is focused upon informing the patient about the agent, its use and possible side effects, as well as teaching self-injection in a comfortable, monitored environment (Box 3). An initial dose of 5–10 µg for the male with vasculogenic ED is recommended, while patients with underlying neurological disease or suspected normal vasculature begin with a lower dose of 2.5 µg. The patient performs the injection under supervision, followed by sexual self-stimulation in private. Adjustments are made based upon erectile response and duration of action, with a goal of rigidity persisting for 15–45 min. An illustrated information packet is provided to the patient and includes information on priapism (prolonged erection greater than 4 h), penile fibrosis and scarring, injection technique and dose adjustment. Recommended dose increases are in increments of 2.5–5 µg, with a minimum of 24 h between injections. Careful physical examination is performed prior to the onset of
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Patient desire for greater rigidity and duration of erection than achievable with oral agents.

Poor visual acuity, not allowing for safe needle delivery of vasoactive injection therapy.

Use of monoamine oxidase inhibitors: limits use of phenylephrine as a concurrent vasoactive agent.

Box 2. Contraindications for intracavernous injection therapy (absolute and relative).

- History of multiple episodes of priapism with vasoactive drug use.
- Severe penile fibrosis.
- Use of monoamine oxidase inhibitors: limits use of phenylephrine as a concurrent vasoactive agent.
- Poor visual acuity, not allowing for safe needle delivery of vasoactive agent.

Box 1. Ideal patient characteristics for intracavernous injection therapy.

- Patient use of nitrates or potential use of nitrates.
- Failure of first-line oral phosphodiesterase-5 inhibitor therapy (sildenafil, tadalafil or vardenafil).
- Neural injury from pelvic radiation, surgery or trauma.
- Diabetic patients or severe vascular disease (often after failed first-line therapy).
- Patient expectations for rapid onset of erection.
- Patient desire for greater rigidity and duration of erection than achievable with oral agents.

Poor visual acuity, not allowing for safe needle delivery of vasoactive injection therapy.

Use of monoamine oxidase inhibitors: limits use of phenylephrine as a concurrent vasoactive agent.

Severe penile fibrosis.

History of multiple episodes of priapism with vasoactive drug use.

Patient discontinuation of PGE-1 therapy represents a urological emergency, and any erection lasting more than 4 h necessitates urgent medical evaluation (Box 4). Most episodes can be prevented by careful patient instruction at the outset of an ICI program.

Patient discontinuation of PGE-1 therapy remains high, with most series describing long-term dropout rates of 40–60%. It is interesting to note that patient attrition is often not based on objective side effects, such as penile pain, fibrosis and priapism. In fact, symptoms including burning sensation and pain are most pronounced initially and often resolve or are minimized after repeated use. Rather, major determining factors include lack of patient motivation, loss/disinterest of partner and dissatisfaction with drug-induced erection [36–38]. The high dropout rate noted during the initial treatment period, and ineffectiveness as the most cited reason, underlines the importance of close patient monitoring in early therapy (Box 3; Table 1). Careful follow-up is key to any successful program of ICI therapy; a scheduled annual reassessment, in addition to patient-requested visits, ensures that penile fibrosis or nodule formation is identified early, therapeutic dosages are optimized and the patient remains well informed regarding their treatment and potential adverse events necessitating re-evaluation.

**Papaverine**

Papaverine was the most commonly administered vasoactive agent until PGE-1 was introduced into clinical practice. Papaverine induces relaxation of cavernous smooth muscle and penile vessels via nonspecific inhibition of phosphodiesterase, elevates cAMP and impairs calcium influx through blockage of voltage-dependent calcium channels [39]. The plasma half-life is 1–2 h, and it is cleared via hepatic metabolism. Papaverine as monotherapy is usually delivered in doses between 20 and 80 mg (range: 5–160 mg). Although papaverine is inexpensive, effective and stable at room temperature, we do not routinely use single-agent papaverine for ICI therapy since efficacy is approximately 55% and compiled reports indicate an increased rate of priapism (up to 6%), fibrosis (6–12%) and penile pain following injection compared with other agents [40–42]. Unlike PGE-1, papaverine has not been approved by the FDA for treatment of ED.

**Phentolamine**

Monotherapy with phentolamine, an α-adrenergic antagonist with equal affinity for α1 and α2 receptors, has been disappointing [43,44]. Although intracavernous injection increases corporal blood flow, a concurrent increase in norepinephrine prevents complete sinusoidal relaxation [45]. Clinically, we limit the use of phentolamine to vasoactive drug combinations.

**ICI technique: functional anatomy & physiology**

Injection into the corpora at the proximal part of the penis results in a rapid infusion of drug into both corporal bodies owing to the presence of the penis.
of an incomplete midline septum. The resultant bilateral increase in cavernous blood flow is rapid, creating an equalized pressure system, and occurs in the presence of normal bilateral cavernosal arteries, unilateral arterial injury or asymmetric flow [2,46]. Injury to one of the paired cavernous arteries is unlikely with ICI since these vessels are found close to the midline septum and the small gauge needle used (27–30 g) [47].

Self injection is performed on the dorsolateral aspect of the penile shaft, not close to the dorsal nerve, artery or vein (Figures 1a & 1b). Following injection and sexual stimulation, rigidity is achieved within 2–10 min as a rapid increase in cavernosal artery blood flow leads to compression of subtunical venules located between the smooth muscle of the corpora cavernosa and the inner tunica albuginea. With venous outflow blocked, intracavernous pressures reach greater than 100 mmHg [48]. Vasoconstriction and the loss of penile rigidity occurs as a result of an increase in sympathetic tone coincident with ejaculation.

A misdirected needle during injection is easily recognized as a higher-pressure injection or patient discomfort. The cavernosal smooth muscles are found deep in the tunica albuginea, arranged as a series of sinuses or potential spaces lined by endothelium [49]. These are separated by smooth muscle trabeculae surrounded by elastic fibers, collagen, and loose areolar tissue [50]. In our experience, we recommend rotating the needle, as the bevel will usually dislodge from the trabeculae and the vasoactive agent will enter the penis at minimal pressure. The depth of needle advancement can be gauged by the resistance of tunica albuginea, serving as a landmark anatomical structure.

Intracavernous pharmacotherapy has proven to be a robust means of treating ED [25]. Vasoactive agents relax smooth muscle directly by altering calcium or potassium ion channel permeability or via activation or decreased degradation of second-messenger molecules, such as cyclic guanosine monophosphate (cGMP) and cAMP [51–52]. Any substance that induces smooth muscle relaxation within the penis may potentiate an erection, independent of neural nonadrenergic noncholinergic pathways. Advances in the understanding of normal erectile function, especially the role of nitric oxide (NO) and cGMP second-messenger pathways, have expanded our knowledge of ED pathophysiology, identified several new potential intracavernous agents and ensured that ICI will continue to play an important role in the management of ED in the future [53].

Special populations of ED in the aging male

Nonresponders to PDE-5 inhibition

The introduction of PDE-5 inhibitors for the elderly ED population drastically changed medical management, becoming the preferred first-line therapy for most patients owing to efficacy and safety. In the case of failed PDE-5 inhibitor therapy and a preference by the patient to continue with oral agents, patient re-education and retraining, change of agent/dosage, select investigations (e.g., screening for hypogonadism) and lifestyle modifications (increased exercise, cessation of smoking and control of medical comorbidities) are suggested. Nevertheless, at least 30% of men treated with oral agents will demonstrate no substantial improvement [2]. From an efficacy standpoint, ICIs of PGE-1, papaverine or combination therapy using one or both of these agents with phentolamine (bimix or trimix) remains the standard against which treatments of ED in the aging male are measured [25]. Nonresponders to oral therapy

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**Box 3. Strategies to optimize patient success with intracavernous injection therapy.**

- Comfortable, stress-free environment.
- Initial instruction and observation of injection technique by trained staff in outpatient clinic.
- Direct injection into proximal corpora (Figure 1).
- Sexual stimulation following injection.
- Gentle local pressure applied to injection site to prevent hematoma or ecchymoses (2–3 min).
- Step-wise dose escalation if initial attempt unsuccessful until the recommended maximum dose is achieved (minimum 24 h between attempts).
- Patient (with/without partner) information and support.

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**Box 4. Priapism and intracavernous injection therapy**

- Uncommon adverse events (<3%), can result in penile fibrosis and further impairment of erections.
- Priapism is defined as penile erection lasting more than 4 h.
- Lack of bloodflow results in local ischemia (corporal compartment syndrome).
- Patients must be aware that priapism is a urological emergency.
- Treat priapism first, then the underlying disorder, since causes other than ICI therapy are possible.
- Treatment consists of aspiration and irrigation, followed by penile injection of sympathomimetic agent (repeat as needed).
- Phenylephrine preferred (dose: 250–500 μg every 3–5 mins for up to 1 h)
- Observe for side effects, shunt procedures are considered if injection therapy fails.
- Oral systemic therapy is not warranted.
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can be salvaged by patient re-education and retrial (with lifestyle modification), dose escalation of PDE-5 inhibitors or a change of oral agents, alprostadil alone or combination ICI (bimix or trimix) as part of a progressive treatment program [54]. Several recent reports have addressed the efficacy in this population. Shabsigh and colleagues reported results from a large, multicenter randomized trial demonstrating 85–90% improvements in the ability to achieve and maintain an erection (international index of erectile function [IIEF]-5 questions 3 and 4) for men using intracavernous alprostadil alfadex treatment, having previously failed sildenafil 100 mg therapy [55]. Another novel regimen showing initial promise consists of on-demand sildenafil and scheduled ICI (20 µg bi-weekly); two-thirds of men demonstrated a substantial improvement in their erectile function, but further evaluation of such schedules is required [56].

Patient preference commonly determines the eventual treatment of choice. Although the majority of men with ED have satisfactory results using PDE-5 inhibitors, some prefer ICI over oral agents owing to a more rapid onset of action and improve penile rigidity; others choose oral therapies due to discomfort with injections or fear of potential adverse events even if somewhat poorer erections occasionally occur [57].

Erectile dysfunction following radical prostatectomy
Recovery of erectile function following radical prostatectomy for malignancy is most influenced by patient age, pre-operative erectile function, and the ability of the surgeon to spare the cavernous nerves [58]. A lack of spontaneous erections following nerve-sparing surgery results from neuropaxia, predisposing to cavernous hypoxia and possible fibrosis owing to the accumulation of collagen [59]. Advances in the understanding of erectile physiology have resulted in ICI therapy playing a prominent role in the efforts of early penile rehabilitation for men undergoing nerve-sparing prostatectomy. Montorsi and colleagues demonstrated that early postoperative treatment with ICI alprostadil improved the return of natural erections in 67% of men, compared with 20% in the observational group [24]. For men in whom the cavernous nerves cannot be spared at time of surgery due to more advanced prostate cancer, ICI is an appropriate treatment option as NO release from these nerves, upon which PDE-5 inhibitor enhanced erections are dependent, is bypassed [60]. ICI as monotherapy for erectile dysfunction after radical prostatectomy is considered a safe, effective, second-line therapy, with success rates of 75–85% [61].

Advances in surgical technique have resulted in a greater proportion of men with localized prostate cancer undergoing uni- or bilateral cavernous nerve-sparing procedures. PDE-5 inhibitors are considered the first-line therapy, barring contraindications, for these patients. Limited success is often observed in the early postoperative period, as nerve integrity has been compromised to varying degrees by traction, laceration or thermal injury, and erectile recovery may take up to 24 months. PDE-5 inhibitor success is linked to nerve-sparing status (as well as patient age, preoperative erectile function and adjuvant radio- or hormonal therapy) and ranges from 75% in men with bilateral nerves spared to 54 and 14% for unilateral and non-nerve sparing

<table>
<thead>
<tr>
<th>Table 1. Trouble-shooting and solutions for common causes of inadequate response to injection therapy.</th>
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<tr>
<td><strong>Inadequate patient response to intracavernous injection</strong></td>
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<tr>
<td>Inadequate dose</td>
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<tr>
<td>Injection into wrong location (trabecular or subcutaneous)</td>
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<tr>
<td>Loss (leakage) of vasoactive agent from syringe prior to injection</td>
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<tr>
<td>Penile discomfort</td>
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<tr>
<td>Inadequate sexual stimulation following injection</td>
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<tr>
<td>Premature ejaculation and other sexual problems other than erectile dysfunction</td>
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<tr>
<td>General principal: encourage partner involvement</td>
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groups, respectively, at 1 year [61]. Daily use of sildenafil following surgery also appears to improve erectile recovery, as reported by Nandi- pati and colleagues for men undergoing bilateral nerve-sparing procedures (27 vs 4% for placebo at 11 months) [59]. Large-cohort studies are currently underway to further define the role of PDE-5 inhibitors in postoperative penile rehabilitation. There have also been recent reports of using intermittent ICI as a ‘booster’ for men with a suboptimal response to sildenafil; 68% of men reported significant improvements in the quality of erections [62].

**Cardiovascular disease**

Men with ED and cardiovascular disease may require intracavernous therapy owing to treatment failure, adverse effects or contraindications to oral PDE-5 inhibitors [19]. Given the high prevalence of cardiovascular disease among men with ED, the clinician must determine cardiac risk status prior to initiating a treatment program. Patients deemed to be at intermediate or higher cardiac risk (cardiac status uncertain, moderate-to-severe symptoms or unable to perform exercise of modest intensity) should be assessed by a cardiologist/internist and sexual activity deferred until cardiac condition is stabilized or resumption of sexual activity is deemed safe by the consultant. Low-risk patients, those able to perform exercise of modest intensity (6 or more metabolic equivalents [METS]) without symptoms, do not generally require cardiological assessment [63].

Local injection therapy is suitable as there is minimal systemic exposure of vasoactive drugs and success rates approach 75–90% when using combination therapies of PGE-1, phentolamine and papaverine [19,64]. For patients failing or unable to use PDE-5 inhibitors, a progressive program of
ICI (mono- to combination therapy) represents a safe and efficacious alternative for the treatment of ED in men with cardiovascular disease.

**Combination therapy of intracavernous agents**

Clinical use of combination therapy was first described in 1985, combining papaverine and phentolamine [65]. Combination therapy is more robust than single-agent use; multiple vasoactive drugs (trimix) have been reported to produce a full erectile response in up to 90% of patients [66]. Side effects are reduced since smaller amounts of each agent are required, and the targeting of multiple pathways (PGE-1 and increased cAMP; papaverine and nonspecific PDE-5 inhibition; phentolamine and decreased adrenergic tone) increases therapeutic efficacy. Multiple series have demonstrated patient satisfaction rates of greater than 75% and low rates of priapism or fibrosis [67–69]. The main advantage of the bimix (papaverine and phentolamine) combination versus trimix (papaverine, phentolamine and PGE-1) is stability without refrigeration [70]. The three-agent formulation is more potent than its bimix predecessor, demonstrating a level of patient satisfaction approaching 90% with decreased incidence of painful erection when compared with papaverine/phentolamine or PGE-1 therapy owing to the use of lower doses of each component [71,72]. Dosing for these agents is presented in Table 2, although some variation exists between investigators. Of note, combination therapy is more cost-effective than PGE-1, especially at the lower doses usually required. More recently, quadmix formulations have been reported, with agents such as atropine or forskolin added in an attempt to salvage trimix ICI nonresponders; few studies have assessed efficacy and safety of these combinations that, to date, have not gained widespread acceptance [73–75].

Although bi- and trimix combinations are not formally approved by the FDA for the treatment of ED, these drug combinations are widely available, safe and efficacious, and we recommend their use as second-line ICI agent therapy for men who have failed or experienced significant penile pain with PGE-1.

**Combination therapy of intracavernous agents with PDE-5 inhibitors**

Combining intracavernous therapy and oral PDE-5 inhibitor treatment for patients not responding to either monotherapy is a promising, recently reported approach for difficult-to-treat ED [56,76]. Although there remains a lack of rand-
omized comparative drug trials, using multiple agents with different mechanisms of action and potential synergies has resulted in salvage rates of 30–100% where monotherapy has previously failed [76,77]. For men with ED following radical prostatectomy and a suboptimal response to PDE-5 inhibitors, combined treatment may represent a safe and effective alternative [61,62]. Results from a prospective, placebo-controlled, crossover study support the concept of PDE-5 inhibitor salvage with bi-weekly 20 µg PGE-1 injections and sildenafil, shifting 65% of patients from ‘severe’ or ‘moderate’ ED to ‘mild’ dysfunction [56]. Based on the best available evidence, combination therapy may be appropriate for select patients free of contraindications to either agent and with informed consent; optimal erectile agent dosing, ICI treatment schedules and the molecular mechanisms of combination therapy are yet to be determined. Adverse event data is limited and further studies are required. McMahon and colleagues have reported a 20% incidence of dizziness (one out of 41 patients experienced syncope) using a combination of sildenafil and triple-combination intracavernous therapy [76]. Based on current studies, each patient must be made aware that a combined therapy approach may increase side effects, in addition to therapeutic efficacy, due to the synergy of agents used. As is observed with ICI monotherapy, clinical responses to these regimens are enhanced by quality of instruction, availability of patient supports for troubleshooting and dosage adjustment and partner awareness and/or participation [78].

Future perspectives

Direct ICI holds great promise for several novel and standard vasoactive substances that, alone or in combination, target multiple physiological sites and relax cavernous smooth muscle and/or modify vascular function. Gastrointestinal hydrogen sulfide, NO donors, potassium-channel openers, calcitonin gene-related peptides, guanylate cyclase activators and rho/kinase inhibitors are among the agents currently being investigated for their erectogenic properties, and may represent the next generation of ICI mono- or combination therapies [79–83].

Mesenchymal stem cell (marrow stromal cell) and targeted gene therapy are perhaps the most exciting developments in ED research, with trial agents delivered directly into penile circulation via injection [84]. Progressing from proof-of-concept and animal model experiments (NO synthase, calcitonin gene-related peptide and ion channels), the first human clinical trials using naked DNA transfer for potassium ion channel gene transfer have been published recently [85,86]. No longer limited by the ability to identify molecular targets, research efforts are focused on establishing safety, efficacy and specificity for these state-of-the-art treatments [87].

The ability of currently used intracavernous agents (PGE-1, papaverine and phentolamine) to modify underlying ED pathophysiology and facilitate recovery of spontaneous erectile function continues to be defined. Recent reports describe increased incidence of spontaneous erection and improved hemodynamic parameters following long-term use of PGE-1 [88–90]. Objective measures include significant increases in cavernosal arterial diameter and peak systolic velocity [91]. Vasodilation due to upregulation of NO has been demonstrated with increased arterial flows; however, clinical reports fail to consistently demonstrate improved nocturnal erections [90,92,93]. The concept of curative vasoactive pharmacotherapy is intriguing and further studies are needed to identify how and which ED populations are most likely to experience genuine improvement of spontaneous erections [94]. Therefore, we presently inform our patients that

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<tr>
<th>Drug</th>
<th>Dose per cc (range)</th>
<th>Efficacy (%)</th>
<th>Priapism (%)</th>
<th>Fibrosis (%)</th>
<th>Drop-out rate (%)</th>
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<tr>
<td>Prostaglandin E-1</td>
<td>12–15 µg (5–40 µg)</td>
<td>70–80</td>
<td>1–5</td>
<td>1–3</td>
<td>35–60</td>
</tr>
<tr>
<td>Papaverine</td>
<td>20–80 mg (5–160 mg)</td>
<td>55</td>
<td>2–6</td>
<td>6–10</td>
<td>30–50</td>
</tr>
<tr>
<td>Bimix (phentolamine and papaverine)</td>
<td>0.5/30mg (0.5–2/10–60 mg)</td>
<td>70</td>
<td>7</td>
<td>6–12</td>
<td>25–45</td>
</tr>
<tr>
<td>Trimix (prostaglandin E-1-1, papaverine and phentolamine)</td>
<td>10 µg/30 mg/1 mg (10 µg/8 mg/0.2 mg-20 µg/30 mg/1.0 mg)</td>
<td>up to 90%</td>
<td>&lt;3</td>
<td>2–5</td>
<td>25–40</td>
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improved spontaneous sexual function may occur for a significant minority of men but few reach the point of cure, obviating the need for medication.

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Executive summary

Introduction

• Intracavernous pharmacotherapy (ICI) for erectile dysfunction (ED) is a safe and efficacious treatment option for the aging male.

The role of ICI therapy in the treatment of erectile dysfunction

• With the introduction of oral phosphodiesterase-5 (PDE-5) inhibitors, ICI represents a second-line ED treatment for most men.
• ICI remains the first-line therapy for select patients and a valuable treatment option for nonresponders to PDE-5 inhibitors, those that cannot tolerate the side effects of oral agents or at the patient's preference (rapid action of onset, greater rigidity and duration).

Review of clinical intracavernous vasoactive agents

• Prostaglandin (PG)E-1, the most widely used injectable vasoactive agent, is commonly prescribed for patients who fail first-line oral pharmacotherapy.
• Our current protocol for PGE-1 therapy is focused on informing the patient about the agent, its use and possible side effects, as well as teaching self-injection in a comfortable, monitored environment. Careful physical examination is performed prior to the onset of treatment, with all patients informed of any penile abnormalities, including pre-existing skin lesions, plaques or fibrosis.
• Treatment with single-agent PGE-1 injections is effective. Cumulative data yields a success rate of 70–75% across ED etiologies, with a median dose of 12–15 µg.
• Common adverse effects include burning sensation at the time of injection, small hematoma and bruising, with penile fibrosis (1–3%) occurring much less frequently. Priapism (erection >4 h) occurs infrequently (rate of 1–3%) but constitutes a urological emergency. Most episodes can be prevented by careful patient instruction at the outset of an ICI program.

Special populations of ED in the aging male

• ICI may be used as first-line therapy for patients using nitrates and difficult to treat groups, including nonresponders to oral agents, prostradal prostatectomy, diabetics, severe vascular disease and neural injury from radiation, surgery or trauma.
• ICI as monotherapy for ED after radical prostatectomy is considered a safe, effective, second-line therapy (after PDE-5 inhibitors), with success rates of 75–85%. ICI is also an essential component of penile rehabilitation programs in this population.
• Local injection therapy is suitable for men with cardiovascular disease since there is minimal systemic exposure of vasoactive drugs and success rates approach 75–90%. For patients failing or unable to use PDE-5 inhibitors, a progressive program of ICI (monotherapy to combination therapy) represents a safe and efficacious treatment alternative.

Combination therapy of intracavernous agents

• Combination therapy is more robust than single-agent use; multiple vasoactive drugs (PGE-1, papaverine and phentolamine [trimex]) have been reported to produce a full erectile response in up to 90% of patients.
• Side effects are reduced, as smaller amounts of each agent are required, but they may include penile pain (less than single-agent PGE-1), fibrosis or priapism.

Future perspectives

• Future trends for ICI include the clinical introduction of novel vasoactive agents (alone or in combination), treatment-induced modification of ED pathophysiology and gene therapy. Of note, the first human clinical trial of gene therapy for ED has been reported recently.

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