ABSTRACT

Introduction. Erectile dysfunction (ED) is the most frequently treated male sexual dysfunction worldwide. ED is a chronic condition that exerts a negative impact on male self-esteem and nearly all life domains including interpersonal, family, and business relationships.

Aim. The aim of this study is to provide an updated overview on currently used and available conservative treatment options for ED with a special focus on their efficacy, tolerability, safety, merits, and limitations including the role of combination therapies for monotherapy failures.

Methods. The methods used were PubMed and MEDLINE searches using the following keywords: ED, phosphodiesterase type 5 (PDE5) inhibitors, oral drug therapy, intracavernosal injection therapy, transurethral therapy, topical therapy, and vacuum-erection therapy/constriction devices. Additionally, expert opinions by the authors of this article are included.

Results. Level 1 evidence exists that changes in sedentary lifestyle with weight loss and optimal treatment of concomitant diseases/risk factors (e.g., diabetes, hypertension, and dyslipidemia) can either improve ED or add to the efficacy of ED-specific therapies, e.g., PDE5 inhibitors. Level 1 evidence also exists that treatment of hypogonadism with total testosterone $< 300$ ng/dL (10.4 nmol/L) can either improve ED or add to the efficacy of PDE5 inhibitors. There is level 1 evidence regarding the efficacy and safety of the following monotherapies in a spectrum-wide range of ED populations: PDE5 inhibitors, intracavernosal injection therapy with prostaglandin E1 (PGE1, synonymous alprostadil) or vasoactive intestinal peptide (VIP)/phentolamine, and transurethral PGE1 therapy. There is level 2 evidence regarding the efficacy and safety of the following ED treatments: vacuum-erection therapy in a wide range of ED populations, oral L-arginine (3–5 g), topical PGE1 in special ED populations, intracavernosal injection therapy with papaverine/phentolamine (bimix), or papaverine/phentolamine/PGE1 (trimix) combination mixtures. There is level 3 evidence regarding the efficacy and safety of oral yohimbine in nonorganic ED. There is level 3 evidence that combination therapies of PDE5 inhibitors + either transurethral or intracavernosal injection therapy generate better efficacy rates than either monotherapy alone. There is level 4 evidence showing enhanced efficacy with the combination of vacuum-erection therapy + either PDE5 inhibitor or transurethral PGE1 or intracavernosal injection therapy. There is level 5 evidence (expert opinion) that combination therapy of PDE5 inhibitors + L-arginine or daily dosing of tadalafil + short-acting PDE5 inhibitors pro re nata may rescue PDE5 inhibitor monotherapy failures. There is level 5 evidence (expert opinion) that adding either PDE5 inhibitors or transurethralPGE1 may improve outcome of penile prosthetic surgery regarding soft (cold) glans syndrome. There is level 5 evidence (expert opinion) that the combination of PDE5 inhibitors and dapoxetine is effective and safe in patients suffering...

**Key Words.** Erectile Dysfunction; Oral Drug Treatment; Phosphodiesterase Inhibitors; Intracavernous Self-Injection Therapy; Transurethral Alprostadil Therapy; Combination Therapies; Vacuum Device Therapy

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**Introduction**

Sexuality is a key domain in the lives of humans. In the majority of partnerships, sexuality remains the most important or at least a very important bonding factor regardless of an individual's homosexual or heterosexual orientation. Until recently, sex (which in this context refers both to an active sex life and interest in sexual activities) is commonly associated in the public domain with younger age groups, whereas sexual activities in elderly individuals (>70 or even 80 years) are considered in many cultures to be somewhat uncommon or even strange. Therefore, in the scientific literature, few representative data exist regarding the importance of sex life in the elderly population. In a population-based cohort study from Perth, Australia of 3,274 men, aged 75–95 years, sexual life and activities were explored via questionnaires from 1996 to 1999, from 2001 to 2004, and from 2008 to 2009 [1].

A total of 2,783 (85%) provided data on their sexual activity (Table 1).

In two previous studies from Germany and Japan investigating sexual activities in age groups between 30 and 80 years of age, the frequency of sexual activity (coitus, masturbation, erotic movies, etc.) over the months prior to the study was between 70% and 96% (Table 2).

These three large studies from three different cultures provide convincing evidence that for the majority of older men, sexual activities play an important role as a bonding factor for partnerships.

Alternatively, many studies suggest that sexual health is not maintained in many elderly men. Declining sexual health is a process that usually starts in the fifth decade and increases progressively with age. This statement applies generally for all male sexual functions including sexual desire, sexual arousal, erectile function, and ejaculatory/orgasmic capacity, as has been shown in a Norwegian epidemiologic study (see Figure 1).

From a clinical standpoint, erectile dysfunction (ED) is categorized in two major subtypes: (i) primary ED defined as ED that occurs from the beginning of sexual activities and (ii) secondary or acquired ED defined as ED that occurs after a period of normal sexual life in which erectile function is intact.

Many men experience erectile problems that are clearly related to temporary life circumstances or problems. These erectile problems disappear once the temporary circumstances are resolved. In these cases, consultation with a physician is not needed.

In contrast to these temporary erectile problems, a man experiencing longer-lasting ED of greater than 3–6 months should seek professional help and undergo a thorough medical evaluation both because of the increasing risk of partnership...
problems and the likelihood of underlying and principally treatable medical risk factors/diseases contributing to the onset or progression of ED.

**Epidemiology**

ED and premature ejaculation (PE) are the most common male sexual disorders (Table 3). The prevalence of these disorders is similar. In contrast to PE, ED is clearly age dependent with a steep increase beyond the fifth decade. In age groups < 50 years, the reported prevalence rates for ED range between 9% and 39% (<20% in most series). In men > 70 years of age, the prevalence of ED increases to between 40% and 80% depending on the populations investigated [6].

For standardization of clinical trials, categorization of ED severity was based on the International Index of Erectile Function (IIEF) using a scoring system from 1 to 30 in the erectile function domain (EF) of the IIEF [7]. ED is subdivided into mild (IIEF-EF score 17–25), moderate (IIEF-EF score 11–16), and severe ED (IIEF-EF score 1–10) with an IIEF-EF score of between 26 and 30, indicating a normal erectile function. The IIEF has been tested only for heterosexual activities over the prior 4 weeks. It has not been tested in sexually inactive men or in homosexual men.

**Risk Factors for ED**

In patients > 40 years of age, ED is significantly associated with cardiovascular risk factors such as diabetes, hypertension, coronary artery disease (CAD), dyslipidemia, atherosclerosis, and metabolic syndrome [8–11; Table 4]. In addition many epidemiological studies have provided convincing evidence that men with BPH and LUTS show a significantly increased risk of both simultaneous erectile dysfunction and ejaculatory disorders [12]. The increased risk of cardiovascular risks/events in men with ED compared with age-matched men without ED has been demonstrated repeatedly, most notably, in a meta-analysis reviewing 12 prospective cohort studies with a total of 36,744 participants [9]. The overall combined relative risks for men with ED compared with the reference group were the following: 1.48 (95% confidence interval [CI]; 1.25–1.74) for cardiovascular disease (CVD); 1.46 (95% CI; 1.31–1.63) for coronary heart disease; 1.35 (95% CI; 1.19–1.54) for stroke, and 1.19 (95% CI; 1.05–1.34) for all-cause mortality. Sensitivity analysis restricted to studies with control for conventional cardiovascular risk factors yielded similar results. No evidence of publication bias was observed. Therefore, the manifestation of ED must absolutely be considered a marker (warning sign) for occult CAD with a significant likelihood of later event.

**Table 3** Prevalence of male sexual disorders in the elderly U.S. population [4]

<table>
<thead>
<tr>
<th>Sexual disorder</th>
<th>57–64 years</th>
<th>65–74 years</th>
<th>75–85 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature ejaculation</td>
<td>29.5% (23.4–35.7%)</td>
<td>28.1% (23.4–32.9%)</td>
<td>21.3% (13.2–29.3%)</td>
</tr>
<tr>
<td>Delayed/absent ejaculation/orgasm</td>
<td>16.2% (11.9–20.5%)</td>
<td>22.7% (17.5–27.9%)</td>
<td>33.2% (25.0–41.5%)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>30.7% (25.3–36.9%)</td>
<td>44.6% (38.7–50.5%)</td>
<td>43.5% (34.5–52.4%)</td>
</tr>
</tbody>
</table>

**Figure 1** Decline of male sexual function related to age as evaluated by the Brief Sexual Function Inventory. Results of a Norwegian epidemiological study (reprinted with permission from [5]).
Table 4  Etiology and risk factors of erectile dysfunction (ED)

<table>
<thead>
<tr>
<th>Psychological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosexual development in childhood/adolescence (special negative experiences, etc.)</td>
</tr>
<tr>
<td>Sexual orientation problems?</td>
</tr>
<tr>
<td>Partnership problems?</td>
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</tbody>
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<table>
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<tr>
<th>Lifestyle factors and individual health conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent stress factors? (private/business life)</td>
</tr>
<tr>
<td>Sedentary lifestyle?</td>
</tr>
<tr>
<td>Nicotine?</td>
</tr>
<tr>
<td>Alcohol abuse?</td>
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<tr>
<td>Drug addictions?</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (including antihypertensive medications with potential negative impact on erectile function)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Peripheral arterial occlusive disease</td>
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<tr>
<td>Diabetes mellitus (types 1 and 2)</td>
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<thead>
<tr>
<th>Endocrine factors</th>
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</thead>
<tbody>
<tr>
<td>Hypogonadism (primary/secondary)</td>
</tr>
<tr>
<td>Hyperprolactinemia (microprolactinoma/macroprolactinoma or drug induced)</td>
</tr>
<tr>
<td>Thyroid disorders (hypothyroidism/hyperthyroidism)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iatrogenic ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug induced (drugs with a negative impact on central and peripheral erectile functions including hormones—hyperprolactinemia and hypogonadism)</td>
</tr>
<tr>
<td>Postoperative (pelvic, perineal, urethral, and penile surgery → radical prostatectomy, cystectomy rectum resection/amputation, aorto-iliac vascular surgery (aneurysms)</td>
</tr>
<tr>
<td>Postradiation (prostate cancer, bladder cancer, and rectum cancer)</td>
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<table>
<thead>
<tr>
<th>Medical/metabolic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
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<tr>
<td>Hepatic insufficiency</td>
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<tr>
<td>Dyslipidemia</td>
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<table>
<thead>
<tr>
<th>Urological disorders</th>
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</thead>
<tbody>
<tr>
<td>Benign prostate hyperplasia (BPH) and lower urinary tract symptoms (LUTS)</td>
</tr>
<tr>
<td>Chronic prostatitis</td>
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<table>
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<tr>
<th>Respiratory disorders</th>
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<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Sleep apnea</td>
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<table>
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<tr>
<th>Neurologic disorders</th>
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</thead>
<tbody>
<tr>
<td>Cerebral, spinal, and peripheral affections: central (brain) diseases such as multiple sclerosis, cerebrovascular atherosclerosis, Parkinson’s disease, dementia, etc.</td>
</tr>
<tr>
<td>Somatic and autonomic polyneuropathy</td>
</tr>
<tr>
<td>Pudendal nerve lesions (“vulnerable perineum”)</td>
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</tbody>
</table>

<table>
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<tr>
<th>Penile/cavernous factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>cavernous myopathy and fibrosis (veno-occlusive dysfunction)</td>
</tr>
<tr>
<td>Peyronie’s disease or penile fracture</td>
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<table>
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<tr>
<th>Posttraumatic ED</th>
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</thead>
<tbody>
<tr>
<td>Brain/spinal cord injuries</td>
</tr>
<tr>
<td>Pelvic fractures, urethral ruptures, straddle traumas, and penile injuries</td>
</tr>
</tbody>
</table>
major cardiovascular events [10,11]. In the Italian Cobra study, comprising 162 men with CAD, documented by catheter angiography, the onset of ED occurred in 71% of the study population with a mean interval of 25 months before myocardial infarction or angina symptoms occurred [11].

In summary, there is level 1a evidence that ED in men >40 years is associated with an increased all-cause mortality primarily due to increased cardiovascular mortality (fatal myocardial infarction or cerebral insult). Therefore, each man >40 years with chronic ED should be considered a potential cardiovascular risk patient and investigated accordingly.

The Princeton II Consensus Conference on the cardiovascular risk management of any ED patient is shown as an algorithm in Figure 2 [10].

**ED and Hypogonadism**

The incidence of hypogonadism in men with ED depends both on age and the total testosterone (T) cutoff values, which are used for the definition of hypogonadism. As a rule, between 20% and 40% of men >40 years and suffering from ED have hypogonadal T values (see Figure 3).

**Treatment of Hypogonadism in Patients with ED**

Hypogonadal men with ED should be offered T-replacement therapy because it is well established that ED-specific medications are less effective if applied to men with untreated T deficiency. Several well-designed studies provide convincing evidence that in untreated hypogonadal men, responsiveness to phosphodiesterase type 5 (PDE5) inhibitors is substantially impaired and can be significantly increased by testosterone. Adding T-replacement therapy to PDE5 inhibitor therapy can convert PDE5 inhibitor nonresponders to PDE5 inhibitor responders especially in men with T levels <300 ng/dL or 10.4 nmol/L [14–16]. In a subset of untreated hypogonadal men with ED, T substitution alone may restore impaired sexual functions, especially libido and erection [16–18]. According to several well-designed studies, the threshold T value below which ED becomes evident is <300 ng/dL [19] (see Figure 4). For low libido disorder, the T-threshold values were 15 nmol/L (432 ng/dL).

In conclusions on ED and simultaneous hypogonadism, testosterone plays a key role in the maintenance of men’s sexual functions and sexual health. Depending on the plasma T levels, hypogonadal men develop libido, erectile, or ejaculatory/orgasmic disorders. The respective threshold levels below which sexual symptoms become evident are about 15 nmol/L (432 ng/dL) for libido and 8–10.4 nmol/L (230–300 ng/dL) for ED. T-replacement therapy in hypogonadal men with sexual disorders should start first followed by specific ED medications such as PDE5 inhibitors. Recovery of sexual functions takes usually 4–12 weeks depending on the sexual symptoms in ques-
Responsiveness to specific ED medications is substantially disturbed in untreated hypogonadal men if T values are <300 ng/dL (10.4 nmol/L). There is level 1b evidence that T-replacement therapy in hypogonadal men can convert nonresponders to PDE5 inhibitors to responders.

Medical Treatment of ED

Oral Drug Therapy of ED

PDE5 Inhibitors

Mechanism of Action. PDE5 inhibitors are widely considered as first-line therapy for ED [20,21]. All approved PDE5 inhibitors have the same mode/site of action: they inhibit the enzyme PDE5 competitively, thereby blocking the cleavage of its physiological target substance 3′,5′-cGMP (cycloguanosine monophosphate). The PDE5 enzyme is found in high concentrations in the entire urogenital system and especially in the cavernous bodies [22] (Figure 5).

In general, above a certain threshold concentration of the key mediator for erection—3′,5′-cGMP—the physiological cascade of erection is triggered and erection occurs. The formation of 3′,5′-cGMP in the cavernous tissue is triggered after parasympathetic nerve stimulation resulting in nitric oxide (NO) release and guanylate cyclase activation. The enzyme PDE5 regulates hydrolysis of 3′,5′-cGMP. By lowering its concentration, erection subsides.

It is believed that in men with erectile problems, regardless of whether their underlying etiology is psychogenic or organic, intracavernous 3′,5′-cGMP concentrations are principally below the threshold level above which erection occurs. By inhibiting the enzyme PDE5 via a PDE5 inhibitor, 3′,5′-cGMP cannot be further hydrolyzed, resulting in achievement of the threshold concentration above which erection is triggered [23] (see Figure 6).

Regarding the mechanism of action of PDE5 inhibition, it is logical that PDE5 inhibitors need the substrate 3′,5′-cGMP to exert any efficacy regarding erectile function. As 3′,5′-cGMP is only...
generated after adequate sexual stimulation, it is obvious that PDE5 inhibitors need prior sexual stimulation to develop clinical efficacy and to support the onset and maintenance of a rigid erection.

PDE5 inhibitors prevent breakdown of 3′5′-cGMP resulting both in achieving the 3′5′-cGMP threshold concentration despite impairment of 3′5′-cGMP formation and in achieving suprathreshold 3′5′-cGMP concentrations with subsequent maintenance of a rigid erection.

In summary, after adequate sexual stimulation, PDE5 inhibitors elevate the concentrations of the mediator 3′5′-cGMP above the threshold level that is needed to trigger erection. This mechanism works in the majority of ED etiologies except those in which severe damage/injury of the parasympathetic cavernous nerves prevents NO release, guanylate cyclase activation, and 3′5′-cGMP formation, such as after major pelvic cancer surgery with resection of the cavernous nerves at both sides or diseases with severe autonomic neuropathy such as diabetes.

Pharmacokinetics
The pharmacokinetic profile of a drug is determined by many steps between the drug’s entry into the body and its elimination. Two key pharmacokinetic parameters related to the speed of absorption are $T_{Max}$ which is defined as the time needed to reach $C_{Max}$ (the maximum plasma concentration), and $T_{1/2}$ (half-life time), which is defined as the time it takes for the fall of the plasma concentrations of a drug to half of its $C_{Max}$ values. In the clinical setting, the $T_{Max}$ corresponds quite well with the speed of clinical efficacy (onset of

**Figure 5** Quantitative expression, by real-time RT-PCR, of PDE5 mRNA in (A) human and (B) rat male urogenital tissues. (A) Data are expressed as PDE5 mRNA molecules/µg total RNA ± SEM obtained according to a standard curve method for absolute quantitation. (B) Data are expressed as mean ± SEM of arbitrary units (a.u.) calculated according to the comparative Ct method and using the β2-microglobulin as reference gene for normalization. n, number of analyzed samples. *P < 0.05 vs. human kidney; °P < 0.001 vs. human corpus cavernosum (CC); **P < 0.01 vs. rat CC (reprinted with permission from [22]). mRNA = messenger RNA; PDE5 = phosphodiesterase type 5; RT-PCR = real-time polymerase chain reaction; SEM = standard error of mean

**Figure 6** Physiology of erection and impact of PDE5 inhibitors on erection (from [23]). ACH = Acetylcholine; ACTH = Adrenocorticotropic hormone; ATP = Adenosine triphosphate; 3′5′-cAMP = cyclic adenosine monophosphate; 3′5′-cGMP = cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; GTP = Guanosine triphosphate; MSH = Melanocyte stimulating hormone; NANC = non adrenergic, non cholinergic; NE = Norepinephrine; NO = Nitric oxide; VIP = Vasoactive intestinal polypeptide
erection) and the \( T_{1/2} \), with the duration of clinical efficacy. As illustrated in Table 5, all three drugs show similar earliest onset of action times with vardenafil being slightly most rapid. The \( T_{\text{max}} \) and \( C_{\text{Max}} \) of sildenafil and vardenafil are clearly dependent on food intake. After intake of a high-fat (59% fat) meal, a delay in \( T_{\text{max}} \) of 60 minutes and a reduction in \( C_{\text{Max}} \) of 29% was observed with sildenafil (Viagra® U.S. label; Pfizer Corp, New York, NY, USA). Similar data apply for vardenafil ([24], Levitra® U.S. label; Bayer Healthcare, Leverkusen, Germany). On the other hand, no food interaction has been reported for tadalafil, even with a high-fat meal [25,26].

### Pharmacodynamics

The term pharmacodynamics covers all actions of a drug on the different body organs/tissues and in turn on their functions (for example, blood pressure, heart rate, and vision). The pharmacodynamic interactions of any drug are influenced by the number of molecules available in the target organ and the affinity of the compound for the target molecule in question. For example, it has been reported that the proportion of high-affinity components for the PDE5 catalytic site of vardenafil is 85% compared with 50% for sildenafil and 60% for tadalafil [27]. High-affinity components of a PDE5 inhibitor show a considerably longer dissociation time from the target molecule. This explains why vardenafil showed in clinical use a clearly longer duration of efficacy than it would be suspected by its half-life time [28].

### Intrinsic and Extrinsic Factors

**Renal and Hepatic Insufficiency.** Special dose adjustments must be made in patients with renal and hepatic insufficiency (see Table 6).

### Table 5

<table>
<thead>
<tr>
<th>Drug</th>
<th>( T_{\text{max}} ) (minutes)</th>
<th>Earliest &gt;50% patient response</th>
<th>( T_{1/2} ) (hour)</th>
<th>Duration of efficacy (hour) (% successful coitus)</th>
<th>( C_{\text{Max}} ) (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil 100 mg</td>
<td>70 (30–120)</td>
<td>14</td>
<td>3.82 ± 0.84</td>
<td>8 (85%)</td>
<td>327 ± 236</td>
</tr>
<tr>
<td>Tadalafil 20 mg</td>
<td>120 (30–720)</td>
<td>16</td>
<td>17.5</td>
<td>36 (59% and 62%)</td>
<td>378</td>
</tr>
<tr>
<td>Vardenafil 20 mg</td>
<td>40 (15–180)</td>
<td>11</td>
<td>3.94 ± 1.31</td>
<td>8 ± 2 (69%)</td>
<td>20.9 ± 1.83</td>
</tr>
</tbody>
</table>

### Table 6

<table>
<thead>
<tr>
<th>Parameter/condition</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Vardenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 3A4 inhibitors*</td>
<td>Start dose 25 mg</td>
<td>Max. dose 10 mg/72 hours</td>
<td>Max. 2.5 mg/day</td>
</tr>
<tr>
<td>CYP 3A4 inhibitors†</td>
<td>Start dose 25 mg</td>
<td>Max dose 10 mg/72 hours</td>
<td>Max. dose: 2.5 mg/72 hours</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>No dose adjustment</td>
<td>Max. dose 5 mg</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Severe renal failure (creat. clearance &lt; 30 mL/minutes)</td>
<td>Start dose 25 mg</td>
<td>Max. dose 10 mg</td>
<td>Start dose 5 mg</td>
</tr>
<tr>
<td>Mild/mod. hepatic failure (Child Pugh A/B)</td>
<td>Start dose 25 mg</td>
<td>Max. dose 10 mg</td>
<td>Start dose 5 mg</td>
</tr>
<tr>
<td>Blood pressure drop syst./diast.</td>
<td>8.4/5.5 mm Hg</td>
<td>1.6/0.8 mm Hg</td>
<td>7/8 mm Hg</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>Interval of 4 hours recommended</td>
<td>Stable alpha-blocker therapy recommended. Start dose 5 mg</td>
<td>Stable alpha-blocker therapy recommend. Start dose 10 mg</td>
</tr>
<tr>
<td>Antihypertensives (all drug classes)</td>
<td>No interactions of clinical relevance</td>
<td>No interactions of clinical relevance</td>
<td>No interactions of clinical relevance</td>
</tr>
<tr>
<td>Alcohol intake (0.5–0.6 g/kg)</td>
<td>No additional hypotensive effect</td>
<td>No additional hypotensive effect</td>
<td>No additional hypotensive effect</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Nitrites and NO donors*</td>
<td>Nitrites and NO donors</td>
<td>Nitrites and NO donors</td>
</tr>
<tr>
<td>Safe interval for nitrate medication in emergencies</td>
<td>24 hours</td>
<td>48 hours</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

\*CYP 3A4 inhibitors: erythromycin, ketoconazole, itraconazole: up to 3- to 10-fold increases of the plasma concentrations of the respective PDE5 inhibitors, cimetidine (56% increase of sildenafil plasma concentrations, not valid for vardenafil, tadalafil not reported)

†CYP 3A4 inhibitors: protease inhibitors ritonavir, indinavir, saquinavir: increase of plasma concentrations of the respective PDE5 inhibitors between onefold and fivefold for tadalafil and 16-fold for vardenafil

\*Nitrites and NO donors: All short- and long-acting nitrates containing drugs including recreational drugs such as “poppers” as well as molsidomine and nitroprusside sodium containing medications.

NO = nitric oxide; PDE5 = phosphodiesterase type 5

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Bleeding Time. Both with aspirin 150 mg and warfarin, no increase in bleeding time was observed
with the PDE5 inhibitors. After heparin, sildenafil showed an additive effect on bleeding time in
rabbits, but this interaction trial was not conducted in humans.

CVD. Patients with CVD can be particularly sen-
sitive to the systemic actions of PDE5 inhibitors
and may need reduced doses. This includes patients
with left ventricular outflow obstruction (aortic and
subaortic stenosis), recent (<6 months) myocardial
infarction, stroke, life-threatening arrhythmias,
and hypotensive (blood pressure < 90/50 mm Hg)
and hypertensive (blood pressure > 170/
110 mm Hg) blood pressure values.

Priapism. In conditions/drugs with a known risk
of priapism such as sickle cell disease, leukemia, and
multiple myeloma, PDE5 inhibitors must be used
with special precautions because of the concern
that the drugs may heighten this risk.

Drug Interactions
Alpha Blockers. Both sildenafil 25 mg and tadalafil
20 mg used simultaneously with doxazosin 4 mg
resulted in symptomatic postural hypotension
(Viagra® U.S. label; Cialis® U.S. label; Eli Lilly
Comp., Indianapolis, IN, USA). Tamsulosin
0.4 mg with either tadalafil 20 mg or vardenafil
5 mg did not show any clinically relevant influence
on the blood pressure. Vardenafil 5 mg used simulta-
neously with terazosin 10 mg resulted in symp-
tomatic hypotension. This effect was not observed
when both drugs were taken 6 hours apart ([29],
Cialis® U.S. label; Levitra® U.S. label). Tadalafil
20 mg used with alfuzosin 10 mg did not result in
clinically significant hemodynamic interactions
[30].

Nitrate-/NO-Donor Interactions. All three PDE5
inhibitors showed clinically relevant interactions
with nitrates. The most threatening of these inter-
actions is severe hypotension, which can be lethal
if not recognized and managed properly ([31,32],
Cialis®, Levitra®, and Viagra® U.S. labels). Therefore, all three PDE5 inhibitors are abso-
lutely contraindicated for patients using nitrate
medications.

The time interval considered to be safe between
the administration of a PDE5 inhibitor and a
nitrate medication is 24 hours for the shorter-
acting sildenafil and vardenafil and 48 hours for
the longer-acting tadalafil (Cialis®, Levitra®, and
Viagra® U.S. labels).

CYP 3A4 Inhibitors. Erythromycin, ketoconazole,
and itroconazole have been reported to cause up
to 3- to 10-fold increases of the plasma concen-
trations of PDE5 inhibitors. Cimetidine has been
reported to cause a 56% increase of sildenafil
plasma concentrations, but this effect has
not been found with vardenafil (interaction
between cimetidine and tadalafil has not been
reported).

Protease inhibitors ritonavir, indinavir, and
saquinavir have been reported to cause an increase
of plasma concentrations of onefold to fivefold
for tadalafil and 16-fold for vardenafil.

CYP 3A4 Inducers. Rifampin has been reported to
decrease tadalafil plasma levels up to 88%.

Efficacy of PDE5 Inhibitors
General Considerations on PDE5 Inhibitors
For a better understanding of differences among
and comparisons between the three widely avail-
able PDE5 inhibitors, some terms have to be
explained:

IC₅₀: IC₅₀ (Inhibitory concentration) is defined as
the concentration of a PDE5 inhibitor, which is
required to reduce the activity of PDE5 by
50%. The IC₅₀ value provides an overview of
the clinical efficacy of a PDE5 inhibitor. Gen-
erally speaking, the lower the IC₅₀ value, the
more potent and therefore more effective a
compound is for inhibiting this enzyme. The
IC₅₀ values vary greatly among the available
PDE5 inhibitors as is illustrated in Table 7 [33].
In the clinical setting, the IC₅₀ translates to the
dose used to reach the same clinical efficacy.
The higher the IC₅₀, the higher the dose needed
to reach the same clinical efficacy as compared
with a competitive PDE5 inhibitor with a lower
IC₅₀.

Clinical efficacy: Regarding the clinical efficacy of a
PDE5 inhibitor, several tools are used in clinical
trials:

General Assessment Question: “Has the treatment
you have been taking improved your erec-
tions?” Although this efficacy tool does not
really tell whether the patient is able to attain
an erection sufficient for sexual intercourse,
this relatively weak efficacy measure has been
widely used especially by pharmaceutical
companies because usually it yields the
highest success rates.

IIEF: The International Index of Erectile
Function (IIEF) was originally developed to
evaluate the clinical efficacy of sildenafil
It became the most accepted and used efficacy tool worldwide for ED drugs. It comprises 15 questions, which cover five domains of sexual function. These domains are erectile function, orgasmic function, sexual desire, sexual satisfaction, and overall satisfaction. Each question has six possible response options with scoring between 0 (worst) and 5 (best result) [7]. Questions 1–5 have six response options from score 0 if there was no sexual activity over the last 4 weeks to score 5 if erection/sexual intercourse was always successful.

**IIEF-EF:** For the evaluation of the erectile efficacy of a drug, the IIEF-EF domain, comprising questions 1–5 and 15 of the IIEF, represents the strongest efficacy tool. A score > 25 indicates normal erectile function.

**Sexual Encounter Profile (SEP):** The SEP is a five-question patient diary, which is completed by the patient after each sexual encounter. The SEP comprises the following questions:

**Question 1:** Were you able to achieve at least some erection (some enlargement of the penis)?

**Question 2:** Were you able to insert your penis into your partner’s vagina?

**Question 3:** Did your erection last long enough for you to have successful intercourse?

**Question 4:** Were you satisfied with the hardness of your erection?

**Question 5:** Were you satisfied overall with this sexual experience?

SEP question 3 (ability to complete sexual intercourse) is considered the most rigorous and most frequently used efficacy measure in clinical ED trials.

**On-Demand (Pro Re Nate [P.R.N.]) Therapy with PDE5 Inhibitors**

The efficacy of the on-demand or p.r.n. use of PDE5 inhibitors was investigated in large scale trials worldwide both in mixed ED populations and in subpopulations such as patients with diabetes and after nerve sparing radical prostatectomy (see Table 8). To interpret Table 8 correctly, it has to be emphasized that SEP 2 and 3 diary data were only available in the tadalafil and vardenafil trials, whereas in the early sildenafil trials SEP 2 and 3 were not yet used. All three PDE5 inhibitors provided impressive efficacy data in a variety of ED subpopulations including patients with diabetes, patients with neurological disorders such as spinal cord injuries and multiple sclerosis, patients after radical prostatectomy (provided they have undergone a nerve sparing procedure), patients with hypertension or CAD, and patients with renal insufficiency or after kidney transplantation.

The efficacy of all PDE5 inhibitors is clearly less in special ED subpopulations such as after radical prostatectomy and diabetes mellitus in which either the autonomic parasympathetic innervation (cavernous nerves) to the penis or the functional capacity of the cavernous bodies (veno-occlusive dysfunction in diabetes or untreated hypogonadism) is clearly impaired (Table 8).

**Long-Term Efficacy/Satisfaction**

Long-term studies (2 years) have shown that efficacy is maintained over a long period and that there is no loss of efficacy, i.e., no tachyphylaxis, among the three PDE5 inhibitors: sildenafil, tadalafil, and vardenafil [42–44]. In addition, in experimental research studies, no upregulation of PDE5 in the penis was observed with the long-acting PDE5 inhibitor tadalafil [45].

---

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PDE5 inhibitor therapy also improved other sexual domains such as orgasmic function and overall satisfaction with the sexual experience and quality of life [46]. In addition, improvement of depressive symptoms [46] and increases in partner satisfaction with sexual life were repeatedly reported with the use of PDE5 inhibitors [47–49].

First-Dose Success
Large cohort studies were able to show that even with the very first dose of a PDE5 inhibitor, the overwhelming majority of patients could be successfully treated, e.g., 87% SEP 2 rates (successful vaginal penetration) for vardenafil 10 mg [50] and 79% SEP 2 rates for tadalafil 20 mg [51]. However, it has also been shown in clinical trials that it takes the majority of couples between three to eight attempts (2–8 weeks) before the maximum efficacy of either PDE5 inhibitor is reached [35,52].

Treatment Adherence/Discontinuation Rates
The advent of PDE5 inhibitors has revolutionized the management of ED. Many experts expected that with easy oral administration of a small pill, the high discontinuation rates previously observed with intracavernosal injection therapy would disappear. However, against all expectations, this was not the case. Even with the ease of oral drug therapy, unexpectedly high drop-out rates were reported ranging between 45% and 78% after 6–24 months, depending on the population being treated and the specialization of the physicians prescribing the pill [53–55]. Reasons frequently mentioned for early discontinuation of PDE5 inhibitor therapy are listed in Table 9.

Nonresponders to PDE5 Inhibitors
Considering all the data of clinical trials with PDE5 inhibitors, between 30% and 40% of a mixed ED population of patients do not sufficiently respond to the maximum dose of the PDE5 inhibitor. As mentioned above, responsiveness to PDE5 inhibitors depends on the underlying etiology of ED and is clearly less favorable in all ED etiologies, which are associated with either damage to the penile autonomic nerve supply or linked to veno-occlusive dysfunction. Real nonresponders mostly have severe end-organ failure, which means that the cavernosal tissue has lost a considerable portion of its functional smooth musculature [56]. In the clinical setting, these PDE5 inhibitor nonresponders show severe veno-

### Table 8 Efficacy of the three PDE5 inhibitors in a variety of ED populations

<table>
<thead>
<tr>
<th>ED population</th>
<th>Sildenafil/placebo (50/100 mg)</th>
<th>Tadalafil/placebo (10/20 mg)</th>
<th>Vardenafil/placebo (10/20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GAQ (%)</td>
<td>SEP 2/3 (%)</td>
<td>GAQ (%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>82/24</td>
<td>66/20</td>
<td>81/35</td>
</tr>
<tr>
<td></td>
<td>(N = 1,600–1,787)*</td>
<td></td>
<td>(N = 1,112)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>56/10</td>
<td>48/12</td>
<td>64/25</td>
</tr>
<tr>
<td></td>
<td>(N = 268)**</td>
<td></td>
<td>(N = 216)**</td>
</tr>
<tr>
<td>BNSP RRP</td>
<td>No controlled multicenter</td>
<td></td>
<td>62/23</td>
</tr>
<tr>
<td></td>
<td>studies</td>
<td></td>
<td>(N = 903)†</td>
</tr>
</tbody>
</table>

*Viagra® (sildenafil citrate) U.S. label (LAB-0221-2.4, July 2005)
†Brock et al. [34]
‡Porst et al. [35]
§Hellstrom et al. [36]
¶Rendell et al. [37]
**Saenz de Tejada et al. [38]
††Goldstein et al. [39]
‡‡Montorsi et al. [40]
§§Brock et al. [41]
BNSP RRP = bilateral nerve sparing retropubic radical prostatectomy; ED = erectile dysfunction; GAQ = General Assessment Question; PDE5 = phosphodiesterase type 5; SEP 2/3 = Sexual Encounter Profile 2/3
occlusive dysfunction with many of them also failing to respond to intracavernosal injection of vasoactive drugs such as alprostadil or trimix combination. This veno-occlusive dysfunction, also known as venous leak or cavernous insufficiency, is frequently associated with severe impairment of the penile arterial blood supply, also known as “arteriogenic” ED.

According to an international expert panel, the definition of a nonresponder to oral pharmacotherapy for ED is as follows [57]:

“Any patient who, after four successive or closely timed trials of the maximum tolerated dose of the medication, in accordance with the regulatory agency’s guidelines with respect to timing relative to meals, alcohol ingestion, use of concomitant medications and adequate sexual stimulation, is unable to achieve or sustain adequate penile rigidity until completion of sexual performance.”

“Pseudo-nonresponders”

Many so-called nonresponders may be rescued through appropriate counseling regarding specific drug-related pharmacokinetics/dynamics, change of sedentary lifestyle, adequate treatment of concomitant diseases, and/or exchange of concomitant medications in favor of more erection protective drugs (see antihypertensives). The definition of a real nonresponder is justified if no success is seen under the following conditions:

The use of at least four tablets with the highest dose of any PDE5 inhibitor at four different occasions under optimal conditions (appropriate sexual stimulation and appropriate interval between tablet intake and sexual activity, with sildenafil and vardenafil under fasting conditions for 2 hours and with tadalafil keeping an interval of at least 2 hours between intake and sexual activity to guarantee maximal plasma concentrations and maximal efficacy). In individual cases according to literature reports, it has been observed that after PDE5 inhibitor administration the following measures/actions were able to salvage “pseudo-nonresponders” to PDE5 inhibitors and convert them to responders.

Measures to Improve Responsiveness to PDE5 Inhibitors

1a. **Re counseling of the patients/couples** in the appropriate use of PDE5 inhibitors [58–60]: Early adjustment of dosing to the highest doses resulted in salvage rates of up to 60%.

1b. **Reeducation regarding the pharmacokinetic/dynamic characteristics and the individual differences of PDE5 inhibitors**: Onset of action and maximum efficacy of sildenafil and vardenafil are clearly dependent on food intake and content.

Maximal efficacy, i.e., time to maximal plasma concentrations of tadalafil, shows a broad individual range between 30 and 720 minutes. In rare individuals, best efficacy may not occur until 12 hours after dosing.

2. **Optimal treatment of concomitant diseases**: Optimal diabetes control mirrored by glycated hemoglobin [61] or treatment of hypertension with more erection protective drugs such as angiotensin receptor blockers, sartans, or the beta-blocker nebivolol [8] may improve responsiveness to PDE5 inhibitor therapy. In addition, treatment of hypercholesterolemia with statins such as atorvastatin may improve erectile function per se due to the fact that statins decrease low-density lipoprotein (LDL) levels and subsequently reduce the negative effect of oxidized LDL on endothelial function [62] or may increase the efficacy of PDE5 inhibitors if given simultaneously [63].

3. **Treatment of concomitant hypogonadism**: It has been shown that testosterone regulates the expression of PDE5. Hypogonadal men have a poorer response to PDE5 inhibitors [64] and also other erectogenic drugs. Several studies have provided evidence that many hypogonadal ED patients, originally unresponsive to PDE5 inhibitors, can be rescued by adding T-replacement therapy [14–17,65,66]. These findings especially apply to patients with total T values of <300 ng/dL (<10.4 nmol/L) [14].

4. **“High-dose” (overdosing) PDE5 inhibitor therapy**: High-dose PDE5 inhibitor therapy, i.e., doubling the maximal dose, resulted in a 24% salvage rate of ED patients (N = 54) previously unresponsive to 100 mg of sildenafil [67]. According to the principal author’s personal experience, this may also apply to vardenafil and tadalafil in some individual patients especially in unresponsive diabetics.

5. **Shifting patients to another PDE5 inhibitor**: Shifting of real nonresponders from sildenafil to vardenafil resulted in a rescue/success rate of 12% [68]. According to the principal author’s personal experience with more than 7,000 patients on PDE5 inhibitors, only a small minority (5–8%) of real nonresponders to one PDE5 inhibitor are satisfactorily rescued by another one.
6. Daily dosing of PDE5 inhibitors: Daily dosing of tadalafil [69] or sildenafil [70] for several months in patients previously unresponsive to on-demand therapy at maximum doses salvaged more than 50% of failures. Although salvage was proven in these preliminary small series for tadalafil and sildenafil, it can be assumed that this concept may apply also for other PDE5 inhibitors, in particular in patients with severe organic ED (Figure 7).

Preference Studies Between Marketed PDE5 Inhibitors

Several sponsored and independent nonsponsored studies have investigated whether patients/couples prefer one PDE5 inhibitor over others after patients tried sildenafil, vardenafil, and/or tadalafil over a reasonably long period of time. A recent review of the literature from 2000 to 2010 on this topic concluded that preferences of the patients/couples were the following [71]:

Vardenafil: 12–20%
Sildenafil: 8–30%
Tadalafil: 52–65%

The reasons for preference of tadalafil were mainly because of the longer duration of action that increased patients’ freedom and spontaneity in sexual life. In general, the authors found a consistency in patients’ preference for tadalafil over sildenafil or vardenafil across the studies reviewed.

Safety and Drug-Related Adverse Events of PDE5 Inhibitors

The side-effect profile of the PDE5 inhibitors is mainly related to its mechanism of action, i.e., inhibition of the PDE5 enzyme and their lack of precise specificity. All currently available PDE5 inhibitors have some inhibitory effects on other PDE enzymes as well. Because these enzymes are widely distributed in our body, the inhibition of PDE5 and other isotypes cause special organ-tissue-related undesired effects. The typical side-effect profiles of sildenafil, tadalafil, and vardenafil are shown in Table 10.

Whereas headache, flushing, dyspepsia, and rhinitis are typical side effects for all three PDE5 inhibitors, back pain and myalgia are more commonly reported with tadalafil. In contrast, color vision disturbances are nearly exclusively observed with sildenafil because of its partial inhibition of PDE6, an enzyme located in the retina, and responsible for brightness sensitivity and color discrimination.

The side-effect profiles of sildenafil, vardenafil, and tadalafil as reported in the most recent U.S. label revisions are shown in Tables 11–13.

Cardiovascular Safety of PDE5 Inhibitors in Clinical Trials

Shortly after gaining regulatory approval of the PDE5 inhibitor sildenafil in the United States,

Table 10 Frequent (>2%) side effects of the three phosphodiesterase type 5 inhibitors: sildenafil, tadalafil, and vardenafil (sources: Padma-Nathan et al. [72], Kloner et al. [73], and Brock et al. [34])

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Sildenafil [72] (N = 5,918)</th>
<th>Vardenafil [73] (N = 2,203)</th>
<th>Tadalafil [34] (N = 804)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14.6%</td>
<td>14.5%</td>
<td>14%</td>
</tr>
<tr>
<td>Flush</td>
<td>14.1%</td>
<td>11.1%</td>
<td>4%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6.2%</td>
<td>3.7%</td>
<td>10%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2.6%</td>
<td>9.2%</td>
<td>5%</td>
</tr>
<tr>
<td>Back pain</td>
<td>0%</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Color visual disturbances</td>
<td>5.2%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 11 Side-effect profile of sildenafil (Viagra®) (source: Viagra®, U.S. label LAB-0221-11.1, revised January 2011): adverse events reported by >2% of patients treated with Viagra® and more frequent on drug than placebo in Pro Re Nates (PRN) flexible dose phase II/III studies

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Viagra® (N = 734)</th>
<th>Placebo (N = 725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

concerns about its cardiovascular safety profile were expressed in the mass media, after some unexpected deaths were linked to its use. The generally negative perception in the public domain and mass media regarding the cardiovascular safety of these agents prompted their manufacturers to invest in a comprehensive clinical research program evaluating safety.

As shown in Table 14, all trials demonstrate the risk for myocardial infarction and death per 100 patient years among those exposed to PDE5 inhibitors was not greater than that associated with placebo. In addition, several trials in patients with CAD were able to confirm that PDE5 inhibitors do not have any detrimental effect on cardiovascular safety, a finding that also applied to patients using antihypertensive agents. Moreover, many patients currently receiving nitrates can stop their use on the recommendation of a cardiologist, without experiencing adverse cardiovascular consequences, allowing subsequent use of a PDE5 inhibitor [77].

In this context, it once more should be emphasized that concomitant use of any nitrates or NO donors (molsidomine and others) containing medications and PDE5 inhibitors is absolutely contraindicated because of the potential danger of life-threatening hypotension.
Special Safety Issues with PDE5 Inhibitor Use

Ocular Safety

In recent years, reports in the lay press that PDE5 inhibitors may cause blindness due to the so-called nonarteric anterior ischemic optic neuropathy (NAION) made patients and physicians unsure about the safety of these medications. Interestingly, the U.S. Food and Drug Administration (FDA) reports that no causal connection between the cases reported and the use of PDE5 inhibitors exists; the PDE5 manufacturers were requested to include in their new label warnings about a higher likelihood for developing NAION among the following: age > 50 years, heart disease, diabetes, hypertension, high cholesterol, nicotine use, and certain eye problems. Several recent review articles based on the analyses of databases pertaining safety came to the conclusion that there is no causal link between sildenafil and cardiovascular events nor are there any new safety risks relating to cardiovascular events, priapism, NAION, hearing loss, or drug interactions [78]. However, basic recommendations were given that despite the absence of a proven link between PDE5 inhibitor use and serious ocular disorders, physicians should continue to advise patients to stop the use of a PDE5 inhibitor and seek immediate medical attention in the event of a sudden loss of vision as a safety measure [79].

Hearing Safety

Because some cases of sudden hearing loss were linked to the use of PDE5 inhibitors, although no causal relationship has been demonstrated, the FDA requested a label revision stating that patients taking sildenafil, tadalafil, or vardenafil and experiencing a sudden hearing loss should immediately stop taking the drug and seek prompt medical attention.

Reproductive Safety

Because tadalafil may have an inhibitory effect on PDE11, an enzyme related in part to spermatogenesis, concerns have been raised about the reproductive safety of this drug. In this context, two 6-month studies with 10 and 20 mg of tadalafil once a day (OAD) given to 421 healthy men for 6 months [80] and a 9-month placebo-controlled study with 20 mg of tadalafil covering three spermatogenesis cycles and conducted in 253 healthy men were performed. They did not show any adverse effects on spermatogenesis [80,81].

Table 15 Efficacy results of vardenafil ODT trials: mean scores, differences between placebo and vardenafil ODT [82]

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>POTENT I study</th>
<th>POTENT II study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vardenafil ODT</td>
<td>Placebo</td>
</tr>
<tr>
<td>IIEF-EF</td>
<td>14.4</td>
<td>21.7</td>
</tr>
<tr>
<td>SEP 2</td>
<td>46.7</td>
<td>73.7</td>
</tr>
<tr>
<td>SEP 3</td>
<td>26.7</td>
<td>64.9</td>
</tr>
</tbody>
</table>

POTENT I study conducted in Europe and South Africa
POTENT II study conducted in the United States, Canada, Mexico, and Australia
IIEF-EF = International Index of Erectile Function-erectile function domain
ODT = orodispersible tablet; SEP 2/3 = Sexual Encounter Profile 2/3

Vardenafil Orodispersible Formulation

Just recently, a new formulation of vardenafil was introduced in the market called vardenafil orodispersible tablet (ODT) 10 mg. This vardenafil ODT is applied on the tongue without the need of water or any other fluid and provides a rapid disintegration within the mouth before swallowing [82]. The two international studies conducted with that new ODT formulation showed a similar efficacy and safety profile as compared with the oral vardenafil film-coated tablets 10 mg with SEP 3 data (completion of sexual intercourse) success at 65% and 70% (Table 15, [82]). The key pharmacokinetics of vardenafil ODT 10 mg as compared with the film-coated tablets are summarized in Table 16 and showed longer Tmax and lower Cmax data for the ODT formulation but 20–44% higher area under the curve, indicating a higher bioavailability [83]. Whether this higher

Table 16 Pharmacokinetic parameters of vardenafil and its N-desethyl metabolite (M-1) after single or multiple doses of vardenafil orodispersible tablet (ODT) (without water) or a single dose of vardenafil film-coated tablet (FCT) 10 mg in fasting patients with erectile [after Heinig et al. [83]]

<table>
<thead>
<tr>
<th>Vardenafil</th>
<th>Vardenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg ODT</td>
<td>10 mg FCT</td>
</tr>
</tbody>
</table>

| Men aged < 65 years | | |
|--------------------|--------------------|
| Single dose (N = 20) | Single dose (N = 14) |
| Day 4               | Day 4               |
| AUC (µg x hour/L)   | 29.97/48.1          | 23.52/57.6          |
| Cmax (µg/L)         | 7.187/52.9          | 8.167/75.2          |
| Tmax (hour)         | 4.361/38.1          | 4.471/29.8          |
| Tmax (hour, median range) | 1.25 (0.75–2.50) | 0.75 (0.50–1.50) |

| Men aged ≥ 65 years | | |
|--------------------|--------------------|
| Single dose (N = 14) | Day 4 |
| AUC (µg x hour/L)   | 42.16/42.6         | 34.88/32.1         |
| Cmax (µg/L)         | 8.891/60.2         | 11.00/54.6         |
| Tmax (hour)         | 5.952/27.5         | 6.179/28.3         |
| Tmax (hour, median range) | 0.875 (0.50–3.00) | 0.75 (0.50–3.00) |

AUC = area under the curve
bioavailability of the vardenafil ODT formulation translates into any clinical advantage (longer duration of efficacy) over the existing oral vardenafil formulation remains to be shown in clinical studies.

**Daily Dosing of PDE5 Inhibitors**

**Tadalafil OAD**

Since 2009, tadalafil (Cialis®) has been approved for daily application (OAD) in doses of 2.5 and 5 mg as an alternative treatment regimen to on-demand or p.r.n. dosing. In many countries worldwide, including most countries of the European Union, only 5 mg of tadalafil OAD is marketed. In the most recent “EAU Guidelines on Male Sexual Dysfunctions,” OAD tadalafil has been officially listed as a first-line treatment of ED together with on-demand treatment with PDE5 inhibitors [21]. Because of its long half-life with 17.5 hours as compared with PDE5 inhibitors with a half-life of about only 4 hours (i.e., sildenafil and vardenafil), tadalafil is at present the only PDE5 inhibitor that has been approved worldwide for daily dosing therapy.

Several studies have evaluated both the efficacy and safety of OAD tadalafil in doses between 2.5 and 20 mg and in different ED populations (broad spectrum, diabetes, and lower urinary tract symptoms [LUTS]/benign prostatic hyperplasia [BPH]). Both in short-term (3 months) and long-term trials up to 2 years, tadalafil OAD was effective in the treatment of ED of various etiologies even at the 2.5-mg dose without signs of tachyphylaxis or increased drug-related adverse events [84–87].

As illustrated in Figure 8, a historical comparison of data from 16 placebo-controlled trials with tadalafil taken on demand for the treatment of ED and the results of the first large multicenter trial with tadalafil OAD shows that 5 mg of OAD tadalafil provides comparable efficacy to 20 mg of tadalafil taken on demand ([84], data on file with Lilly Corp.).

In pharmacokinetic studies with OAD tadalafil, steady state was attained by day 5, and accumulation (1.6-fold) was consistent with the $T_{1/2}$. From day 5 of OAD tadalafil, plasma levels are 1.6 higher as compared with the respective single dose [25]:

- OAD tadalafil 2.5 mg = 4–5 mg single-dose on demand
- OAD tadalafil 5 mg = 8 mg single-dose on demand
- OAD tadalafil 10 mg = 16 mg single-dose on demand

**First-Dose Success with Tadalafil OAD**

Pharmacokinetic studies have proven that with daily dosing of tadalafil after 5 days, a steady state of plasma concentrations is reached equal to 1.6 times a single dose [25]. In this context, a recent clinical study was able to show that from day 2, tadalafil OAD resulted in significant efficacy that increased over the next 5 days ([88], Figure 9).

**Safety of Tadalafil OAD**

As shown in Table 13, the side-effect profile of tadalafil OAD 5 mg is comparable to that of tadalafil 20 mg p.r.n. Tadalafil OAD may have an improved side-effect profile compared with on-demand use, although this tendency did not

![Figure 8: Historical comparison: SEP 3 question tadalafil once a day and on demand [84]. ED = erectile dysfunction; SEP 3 = Sexual Encounter Profile 3](image-url)
show statistical significance with historical comparisons from pooled data of tadalafl on-demand trials (Table 17).

**Udenafil Once Daily Dosing**

In August 2011, the results of the first daily dosing trial with udenafil, a new PDE5 inhibitor with a half-life time of about 13 hours, were published, showing a 73% change rate from baseline regarding SEP 3 data and a 44% shift rate to normal erectile function (IIEF-EF < 25) for the highest udenafil dose (75 mg) investigated ([89], Table 18). Side-effect rates with daily dosing of udenafil were low with flushing (6.8%), headache (3.4%), and nasal congestion (1.7%) at the highest udenafil dose.

### Table 17  Historical comparison of treatment-emergent adverse events: once a day tadalafl vs. on-demand tadalafl (Porst et al. [84])

<table>
<thead>
<tr>
<th>Events occurring in ≥3% of any treatment group</th>
<th>Once a day</th>
<th>On demand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N = 54</td>
<td>Tadalafil 5 mg N = 109</td>
</tr>
<tr>
<td>Headache</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Back pain</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Pain in limb</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Flushing</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Discontinuations due to adverse events</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

PCT PRN = pooled data from 16 placebo-controlled studies (data on file with Lilly Corp.)

### Table 18  Changes of secondary efficacy outcome variables after 12 weeks in the first udenafil daily dosing trial [89]

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 59)</th>
<th>Udenafil 25 mg (N = 59)</th>
<th>Udenafil 50 mg (N = 60)</th>
<th>Udenafil 75 mg (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEP 2 (%)</td>
<td>11.95</td>
<td>22.10</td>
<td>27.90*</td>
<td>39.11*</td>
</tr>
<tr>
<td>SEP 3 (%)</td>
<td>23.46</td>
<td>42.09*</td>
<td>51.41*</td>
<td>73.50*</td>
</tr>
<tr>
<td>GAQ (%)</td>
<td>35.60</td>
<td>69.50*</td>
<td>75.00*</td>
<td>88.10*</td>
</tr>
<tr>
<td>Shift to normal IIEF-EF</td>
<td>13.60</td>
<td>30.50*</td>
<td>40.00*</td>
<td>44.10*</td>
</tr>
</tbody>
</table>

Values are changes of percentage of positive responses from baseline after 12-week treatment.

*P values were calculated using chi square or Fisher exact tests for comparison of subject numbers and analysis of variance for comparison of mean values.

*P < 0.001

GAQ = General Assessment Question; IIEF-EF = International Index of Erectile Function-erectile function domain; SEP 2/3 = Sexual Encounter Profile 2/3
Men with ED and Simultaneous LUTS/BPH

In the past years, several placebo-controlled studies with daily dosing of both short-acting PDE5 inhibitors (i.e., sildenafil and vardenafil) and long-acting PDE5 inhibitors (tadalafil and udenafil) provided convincing evidence that daily dosing of PDE5 inhibitors results in relief of LUTS symptoms due to BPH, as assessed by the International Prostate Symptom Score (IPSS) score. Improvements in the IPSS score after PDE5 inhibitors were found to the same extent in terms of IPSS improvement as has been reported with uroselective and nonselective alpha blockers [90–96].

In this context, it has been demonstrated that after oral administration, both tadalafil and udenafil concentrations were significantly higher in the prostatic tissue as compared with the maximum plasma levels and that both PDE5 inhibitors significantly increased cyclo adenosine monophosphate (cAMP) and cyclo guanosine monophosphate (cGMP) concentrations ([97], Table 19).

On October 7, 2011, the U.S. FDA approved tadalafil (Cialis®) OAD for the treatment of men who have both ED and the signs and symptoms of BPH. In addition, the FDA also approved tadalafil OAD for the separate indication for the treatment of the signs and symptoms of BPH (Figure 10).

In summary, all currently marketed PDE5 inhibitors have shown in randomized placebo-controlled trials significant efficacy improving LUTS symptoms as assessed by the IPSS [90–94], comparable to that of alpha blockers (Level of Evidence 1). In addition, daily dosing of tadalafil was able to improve both ED and LUTS given that both diseases are frequently present in the same patient ([93]; Figure 10). In the United States and the countries of the European Union, tadalafil OAD is approved for the treatment of both conditions—ED and/or BPH.

Selectively Marketed PDE5 Inhibitors

Several PDE5 inhibitors have been investigated in randomized controlled trials (RCTs) and have shown similar efficacy and safety profiles to sildenafil, tadalafil, and vardenafil.

Avanafil (VIVUS, Inc., Mountain View, CA, USA) is a very short-acting PDE5 inhibitor with a $T_{\text{Max}}$ of between 0.5 and 1 hour and a $T_{1/2}$ of <1.5 hours [98]. In a large multicenter trial with a total of 646 patients allocated to either placebo or avanafil 50, 100, or 200 mg, respectively, all doses of avanafil were significantly superior ($P < 0.001$) in all main end points being investigated such as SEP 2, SEP 3, and IIEF-EF domain score [99]. In addition, the authors evaluated the window of efficacy and reported that avanafil in as early as 15 minutes and >6 hours after dosing is effective [99]. Side effects were the same as established for other PDE5 inhibitors.

Similar results were found in a recently published multicenter, randomized, double-blind, placebo-controlled, fix-dosed phase III clinical trial with 100 and 200 mg of avanafil involving 200 patients with ED from South Korea [100].

### Table 19 Prostatic and plasma concentrations of phosphodiesterase type 5 inhibitors in patients with lower urinary tract symptoms due to benign prostatic hyperplasia [97]

<table>
<thead>
<tr>
<th></th>
<th>Plasma concentration (ng/mL)</th>
<th>Prostate concentration (ng/g)</th>
<th>Prostate/plasma ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Udenafil</td>
<td>436.7 ± 39.1</td>
<td>2,028.6 ± 360.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>305.8 ± 41.1</td>
<td>385.7 ± 83.8</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**Figure 10** Tadalafil once a day significantly improves ED and LUTS/BPH symptoms in men suffering from both conditions [93]. ANCOVA = analysis of covariance; BPH = benign prostatic hyperplasia; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-erectile function domain; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms.

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All $p < 0.001$ for tadalafil vs. placebo at Weeks 4, 8, and 12

*p < 0.05 for tadalafil vs. placebo*

---

Table 20  Pharmacokinetics of new phosphodiesterase type 5 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Avanafil</th>
<th>Mirodenafil</th>
<th>Lodenafil</th>
<th>Udenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg</td>
<td>10 mg</td>
<td>160 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>$T_{\text{Max}}$ (hour)</td>
<td>0.5–1.5</td>
<td>1.25</td>
<td>1.2</td>
<td>1–1.5</td>
</tr>
<tr>
<td>$T_{1/2}$ (hour)</td>
<td>&lt;1.5</td>
<td>2.5</td>
<td>2.4</td>
<td>11–13</td>
</tr>
</tbody>
</table>

*Limin et al. [98] *Paick et al. [101] *Glina et al. [102] *Kim et al. [93]

Considering the $T_{\text{Max}}$ of avanafil that is distinctly shorter than the other PDE5 inhibitors on the market and the available data from clinical trials in terms of onset of action, it seems that avanafil reports the quickest onset of action (see Table 20). Avanafil has been recently (April 27, 2012) approved by the FDA as Stendra® in the United States.

Lodenafil (Helleva; Cristalia Pharmaceuticals Ltd., Itapira, Brazil), also a short-acting PDE5 inhibitor with $T_{\text{Max}}$ of 1.2 hours and $T_{1/2}$ of 2.4 hours, is approved for the treatment of ED in Brazil. Two multicenter trials in a broad-spectrum ED population have provided SEP 3 data as shown in Table 21 [102,104].

The lodenafil data show both efficacy and safety profiles comparable to sildenafil, tadalafl, and vardenafil [102,104].

Mirodenafil (SK Chemicals, Seoul, South Korea), a short-acting PDE5 inhibitor with $T_{\text{Max}}$ of 1.25 hours and $T_{1/2}$ of 2.5 hours, is available in South Korea and has shown impressive efficacy data in a variety of clinical trials with SEP 3 results of 68.9% after mirodenafil 100 mg vs. 22.3% after placebo ($P < 0.0001$) in a Korean diabetic ED population [101,105].

Udenafil (Dong-A PharmTech Co. Ltd, Seoul, South Korea) is the only long-acting drug among the new PDE5 inhibitors with $T_{\text{Max}}$ of 1–1.5 hours and $T_{1/2}$ of 11–13 hours. The drug is licensed as Zydena® in South Korea, Russia, and other countries of the previous Russian Federation. In a variety of clinical trials, efficacy and safety data similar to sildenafil, vardenafil, and tadalafil with SEP 3 data in diabetics of 53% (udenafil 100 mg), and 63% (udenafil 200 mg) vs. 22% after placebo [103,106] have been reported.

In a published review of available udenafil, data from five RCTs totaling 1,109 patients [107] showed that udenafil had greater efficacy than placebo in the change from baseline for the IIEF-EF score (mean difference 5.65, 95% CI 4.41–6.89, $P < 0.00001$). Most adverse events were either mild or moderate in severity, and no serious adverse events were observed in these trials. The most common drug-related adverse events were flushing and headache (udenafil vs. placebo, 5.6% vs. 1.8% and 3.1% vs. 0%, respectively) [107].

Udenafil was recently investigated in a daily dosing trial using doses of 25, 50, and 75 mg or placebo, respectively [89]. Patients taking 50 or 75 mg of udenafil reported better IIEF domain scores than placebo (Figure 11).

In conclusions on PDE5 inhibitors, at present, all PDE5 inhibitors represent a first-line choice for the majority of all ED patients and their partners, regardless of the underlying ED etiology, and are recommended in all guidelines of urological societies as first-line therapy (Level of Evidence 1). Their use in more than 100 million men worldwide has shown convincing evidence of their acceptance, efficacy, and safety profile. In general, all PDE5 inhibitors are successfully used on an on-demand (p.r.n.) basis. Tadalafil OAD low-dose use has been approved in some markets for up to 3 years and has provided similar efficacy and safety as compared with the on-demand use of all other available PDE5 inhibitors. (Level of Evidence 1) Tadalafil OAD represents an effective, safe, and attractive alternative to the p.r.n. dosing, taking away the need to schedule sexual activities and thus allowing a spontaneous and natural sex life. Udenafil has also shown both efficacy and safety in a daily dosing regimen but is not yet approved for chronic dosing. In addition in men suffering from both ED and LUTS, tadalafl OAD is able to treat both condi-

Table 21  Results of two different randomized, placebo-controlled, and double-blind lodenafil trials

<table>
<thead>
<tr>
<th></th>
<th>*SEP 3 baseline</th>
<th>*SEP 3 after</th>
<th>†SEP 3 baseline</th>
<th>†SEP 3 after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23.3 ± 27.6%</td>
<td>33.6 ± 42.3%</td>
<td>20.2 ± 32.3%</td>
<td>29.7 ± 38.1%</td>
</tr>
<tr>
<td>Lodenafil 20 mg</td>
<td>32.3 ± 38.9%</td>
<td>51.2 ± 41.7%</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
<tr>
<td>Lodenafil 40 mg</td>
<td>39.7 ± 44.7%</td>
<td>46.7 ± 41.1%</td>
<td>18.6 ± 34.3%</td>
<td>50.8 ± 44.4%</td>
</tr>
<tr>
<td>Lodenafil 80 mg</td>
<td>17.2 ± 29.5%</td>
<td>74.3 ± 36.3%</td>
<td>20.8 ± 33.2%</td>
<td>66.0 ± 39.3%</td>
</tr>
</tbody>
</table>

*Glina et al. [102] ($P < 0.05$ for difference to placebo) *Glina et al. [104] ($P < 0.01$ for difference to placebo) SEP 3 = Sexual Encounter Profile 3
tions successfully with one pill (Level of Evidence 1) and has recently received the official approval for both indications in several markets worldwide.

Oral Therapies Other than PDE5 Inhibitors

Yohimbine

Yohimbine is the main alkaloid from the bark of the tree called Coryanthe johimbe K. Schum (yohimbe tree), particularly growing in Central Africa. The alkaloid was first isolated from the bark of the yohimbe tree (hence the name) by L. Spiegel in 1896. The bark of this tree is still used today as the raw material for the various yohimbine preparations. First information on its use combined with papaverine to treat ED was published in 1923 [108]. Until the launch of sildenafil and the other PDE5 inhibitors, yohimbine was the most prescribed substance worldwide for the treatment of ED.

Pharmacological Profile

The sites of action of yohimbine are the following:

**Central:** Unlike alpha1 adrenoceptors, cerebral alpha2 adrenoceptors mediate erection-inhibiting impulses. Yohimbine facilitates erection in part through a central level.

**Peripheral:** Yohimbine directly blocks alpha2 adrenoceptors that dominate in the penile arteries. It is believed to counteract the vasoconstriction induced by norepinephrine/epinephrine release and in turn the reduction in blood flow.

**Endothelium and androgen-dependent NO formation:** Experimental studies aimed at exploring yohimbine-induced relaxation in human and rabbit corpora cavernosa (CC) have provided evidence that yohimbine interferes with NO release from the endothelium: yohimbine-induced CC relaxation was inhibited by mechanical removing of the endothelium and by blocking NO synthesis or signaling via guanylate cyclase and cGMP formation [109]. In contrast, inhibition of cGMP degradation strongly increased yohimbine activity. In an experimental chemical castration model, conducted in rabbits by chronic treatment with a long-lasting Gonadotropin Releasing Hormone (GnRH) agonist, the relaxant yohimbine activity was also decreased but completely restored by androgen supplementation [109]. These experimental data indicate that yohimbine’s efficacy in ED is not only due to its inhibitory effects on the presynapticalpha1-adrenoceptor activity in the cavernous smooth muscle cells but also includes an impact on NO and cGMP formation involving endothelium and endothelial nitric oxide synthase (eNOS) activity which again is testosterone dependent.

Pharmacokinetics and Dosage

Yohimbine hydrochloride is orally well absorbed and has a plasma half-life of between 0.25 and 2.5 hours. However, the effects triggered by yohimbine, which can be traced back to an increase in plasma norepinephrine, may last for more than 13 hours. Only about 1% of yohimbine appears in the urine, indicating a predominantly hepatic clearance [110].

Doses described both in trials and in the literature ranged commonly from 5 to 15 mg three times a day [111].

Efficacy

The efficacy and safety of yohimbine have been analyzed in numerous studies, some of them with
a placebo-controlled, double-blind, prospective design. The efficacy rates ranged from no effect to 71% as compared with 40% for placebo in nonorganic impotence. A meta-analysis of seven large yohimbine studies, which met strict quality criteria, showed a superiority of yohimbine vs. placebo. Based on these data, the authors concluded that there is a rationale for the use of yohimbine in suitable ED patients [111]. The Clinical Guidelines Panel on Erectile Dysfunction of the American Urological Association (AUA) concluded that the data currently available on yohimbine do not allow it to be recommended as standard treatment in ED, particularly not in organic etiologies, and this statement of the AUA ED Guideline Panel was not changed with the 2005 update [112].

Apart from its use in ED yohimbine has also been reported effective in orgasmic disorders, i.e., delayed ejaculation or orgasm [113].

**Side Effects and Contraindications**

The common side effects observed with yohimbine can mostly be traced back to its partially increased sympathetic activity: anxiety, nausea, restlessness, agitation, sleeplessness tachycardia, palpitations, diarrhea, and manic symptoms. In addition, yohimbine is reported to either increase or more infrequently decrease blood pressure, which may be clinically relevant if hypertensive patients are taking this medication. In cases of severe CVD such as unstable angina or recent myocardial infarction, difficult to treat hypertension and severe psychiatric diseases, as well as severe hepatic impairment, should be considered contraindications for yohimbine use.

In conclusions on yohimbine, if yohimbine has any potential indications for use in ED management, it would be among nonorganic ED. In these patients, yohimbine may be used for a maximum of 2 months either as a regular regimen (3 × 5–10 mg/day) and has shown in a review a superiority to placebo (Level of Evidence 1b). Apart from ED, yohimbine has shown a limited efficacy in the medical treatment of delayed ejaculation.

### L-Arginine

L-arginine is the precursor of NO synthesis (Figure 6). Zorgniotti and Lizza conducted a placebo-controlled study with 2,800 mg of L-arginine per day in 20 impotent men for 2 weeks. Of the 15 men who completed the study, six reported an improvement in their ability to achieve an erection and nine experienced no improvement [114].

A high-dose, prospective, randomized, double-blind, and placebo-controlled study with 5 g of L-arginine per day for 6 weeks was conducted in 50 patients (aged 55–75 years) with organic, complete ED (unable to perform coitus) for at least 6 months [115]. This study resulted in a success rate (sexual intercourse possible) of 31% in the L-arginine group compared with 12% in the placebo arm. It was interesting to note that significantly higher urine concentrations of the stable NO metabolites NO2 and NO3 were measured in the L-arginine responders than in the nonresponders, although the responders had lower urine concentrations of NO3 prior to treatment. Thus, the question arises as to whether supraphysiologic doses of L-arginine given over a long period of time can lead to a permanent improvement in cavernous function in some ED patients. No side effects were observed except a fall in maximal blood pressure of 10% in some patients, which did not result in clinical symptoms.

Just recently, the results of a double-blind, placebo-controlled study with Prelox® (Horphag Research Ltd, Geneva, Switzerland; commercially available L-arginine product in some European countries) in 124 patients (aged 30–50 years) with moderate ED over an investigational period of 6 months were published [116]. The IIEF-EF improved after Prelox® from a baseline mean (standard deviation) score of 15.2 (6.6) to 25.2 (2.1) after 3 months and to 27.1 (2.1) after 6 months of treatment.

The corresponding figures in the placebo group were from baseline 15.1 (7.0) to 19.1 (3.0) and 19.0 (3.1) after 3 and 6 months, respectively. The effects with Prelox® were statistically significant compared with placebo ($P < 0.05$). It is notable that these efficacy data for Prelox® show an increase of mean IIEF-EF score of 11.9. This exceeds the improvements in IIEF-EF score of about 8–10, which were achieved in clinical trials with the highest doses of PDE5 inhibitors. These exceptional results with Prelox® must of course be reproduced in other large multicenter RCT studies in order for L-arginine (here Prelox®) to be accepted as first-line therapy for ED.

In conclusions on L-arginine, at present, no representative and reliable data from multicenter well-designed randomized trials are available providing evidence of significant efficacy of L-arginine in a broad-spectrum ED population. The trials published on L-arginine and its effects in ED are at best a Level of Evidence 2b that
L-arginine may work in ED patients of not closely specified ED etiology.

**Apomorphine SL**

With Apomorphine SL, a central dopamine-receptor agonist, a comprehensive clinical phase I–III developmental program was conducted, finally resulting in the official approval of Apomorphine sublingual tablets 2 and 3 mg (Ixense®, Tokyo, Takeda Pharma, Japan; and Uprima®, Abbott Laboratories, Abbott Park, IL, USA) in Europe 10 years ago. Because of its significantly inferior efficacy as compared with that of PDE5 inhibitors, the drug was withdrawn from the European market. Because Apomorphine SL is, to the knowledge of the authors, at present not marketed and therefore not officially available in pharmacies in any major regions of the world such as America, Asia, and Europe, no further details on Apomorphine are provided in this standard operation procedures (SOP) on ED.

**Topical Therapy**

Several drugs have been investigated in the past for topical application such as ointment/gel either on the glans penis or the penis shaft skin. The challenge with topical therapy is to reach the level of the CC, i.e., agents applied on penile skin have to permeate fascial layers and the tunica albuginea, which means thick layers of collagen. In view of the proven existence of venous communications between CC and glans penis, some studies have investigated the efficacy of topical application on the glans penis to reach the corpus cavernosum [117].

Drugs used in small trials with very limited number of patients were minoxidil solution, nitroglycerin ointment, and papaverine gel. None of these drugs was neither investigated in larger trials nor reached market approval mainly because of limited efficacy.

**Topical Therapy with Prostaglandin E1 (PGE1, Synonymous Alprostadil)**

**Sites of Action of PGE1**

PGE1 induces relaxation of corpus cavernosum smooth musculature through binding at E-prostaglandin receptors and activating the membrane bound adenylate cyclase, resulting in an increase of intracellular concentrations of cAMP in the cavernous tissue [118]. Further consequences of the PGE1-mediated relaxation of human corpus cavernosum are the activation of Maxi K channels, resulting in hyperpolarization and changes in transmembrane Ca²⁺ flux [119]. These effects are complemented by PGE1-induced inhibition of the release of noradrenaline from sympathetic nerve endings [120] and the suppression of angiotensin II secretion in the cavernosal tissues [121] (Figure 12).

**Topical Alprostadil (Synonymous PGE1)**

With a special topical PGE1 preparation, two large randomized placebo-controlled double-blind
trials with doses of 100, 200, and 300 μg of alprostadil were conducted and the integrated results were published some years ago [122]: a total of 1,732 patients (21% diabetes, 44% hypertension, 12% radical retropubic prostatectomy [RRP], 21% CAD, and 16% nitrate- or alpha-blocker medication) received either placebo (N = 434) or topical alprostadil cream at 100 (N = 434), 200 (N = 430), or 300 μg (N = 434). The mean changes of the IIEF-EF domain scores from baseline to end point were -0.7, 1.6, 2.5, and 2.4 points for each group, respectively (P < 0.001). Scores on SEP questions 2 and 3 improved slightly but significantly for all drug treatment groups compared with placebo (P < 0.001, Figure 13, Table 22). Adverse events were mainly limited locally to the application site with penile edema (1.4%), genital pain (17.5%), penile burning (23%), and penile erythema (11.3%) and resolved in the majority within 2 hours. Partners complained in 4.4% of vaginal burning and in 2.1% of vaginitis.

In conclusions on topical PGE1, compared with oral PDE5 inhibitor therapy with IIEF-EF changes between four and nine depending on dose and study population, topical alprostadil cannot be considered an effective monotherapy for ED (Level of Evidence 1b). Topical PGE1 may be useful in combination therapy with oral drugs if they show limited efficacy; however, data on combination therapies with topical PGE1 (Vitaros, Apricus Bio, San Diego, CA, USA) are not available. Topical PGE1 is produced by the U.S.-based NexMed Inc., a wholly owned subsidiary of Apricus Biosciences, with its special NexACT® drug delivery technology and has recently been filed for approval in some countries. It is approved in Canada.

**Transurethral Alprostadil (PGE1) with Medicated Urethral System for Erection (MUSE®)**

A new alprostadil preparation using a transurethral application with a small applicator for single use was introduced in 1994 and later on after successful phase II/III clinical development program marketed as MUSE® (MEDA Pharma GmbH, Wangen-Brüttisellen, Switzerland). Although the transurethral application route seemed at first glance to be preferable to intracavernous self-injection therapy, this new medical therapy provided limited efficacy data especially in direct comparative trials with intracavernously injected alprostadil (e.g., Caverject®, Edex®, and Viridal®), as is shown in Table 23. MUSE® is applied into the moistened urethra through the external orifice directly after emptying the bladder (Figure 14).

Typical frequent side effects of MUSE® are penile/urethral pain between 25% and 43% and

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**Table 22** Efficacy end points of alprostadil topical cream studies: results of an integrated analysis of two multicenter trials in 1,732 patients [122]

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 411)</th>
<th>Alprostadil 100 μg (N = 418)</th>
<th>Topical Cream 100 μg (N = 410)</th>
<th>Topical Cream 200 μg (N = 410)</th>
<th>Topical Cream 300 μg (N = 410)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IIEF-EF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>14.0</td>
<td>13.6</td>
<td>13.6</td>
<td>13.6</td>
<td>13.6</td>
</tr>
<tr>
<td>End point</td>
<td>13.3</td>
<td>15.3</td>
<td>16.1</td>
<td>16.1</td>
<td>16.1</td>
</tr>
<tr>
<td>Mean change</td>
<td>-0.7</td>
<td>1.7</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>P value*</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>SEP 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>55.9</td>
<td>53.4</td>
<td>52.9</td>
<td>49.9</td>
<td></td>
</tr>
<tr>
<td>End point</td>
<td>51.2</td>
<td>56.6</td>
<td>58.2</td>
<td>57.5</td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>-4.7</td>
<td>3.2</td>
<td>5.3</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>P value*</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>SEP 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29.4</td>
<td>31.3</td>
<td>27.6</td>
<td>28.7</td>
<td></td>
</tr>
<tr>
<td>End point</td>
<td>30.3</td>
<td>38.9</td>
<td>41.9</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>0.8</td>
<td>7.6</td>
<td>14.3</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>P value*</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Least square difference relative to placebo from ANCOVA

ANCOVA = analysis of covariance; IIEF-EF = International Index of Erectile Function-erectile function domain; SEP 2/3 = Sexual Encounter Profile 2/3

---

**Table 23** Review of the literature: efficacy rates of transurethral alprostadil (MUSE®) vs. self-injection therapy with alprostadil (Caverject®, Viridal®, and Edex®) (from Porst and Adaikan [123])

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>MUSE®</th>
<th>i.c. alprostadil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghazi, 1998</td>
<td>125</td>
<td>48%</td>
<td>79% (61)</td>
</tr>
<tr>
<td>Werthman, 1997</td>
<td>100</td>
<td>37%</td>
<td>89%</td>
</tr>
<tr>
<td>Porst, 1997</td>
<td>103</td>
<td>43%</td>
<td>70% (72)</td>
</tr>
<tr>
<td>Shabsigh, 1998</td>
<td>106</td>
<td>27%</td>
<td>66% (buckling test)</td>
</tr>
<tr>
<td>Shabsigh, 2000</td>
<td>68</td>
<td>53%</td>
<td>83% (at home use)</td>
</tr>
<tr>
<td>Flynn, 1998</td>
<td>Literature review</td>
<td>45%</td>
<td>&gt;70%</td>
</tr>
</tbody>
</table>

MUSE = Medicated Urethral System for Erection

---

**Figure 13** Integrated analysis of two phase III trials with topical alprostadil (PGE1): SEP 3 data [122]. PGE1 = prostaglandin E1; SEP 3 = Sexual Encounter Profile 3

---

urethral bleeding (around 5%). Infrequent adverse events are dizziness because of blood pressure fall (1–5%) and even the occurrence of syncope between 0.4% and 3% [123].

Of importance, in order to achieve the best efficacy with MUSE® and to avoid transurethral bleeding, a correct technical application is essential, i.e., to insert MUSE® directly upon micturition with the urethra still being moist.

The efficacy of MUSE® may be enhanced by simultaneous application of a constriction band on the penis’ base to avoid fast drainage of the medication through the penile veins.

Successful salvage of nonresponders to monotherapy either with sildenafil or MUSE® by combination of both methods was reported by several authors [130,131].

Successful use of transurethral alprostadil in men with the so-called soft (cold) glans was reported in 23 out of 28 men after insertion of a penile implant [132].

In conclusions on transurethral PGE1 (MUSE®), transurethral alprostadil therapy with MUSE® has shown significant efficacy in a variety of ED populations as compared with placebo (Level of Evidence 1a), but because of its inferior efficacy both with regard to PDE5 inhibitors and intracavernosal self-injection therapy, transurethral alprostadil therapy with MUSE® must be considered a niche therapy in ED. The main indications for MUSE® are patients who are nonresponsive to PDE5 inhibitors due to damage of the autonomic penile nerve supply (radical prostatectomy, cystectomy, and trauma) or in combination with PDE5 inhibitors in the so-called poor responders to oral therapy. Another rare indication for transurethral PGE1 are those patients complaining about a soft (cold) glans syndrome, which sometimes occurs after insertion of a penile implant or as a clinical entity.

Vasoactive Drugs Used for Intracavernosal Self-Injection Therapy

In general worldwide, the following vasoactive drugs are/were used both for diagnostic and therapeutic purposes in the management of ED:

- PGE1 (synonymous alprostadil) (trade names: Caverject®, Edex®, and Viridal®) [127–129]
- Papaverine (several generics available worldwide)
- Combination of papaverine/phentolamine—bimix (trade name: Androskat®: only in some European countries available)
- Trimix (synonymous triple drug): mixture of PGE1/ papaverine/phentolamine (worldwide, no commercial product available; this combination is often reconstituted by pharmacists on an individual prescription basis)
- Combination of vasoactive intestinal polypeptide (VIP) and phentolamine (trade name: Invicorp®, only available in Europe on patient named prescription basis)

PGE1 (Synonymous Alprostadil), Papaverine, Combination of Papaverine/Phentolamine

Diagnostic Use

The above-mentioned vasoactive drugs are used for diagnostic purposes to investigate cavernosal relaxation capacity and in combination with penile Doppler/duplex to investigate the penile vascular system. When used for diagnostic purposes (only marketed drugs considered), the response rates (complete erection) were highest for PGE1 with
about 73% efficacy and lowest for papaverine with about 61% efficacy ([133], Table 24).

**Therapeutic Use**

Depending on both the availability and the physician’s personal preference/experience, the outcome of self-injection therapy in a representative number of patients was reported in the literature with papaverine, the mixture of papaverine/phentolamine, or with PGE1.

In this context, only with PGE1 two well-designed prospective long-term trials with follow-up of 4 and 5 years, respectively, were published in the literature [135,136].

**PGE1 (Alprostadil—Caverject®, Viridal®, and Edex®)**

The common doses used with PGE1 depend on the underlying ED etiology and the residual relaxant capacity of the cavernous bodies. In this context in a longitudinal study (N = 1,687), it has been shown that men with a poor response to intracavernosal PGE1 testing had both a higher prevalence of hypogonadism-related symptoms and signs along with lower T levels and a higher incidence of major adverse cardiovascular events, with a hazard ratio of 2.745 (P < 0.05) [134]. Both prevalences of diabetes and metabolic syndrome were inversely related to intracavernosal injection (ICI) test response [134]. Doses used in ED usually range between 5 and 40 µg, with the most commonly used doses between 10 and 20 µg [135–138].

In patients after pelvic surgery (RRP and cystectomy), the initial dose should be chosen at 5 µg because of the higher risk of priapism and in patients after cavernous nerve injury the use of PGE1 is associated with pain, which occurs less often with papaverine/phentolamine combinations or trimix solutions.

As shown in Table 25, the individual long-term success rates in the European prospective trial with alprostadil sterile powder (Viridal®/Edex®) were very high, ranging between 91% and 96%, once a patient was successfully introduced to intracavernosal self-injection therapy [135].

The injection frequency in various PGE1 self-injection studies ranged between two and four per month [135–138].

The satisfaction rates with intracavernosal self-injection therapy with PGE1 compared with that of oral drug therapy were evaluated in a study among previous PDE5 inhibitor failures. In an analysis comprising 596 patients with a mean age of 62.1 years, mean duration of ED of 61 months, and mean duration of PGE1 ICI treatment of 35 months, the authors reported the following results [138]:

Before introduction to intracavernosal self-injection therapy, 43% of patients had taken at least one PDE5 inhibitor and 81% discontinued this therapy because of treatment inefficacy. The overall satisfaction rate with ICI was 78.3% and ICI met expectations each time in 78.6% of patients and at least half the time in 90% of patients; 86% of the patients would recommend ICI to friends. Patients reported improvements in their sex life (70.1%), relationship with their partner (50%), quality of life (44.8%), and confidence in attempting sexual intercourse (80.3%). The mean number of injections was 4.4 per month. Most patients (81.1%) found the injections easy to use. The mean score for pain on injection was 2.09/10 and for pain on erection was 2.15/10. Three-quarters of patients (73.1%) thought that their partners were satisfied with ICI [138].

**Table 24** Efficacy of vasoactive substances in the diagnosis of ED. Literature review of evaluable publications (from Porst [133])

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dose (min/max)</th>
<th>Publications</th>
<th>No. of patients</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaverine</td>
<td>30–110 mg</td>
<td>19</td>
<td>2,161</td>
<td>61% (987 out of 1,616)</td>
</tr>
<tr>
<td>Papaverine/phentolamine</td>
<td>15 mg/1.25 mg</td>
<td>13</td>
<td>3,016</td>
<td>68.5% (2,065 out of 3,016)</td>
</tr>
<tr>
<td></td>
<td>60 mg/2 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGE1 (alprostadil)</td>
<td>5 µg–40 µg</td>
<td>27</td>
<td>10,353</td>
<td>72.6% (7,519 out of 10,353)</td>
</tr>
</tbody>
</table>

ED = erectile dysfunction; PGE1 = prostaglandin E1

**Table 25** Number of successful injections resulting in sexual intercourse in the prospective European trial with alprostadil sterile powder (source: Porst et al. [135])

<table>
<thead>
<tr>
<th>Year follow-up</th>
<th>No. of total injections</th>
<th>No. of successful injections</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First year</td>
<td>6,935</td>
<td>3,937</td>
<td>91</td>
</tr>
<tr>
<td>Second year</td>
<td>3,937</td>
<td>3,691</td>
<td>94</td>
</tr>
<tr>
<td>Third year</td>
<td>3,233</td>
<td>3,050</td>
<td>94</td>
</tr>
<tr>
<td>Fourth year</td>
<td>2,781</td>
<td>2,679</td>
<td>96</td>
</tr>
<tr>
<td>Total</td>
<td>16,886</td>
<td>15,713</td>
<td>93</td>
</tr>
</tbody>
</table>
In another study, patients' satisfaction rates with PGE1-induced erections at home were 67.3% [137]. In both multicenter long-term trials with PGE1 (alprostadil sterile powder and Alprostadil Alfadex), patients' self-esteem as well as patients' and partners' satisfaction with sex life increased significantly [135,136,139].

**Return of Spontaneous Erections**

A return or improvement of spontaneous erections while on intracavernosal self-injection therapy with PGE1 demonstrates a wide range with studies reporting between 37.3% and 85% [137,140]. Although many patients on intracavernosal self-injection therapy report an improvement of spontaneous erections, only a minority of patients can give up this therapy because they are considered cured [141].

**Papaverine/Phentolamine Combination (Androskat®)**

The mixture of papaverine/phentolamine also often referred to as 'bimix' is commercially available and approved as Androskat® in several countries worldwide, especially in Europe. Androskat® is marketed in 2-mL ampoules containing 15 mg of papaverine and 0.5 mg of phentolamine per 1 mL, i.e., a total content of 30 mg of papaverine + 1 mg of phentolamine per ampoule. As a rule of thumb, the efficacy of one ampoule of Androskat® is comparable to 10 µg of alprostadil and two ampoules of Androskat® to 20 µg of alprostadil ([133], Table 24).

**Side Effects of Injectable Vasoactive Drugs**

A review of the side-effect profile of intracavernosal vasoactive drugs is provided in Table 26.

Priapism may occur with any vasoactive drug and usually in the early initiation phase when the appropriate dose for intracavernosal self-injection therapy is being determined.

The occurrence of priapism depends on the following:
1. the drug itself,
2. the dose used,
3. the underlying ED etiology.

Priapism often occurs with papaverine and the combination of papaverine/phentolamine rather than with PGE1 monotherapy. It is more often observed in cases of neurogenic ED, especially

<table>
<thead>
<tr>
<th>Substance</th>
<th>No. of publications</th>
<th>Priapism &gt; 6 hours</th>
<th>Pain</th>
<th>Fibrosis</th>
<th>Elevated liver enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaverine</td>
<td>1,527</td>
<td>15</td>
<td>7.1% (92 out of 1,300)</td>
<td>5.7% (60 out of 1,056)</td>
<td>4% (18 out of 452)</td>
</tr>
<tr>
<td>Papaverine/phentolamine</td>
<td>2,263</td>
<td>22</td>
<td>7.8% (122 out of 1,561)</td>
<td>12.4% (288 out of 1,843)</td>
<td>11.6% (141 out of 1,215)</td>
</tr>
<tr>
<td>PGE1 (alprostadil)</td>
<td>2,745</td>
<td>10</td>
<td>0.36% (10 out of 2,745)</td>
<td>0.8% (18 out of 2,180)</td>
<td>7.2% (40 out of 558)</td>
</tr>
</tbody>
</table>

ED = erectile dysfunction; PGE1 = prostaglandin E1
after spinal cord injury or pelvic surgery. In such patients, lower initiation doses should be used.

**Fibrosis** manifests as palpable penile nodules/plaques or in severe cases as cavernosal fibrosis. It occurs much more often after the use of papaverine containing injectables such as the combination of papaverine/phentolamine, and trimix than after PGE1 monotherapy.

In the majority of cases, fibrotic changes manifest as nodules/plaques and in 25–60% penile curvature is present. The follow-up of fibrotic changes, occurring both in the 4-year European multicenter study with Alprostadil Alfadex (Viridal®/Edex®) and in the 5-year U.S. trial with alprostadil sterile powder (Caverject®), showed that between 33% and 47% of these nodules/plaques heal spontaneously ([135,136], Table 27).

**Penile pain** depends on the following:

1. the drug itself,
2. the underlying ED etiology,
3. the injection technique.

Pain occurs more frequently after PGE1 and in neurogenic patients, especially after pelvic surgery.

**Elevated liver enzymes** have only been reported in papaverine-containing preparations.

**Drop-Out Rates**

Reviewing both prospective long-term self-injection trials with PGE1, the drop-out rates were 55% after 18 months in the alprostadil sterile powder (Caverject®) trial [136] and 54% after 2 years and 67% after 4 years in the Alprostadil Alfadex (Viridal®/Edex®) trial [135]. Drop-out rates were less than in the prospective multicenter transurethral PGE1 (MUSE®) trial, with 57% after 3 months and 75% after 15 months [142].

In a smaller study, with 86 patients, who had been on self-injection therapy for at least 3 months, 69 patients (80%) continued and 17 (20%) discontinued the treatment. After interviewing the patients in this study, the authors came to the conclusion that dropouts from self-injection therapy are not based on objective side effects and discomfort. Patients leaving the program were usually less motivated, less satisfied with the quality of pharmaco-induced sexuality, consider the effort to inject to be too substantial, and had not achieved improved self-esteem [143].

**Combination of Papaverine/Phentolamine/PGE1 (Triple Drug, Synonymous Trimix)**

In 1990, Goldstein et al. first reported the triple-drug combination of papaverine/phentolamine/ PGE1 [144]. Since this publication, a variety of reports on the efficacy of this drug combination has been published using a wide range of doses (see Table 24 and 28). The trimix combination is recommended for patients unsuitable for PGE1 injection due to poor response, pain, or cost. A direct comparative study investigated the efficacy of equivalent doses of alprostadil monotherapy to the triple-drug combination [152] (Table 29). In this trial, more patients expressed a preference for the trimix combination as compared with PGE1 (alprostadil) monotherapy (Table 30).

The major disadvantage of the trimix drug combination is that up to now no marketed preparation exists worldwide; patients or pharmacists need to reconstitute this combination on an individual basis, which can be somewhat complicated and cumbersome.

According to personal reports, the trimix combination is superior to alprostadil monodrug efficacy in patients with veno-occlusive dysfunction (the so-called venous leak) and in patients after pelvic surgery for reducing penile pain, which is common in patients using alprostadil monotherapy. The most common high-dose trimix prescribed contains 40 µg of alprostadil + 30 mg of papaverine + 1 mg of phentolamine, which can easily be reconstituted from two ampoules of Caverject® and one ampoule of Androskat®.

Because the application of trimix has a higher risk for priapism than alprostadil monotherapy, the initiation dose of trimix should be accordingly lower with stepwise up-titration.

---

**Table 27**  Penile fibroses in prospective long-term intracavernosal self-injection trials with alprostadil (prostaglandin E1) [135,136]

<table>
<thead>
<tr>
<th></th>
<th>No. Pts.</th>
<th>Follow-up (months)</th>
<th>Fibrosis total</th>
<th>Nodules</th>
<th>Plaques</th>
<th>Deviations</th>
<th>Severe fibros.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprostadil St. Powder (Caverject®-USA)</td>
<td>683</td>
<td>18</td>
<td>7.5% (51)</td>
<td>22</td>
<td>8</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Alprostadil St. Powder (Caverject®-Europe)</td>
<td>848</td>
<td>6</td>
<td>4% (34)</td>
<td>Not published</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprostadil Alfadex (Viridal®-Europe)</td>
<td>511</td>
<td>18</td>
<td>5.1% (26)</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Alprostadil Alfadex (Viridal®-Europe)</td>
<td>162</td>
<td>48</td>
<td>11.7% (19)</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Some patients may experience clinically symptomatic blood pressure decreases when taking high-dose trimix (20–40 μg of PGE1/20–40 mg of papaverine/1–2 mg of phentolamine). In conclusion on PGE1/papaverine/phentolamine (trimix), the trimix combination is a very effective alternative to PGE1 monotherapy. It is indicated in patients with cavernous insufficiency (venous leak) and postradical pelvic surgery, and in patients who often experience penile pain with alprostadil monotherapy. Trimix is associated with a much higher risk of priapism, especially at higher doses, and has a higher rate of cavernous fibrotic changes with mid- and long-term use, compared with alprostadil monotherapy (Level of Evidence 2a). A major disadvantage of trimix is the lack of a marketed preparation and the need for reconstitution, which can be especially cumbersome for some patients.

Combination of VIP and Phentolamine (Invicorp®)

The combination of vasoactive intestinal polypeptide (VIP) and phentolamine in a larger series of patients with ED was first published in 1992 [153]. Thereafter, the mixture of VIP/phentolamine, in doses of 25 μg/1 mg or 25 μg/2 mg, was introduced commercially as Invicorp®. It was available with a very user-friendly automatic injection device for single use (Senetek, Napa, CA, USA) and approved in some countries (Denmark, UK, and New Zealand) [154,155] (Table 31). Although the VIP/phentolamine combination had promise, due to its former self-injection prototype device and relatively high efficacy, it was never marketed globally after the successful introduction of PDE5 inhibitors.
A comparative study of PGE1 (Caverject®) and VIP/phentolamine (Invicorp® autoinjection device) was conducted over a longer interval in over 40 men who were performing self-injection therapy with PGE1 (Caverject®). At that time, over 80% of the patients preferred Invicorp® because of its convenient delivery mode (at that time a single use autoinjection device was provided with Invicorp®) and the more natural sensation of the erection as compared with PGE1 (Porst, unpublished data).

In 2004, Senetec/USA outlicensed Invicorp® to Ardana, a small pharmaceutical company based in Edinburgh/Scotland.

To date, Invicorp® still has not been officially marketed but can be prescribed in Europe on a patient named basis as an injectable ampoule. However, it is no longer offered with the patient-friendly autoinjection device, which was dropped due to cost.

Other Vasoactive Drugs Tried or Used for Self-Injection Therapy

Several other vasoactive drugs have been used for intracavernosal self-injection therapy but received little or no marketing support:

Moxisylyte (thymoxamine) (Viatris, Mérignac, France) is an alpha-adrenoceptor blocker with a preference for alpha1 adrenoceptors. The drug was marketed as Icavex® with moderate success for intracavernous self-injection therapy in France but withdrawn some years later because of small market share [156].

Linsidomine (SIN-1), the biologically active metabolite of the NO-donor molsidomine.

Nitroprusside-natrium, also belonging to the class of NO donors.

Potassium-channel openers: PNU 83757, a new potassium channel opener.

Forskolin, a direct activator of adenylate cyclase.

Chlorpromazine, an alpha1-adrenergic receptor blocker, is used in some countries in combination with papaverine (bimix) instead of phentolamine. In a comparator trial with 50 patients, the efficacy of the combination of papaverine and chlorpromazine, as compared with the combination of papaverine and phentolamine, yielded similar efficacy responses [157].

Figure 15 Correct technique of self-injection therapy (original source: Pharmacia Upjohn, former Caverject® manufacturer, now Pfizer Corp., New York, NY, USA)

Technique and Complications of Self-Injection Therapy

In order to overcome patients’ resistance and to decrease potential complications from self-injection therapy, a thorough education on the proper injection technique with the use of ultrathin needles is mandatory (Figure 14). According to personal experience, it takes at least two instruction sessions before the patient gains enough confidence to administer the technique correctly and to avoid potential injection complications (see Figures 15 and 16).

Spring-Loaded Injector for Intracavernous Self-Injection Therapy

Spring-loaded self-injection devices are available, which insert the needle into the corpus cavernosum with a touch of a button. Some patients, especially those who are needle phobic, find the use of this “automatic” injector much more acceptable than inserting the needle manually. Whether the needle is inserted into the corpus cavernosum manually or “automatically,” the patient still must push the plunger of the needle down to inject the liquid solution into the corpus cavernosum.

The most frequent side effects encountered with self-injection therapy are the following:
Prolonged erections/priapism—the frequency of this complication has been shown to be clearly drug-and-dose dependent (see Table 26). Priapism episodes lasting longer than 6 hours must be treated by intracavernosal injection of a sympathomimetic agent (e.g., etilefrine, phenylephrine, or adrenaline) and/or evacuation of the entrapped blood with a butterfly needle. This is especially required if the patient presents with erections longer than 6 hours. The 6-hour time limit has been established in order to prevent irreversible ischemic damage to the cavernosal tissues (see also manuscript SOP on priapism).

Fibrosis of the cavernosal tissue is dependent on the drug used and on the patients’ ability to correctly inject (see Table 26). On follow-up of fibrotic changes occurring in the 4-year European multicenter study with alprostadil (Viridal®/Edex®) and in the 5-year U.S. trial (Caverject®), it was demonstrated that between 33% and 47% of these nodules/plaques healed spontaneously ([135,136], Table 27). In another study, on the outcome of fibrotic changes related to self-injection therapy in 44 patients, 52% (N = 23) of the patients showed spontaneous improvement despite the majority (91%) continuing with intracavernosal self-injection therapy [158]. The tendency for spontaneous disappearance of fibrotic changes can be augmented by temporary discontinuation of self-injection therapy for 2–4 months, followed by reeducation of the patient as to the correct self-injection technique (see Figure 16). In about half of the patients, fibrotic changes are followed by the development of penile curvatures that may require surgical correction.

Penile hematoma/bruising is the most often reported side effect with intracavernosal self-injection therapy and occurred between 33% and 47% of the time in the 4-year European long-term trial [135]. Hematomas occurred more frequently in those patients who developed fibrotic changes, pointing to the role of postinjection technique. In some patients, a dark coloring of the penile skin due to hemosiderin deposits may follow repeated hematoma occurrence.

Rare complications reported with self-injection therapy include the occurrence of infections/abscesses, needle breakage requiring surgical removal, and the development of cavernous thrombosis with involvement of the pelvic veins and subsequent fatal pulmonary embolism [159].

Special Populations/Features Regarding Self-Injection Therapy

Patients on Anticoagulants
According to the literature, intracavernosal self-injection therapy can be performed in men on warfarin-containing anticoagulants without increasing the risk of bleeding/ecchymosis [160].

Transplant Patients
The literature has not indicated any increased risk with self-injection therapy in patients
having received kidney or heart transplants [161].

**Diabetics**

Observations in the literature indicate that ED patients with diabetes are at increased risk to develop fibrosis and pain with self-injection therapy [162].

In conclusions on intracavernosal self-injection therapy with vasoactive drugs, since the successful introduction of effective oral drug therapy with PDE5 inhibitors, intracavernosal self-injection therapy with vasoactive drugs has diminished in popularity for the management of ED and is not even considered a viable option by the majority of physicians treating patients with ED at present. To date, intracavernosal self-injection therapy is the most effective and reliable medical therapy we can offer to our ED patients. Major obstacles to acceptance of intracavernosal self-injection therapy are the procedure itself and needle phobia. Keys to success of self-injection therapy are a careful and sensitive approach to the patient/couple on the correct application technique and the use of ultrathin needles (27–30 g), which contributes to reduction of pain and injection-related complications and which translates to higher acceptance rates.

PGE1 (alprostadil) monotherapy is considered the standard vasoactive agent with three different marketed products (Caverject®, Edex®, and Viridal®) available worldwide in relative patient-friendly dual-chamber injection devices.

The efficacy and safety of PGE1 (alprostadil) monotherapy have been proven in two international long-term (4 and 5 year) trials (Level of Evidence 2b).

Two alternatives to PGE1 monotherapy, the VIP/phentolamine (Invicorp®) combination, which can be prescribed on an individual patient basis in some European countries, and the combination of papaverine/phentolamine (bimix—available in some European countries, as Androskat®), may be effective for those patients experiencing pain after PGE1. Both combinations were effective and safe in midterm trials (6–12 months) (Level of Evidence 3a). The trimix combination (PGE1/papaverine/phentolamine)—no trade marketed product available worldwide must be reconstituted individually by a pharmacist—may be considered as a reserve medication for those patients in whom PGE1 monotherapy (up to 40 μg) is either ineffective or too painful (which occurs in patients after pelvic surgery). The trimix combination is highly effective, usually higher than PGE1 monotherapy, but is burdened by a higher rate of priapism and penile fibrotic, Peyronie’s like changes (Level of Evidence 3a).

Papaverine monotherapy is not recommended because of high toxicity (liver and cell toxicity with subsequent cavernosal fibrosis) and greater risk of priapism and fibrotic changes (Level of Evidence 3a).

The major risk of self-injection therapy occurs at the initiation phase, with the chance of priapism and fibrotic changes developing over time. Priapism occurs more frequently in papaverine-containing combinations compared with PGE1 monotherapy or VIP/phentolamine. Priapism must be treated by at least 6 hours after administration, by intracavernosal injection of an alpha-adrenoceptor agonist, such as epinephrine (must be diluted accordingly!) and phenylephrine or etilefrine, depending on what drug is more available in that part of the world.

Fibrotic changes are treated by temporary suspension of self-injection therapy for 3–4 months, followed by a thorough reeducation on the correct self-injection technique, with a chance for spontaneous recovery of 30–50%.

Intracavernosal self-injection therapy may be also considered in combination with oral drug therapy (PDE5 inhibitors) for patients where monotherapy fails to produce satisfying erections (Level of Evidence 3b).

### Vacuum-Erection Devices (VEDs)/Vacuum Constriction Devices (VCDs)

The concept of vacuum device therapy in the treatment of ED dates back to the American physician John King, who described in 1874 a method of improving erections by a small vacuum pump. After being granted various patents for vacuum device therapy both in Germany and in the United States, the American entrepreneur Geddings Osbon obtained permission from the FDA to produce a vacuum device that was subsequently named Erec-Aid® in 1982. In that same year, Nadig et al. published the first report on efficacy and safety of VEDs [163].

**General Indications for VEDs**

One of the major advantages of VED is that it can be successfully applied to men with nearly all etiologies of ED. Therefore, VED is considered a first-line therapy option for ED populations in
most current recommendations/guidelines for the management of ED [21,164].

Although a VED can be offered to every ED patient, the acceptance for mechanical ED therapy is somewhat poor. It is especially successful in elderly patients in long-term partnerships with occasional intercourse attempts.

Vacuum therapy can also be used in combination with other ED therapies such as oral drug therapy (e.g., PDE5 inhibitors), transurethral or intracavernosal injection therapy, or even with sex therapy if the patient/couple is dissatisfied with another monotherapy [165,166].

**Special Indications for VEDs**

Besides common ED, special indications in which VEDs have been successfully used are in men after Peyronie’s disease surgery. The VEDs stretch the shortened penis after reconstructive surgery [167] to avoid postoperative, severe penile fibrosis and shortening, similarly after removal of an infected penile prosthesis [168].

**Technique of VED**

VEDs share a common mechanism of action: a plastic cylinder, whose lower rim is made airtight by application of a lubricant gel, is applied over the penis in a standing position and then firmly pressed against the pubic bone (Figure 17). Afterward, a vacuum is created manually, via a pump, which is either separately connected to the cylinder with a tube or is directly integrated and battery operated on the top of the cylinder (Figure 18).

A major disadvantage of VED therapy is that induced erections are not natural by look or feel. First, the rigid erection achieved by creating a
vacuum within the cylinder can only be maintained by a rubber constriction ring, which of course cannot be concealed. The rubber constriction ring must be rolled onto the cylinder prior to the vacuum maneuver and is then rolled onto the base of the penis after creating the vacuum and erection to prevent venous drainage and detumescence. Generally, the application duration of the constriction ring is limited to 30 minutes by the VED manufacturers to avoid ischemic damages of the cavernosal tissue. Sometimes, two constriction rings need to be applied to maintain a rigid erection if one ring is insufficient.

Compared with naturally occurring erections, VED-induced erections are perceived as different by the couple because the constriction ring applied to the base of the penis, the proximal third of the cavernous bodies, i.e., the crura, is uninvolved in the VED-induced erection. This noninvolvement of the crura in the penis in VED-induced erections causes some degree of instability at the penis’ base, occasionally requiring manual assistance while inserting the penis into the vagina.

The VED-erect penis appears more cyanotic in color and is perceptibly cooler by the partner because the cavernous bodies are filled with low oxygenated blood. This is in contrast to natural erections occurring through arterialized and highly oxygenated blood, and thus makes the erect penis feel warmer.

Worldwide, a variety of manufacturers has marketed VED, with the Osbon VED being the market leader.

Therefore, among the relatively sparse literature on VED, most deal with the outcome of the Osbon VCD devices (Osbon Erec-Aid® and Osbon Esteem®). Only a few smaller series have been published with devices of other manufacturers, such as the Innovital System, Post-T, VED, and the Synergist System (Table 32).

When analyzing the data of VED therapy, there is a striking discrepancy between sold VEDs and eligible patients for follow-up. So, for example, in the large series published by Witherington and Lewis, only 10–17% of all VED buyers were considered or eligible, which is in sharp contrast to all other ED therapies [171,175].

In those series, in which a majority of the patients were eligible for follow-up, 40–60% discontinued VED therapy. The generally low acceptance of VED therapy was also shown in the series by Graham et al. among 1,236 new ED patients who were subjected to full diagnostic workup and to whom all available therapeutic modalities were offered only 323 (27%) requested a 2-week trial of VED, with only 74 (6% of the total population) opting for a VED prescription [179].

In a German VED series, it was obvious that the acceptance rate of VED was markedly higher in nonresponders to pharmacotherapy compared with responders (45% vs. 22%) [173,182].

The role and importance of VED in penile rehabilitation therapy after radical prostatectomy was recently discussed in detail [183]. The authors pointed to the fact that VED may be successfully used in combination therapy with PDE5 inhibitors, injection therapy, and transurethral therapy. It could also be used to prevent penile shrinking after RRP or reconstructive penile surgery for Peyronie’s disease.

**Contraindications to VED**

Provided the Princeton II Consensus Conference Algorithm (see Figure 2) is considered, the only real contraindications to VED are patients with a history of recurrent prolonged erections/priapism.

**Table 32** Outcome of VCD therapy—overviews of the literature (source: Glina and Porst [169])

<table>
<thead>
<tr>
<th>Author</th>
<th>Device</th>
<th>N</th>
<th>Evaluable</th>
<th>Mean age (years)</th>
<th>Follow-up (months)</th>
<th>Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadig, 1987</td>
<td>Osbon Erec-Aid®</td>
<td>302</td>
<td>81% (244)</td>
<td>?</td>
<td>up to 72</td>
<td>83%</td>
</tr>
<tr>
<td>Witherington, 1989</td>
<td>Osbon Erec-Aid®</td>
<td>15,000</td>
<td>10% (1,517)</td>
<td>64</td>
<td>8.6</td>
<td>92% good erections</td>
</tr>
<tr>
<td>Blackard, 1993</td>
<td>Osbon Erec-Aid®</td>
<td>47</td>
<td>96% (45)</td>
<td>?</td>
<td>?</td>
<td>42%</td>
</tr>
<tr>
<td>Derouet, 1993</td>
<td>Osbon Erec-Aid®</td>
<td>90</td>
<td>100%</td>
<td>32–75</td>
<td>?</td>
<td>37%</td>
</tr>
<tr>
<td>Baltaci, 1995</td>
<td>Osbon Erec-Aid®</td>
<td>61</td>
<td>80% (49)</td>
<td>?</td>
<td>12.8</td>
<td>67%</td>
</tr>
<tr>
<td>Meinhardt, 1993</td>
<td>Post-T VED</td>
<td>74</td>
<td>100%</td>
<td>55</td>
<td>3 weeks</td>
<td>30%</td>
</tr>
<tr>
<td>Fedel, 1995</td>
<td>Innovital</td>
<td>100</td>
<td>40%</td>
<td>52.4</td>
<td>6</td>
<td>90%</td>
</tr>
<tr>
<td>Cookson, 1993</td>
<td>Osbon Erec-Aid®</td>
<td>?</td>
<td>53% (115)</td>
<td>65</td>
<td>29</td>
<td>84%</td>
</tr>
<tr>
<td>Graham, 1998</td>
<td>?</td>
<td>323</td>
<td>100%</td>
<td>61</td>
<td>2 weeks</td>
<td>23%</td>
</tr>
<tr>
<td>Droupy, 1998</td>
<td>?</td>
<td>53 (RRP)</td>
<td>55% (29)</td>
<td>66.5</td>
<td>27</td>
<td>52%</td>
</tr>
<tr>
<td>Opsomer, 1998</td>
<td>?</td>
<td>170</td>
<td>?</td>
<td>66</td>
<td>48</td>
<td>55%</td>
</tr>
</tbody>
</table>

Post-T VED = post-testosterone vacuum-erection device; RRP = radical retropubic prostatectomy; VCD = vacuum constriction device

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and those with severe bleeding disorders. For patients on anticoagulants such as coumadin and warfarin, a prospective trial demonstrated that bleeding complications, such as hematoma and petechiae, in patients using VED did not exceed those observed in the general urological population [160]. VED therapy is also contraindicated in patients with severe penile curvature, either congenital or acquired (Peyronie’s disease), because of the potential risk of penile fracture while establishing the vacuum in the cylinder.

**Side Effects of VED**

Relatively frequent side effects of VED therapy are penile bruising, petechiae, and extensive hematoma or pain.

A common side effect of VED is the blockade of seminal fluid discharge while the constriction ring is applied, which may cause ejaculatory discomfort in some patients [171,175].

Rare or anecdotal complications with the use of VED are the onset of Peyronie’s disease, skin necrosis, and urethral bleeding [169].

Occasionally, chronic use of VED may result in hyperpigmentation of the penile skin due to repeated skin bruising with subsequent hemosiderin deposition. In this regard, it is important to advise patients to use only prescription devices. Other devices may have no pressure control or safety valves to release the pressure.

**Acceptance and Discontinuation Rates of VED**

Although VED therapy must be considered very effective in producing erections sufficient for vaginal penetration, many couples discontinue vacuum-erection therapy over the long term. The main reasons pertain to the very mechanical and therefore “unsexy” procedure to create an erection, which finally results in an unnatural perceived erection and subsequent lack of acceptance for both the patients and their partners [184]. Once the couples have adapted their sex life to the use of VEDs, a significant increase in frequency of intercourse, sexual arousal, coital orgasm, and sexual satisfaction has been reported [185].

A minority of patients (8–16%) reported on the return of spontaneous erections with the long-term use of VED [174,175,178,180].

In conclusions on VED, among all options, VED can be considered as the safest and most inexpensive form of ED treatment. Although VED efficacy rates are comparable to both PDE5 inhibitors and intracavernosal self-injection therapy, the acceptance- and long-term use rates are relatively low (Level of Evidence 2b). Major reasons for these low acceptance and usage rates are both the very mechanical procedure linked to VED-induced erections and their unnatural feeling due to the filling of the cavernous bodies with poorly oxygenated blood, making the penis appear cyanotic and feel cooler than natural erections. Because the discharge of the seminal fluid is restricted in many patients due to the constriction ring, which is necessary to maintain the erection, VEDs are not an option for those couples desiring to conceive by natural means. Relatively frequent side effects linked to VED are penile bruising/hematoma, which often occur in the initiation phase but are not more commonly found in patients using anticoagulants. In special situations, VED may be used in combination with oral drug therapy and transurethral or intracavernosal injection therapy to increase efficacy (Level of Evidence 3b). Successful application of VED has been suggested for penile stretching after surgical reconstruction for Peyronie’s disease to avoid penile scarring/fibrosis and shortening and after removal of an infected penile implant.

**Combination Therapies**

Combination therapies have been reported in the literature for patients who fail monotherapy to produce a satisfactory erection.

**PDE5 Inhibitors + Self-Injection Therapy**

Successful salvage therapy in nonresponders \(N = 93, \text{mean 53.5 years, range 24–77}\) to monotherapy (here either high-dose alprostadil or trimix, respectively) was reported with the combination of sildenafil (100 mg) and trimix [186]. Of these 93 patients failing successful injection therapy at home, 32 (34%) successfully responded to sildenafil monotherapy 100 mg. Of the remaining 61 patients, 29 (47%) responded to combination therapy with sildenafil 100 mg and trimix. Thirty-two (53%) did not and were defined as nonresponders, even with combination therapy.

**PDE5 Inhibitors + Transurethral PGE1**

Of 214 patients treated for ED, with transurethral PGE1 (MUSE®) or sildenafil up to 100 mg, 65 (30%) were not fully satisfied was reported with the firmness of their erections using either monotherapy. Sixty (92%) out of the 65 patients claimed satisfaction with combination therapy. Questionnaire scores for erectile function were 23.1 ± 2.0
(114%) for combination therapy vs. 19.2 ± 1.8 (77%) and 15.2 ± 1.6 (41%) for sildenafil and alprostadil monotherapies, respectively ($P < 0.05$). There were no significant differences in responses between the two groups. The men also reported improvement in intercourse and overall satisfaction [130].

Sixteen patients (mean 56 years, 11 post-RRP and 5 with other organic ED) failing both 100 mg of sildenafil and 1,000 µg of MUSE® monotherapies underwent combination therapy with 100 mg of sildenafil and 500 µg of MUSE®. Using this combination treatment, all patients were able to have successful intercourse after 3 months [131].

**Vacuum Device Combination Therapies**

Successful augmentation of the erectile response after self-injection of a papaverine 30 mg/ phentolamine 1 mg combination (bimix) with VED was observed in a pilot study with 22 men [166]. In a similar study including 10 men who did not show satisfactory response to either intracavernosal injection of a combination of 60 mg of papaverine + 30 µg of PGE1 or after application of a VED, the combination of both modalities resulted in a significantly ($P < 0.0001$) better response, measured by penile buckle pressure, than either monotherapy alone [165].

In conclusion on combination therapies for ED, although the literature lacks data from prospective and well-designed studies in a representative number of patients, combination therapies in ED patients must be considered routine practice in the management of ED. It is documented that between 20% and 40% do not respond to either monotherapy. A variety of combination strategies exists, which may fit couples’ needs for a satisfying sex life. According to their own experiences, the limiting element of combination therapies is not lack of efficacy or safety, but expense. All the previous listed treatments in combination therapies may cost the patients up to US $100–$200 per month, depending on the choice of therapy and frequency of sexual intercourse. Nevertheless, physicians should be aware of these combination options in order to counsel patients appropriately (Figure 19).

**Disclosures**

**H. Porst:** Investigator, speaker, and consultant for Bayer Healthcare, Eli Lilly, VIVUS; investigator and advisor for Auxilium.

**A.L. Burnett:** Consultant/medical advisor or research support for Endo Pharmaceuticals, Abbott, Auxilium Inc., Pfizer Inc., VIVUS, American Medical Systems, Coloplast, Timm Medical, Shionogi Pharma, and Reflexonic LLC.

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**H. Ghanem:** Speaker for Elli Lilly, Pfizer, and Bayer Healthcare.

**F. Giuliano:** Consultant and speaker for Lilly, consultant and investigator for Bayer Healthcare.

**S. Glina:** Speaker for Lilly, Pfizer, Bayer Healthcare, and Cristalia; investigator for Lilly and AmGen; consultant for Lilly.

**W. Hellstrom:** American Medical Systems—consultant or advisor; Auxilium—meeting participant or lecturer, consultant or advisor, investigator; Coloplast—consultant or advisor, investigator; Cook—consultant or advisor, lecturer; Endo—consultant or advisor, investigator, lecturer; Johnson & Johnson—consultant or advisor, meeting participant or lecturer, investigator; Lilly, USA—consultant or advisor, lecturer; Medtronic—consultant or advisor, investigator, meeting participant or lecturer; NIH—board member, officer, trustee; Slate Pharmaceutical—lecturer, advisor, investigator; Theralogix—board member, officer, trustee; VIVUS—consultant, investigator, lecturer.

**A. Martin-Morales:** Investigator, speaker, and consultant for Bayer, Lilly, AMS, and Coloplast.

**A. Salonia:** Speaker and consultant for Bayer Healthcare.

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Figure 19 Therapeutic algorithm of ED based on history and diagnostic findings and considering cardiac health status according to Princeton II. ED = erectile dysfunction; PDE5 = phosphodiesterase type 5

Andrea Salonia; Ira Sharlip; the ISSM Standards Committee for Sexual Medicine

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References


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