ABSTRACT—Erectile dysfunction (ED) is a common problem with a prevalence of approximately 50% in men aged 40 to 70. There are several etiologies for ED including vasculogenic, neurogenic, hormonal and/or psychogenic factors; one-fourth of ED cases can be drug-related. Penile erection involves a complex interaction between the CNS and local factors. It is a neurovascular event modulated by psychological and hormonal factors. Pharmacologically, neural modulation and endocrine status are very important to attaining penile erection. There have been several significant advances for the pharmacologic treatment of ED. Treatments include agents that are not only orally effective, but possess either local or central acting mechanisms of action. Apomorphine, a centrally-acting agent, is effective in the treatment of ED. Sildenafil, another orally effective agent, acts by inhibiting cyclic GMP-specific phosphodiesterase Type V. Testosterone can be effective transdermally. Non-orally active agents include alprostadil and papaverine. Phentolamine and trazodone are effective in selected cases. Some agents can interact with other medications. Several pharmacological agents, some with central-acting mechanisms and some with locally-acting vascular effects, are therapeutically useful in the treatment of ED.

Keywords: Incidence of erectile dysfunction, Alprostadil, Apomorphine, Phenolamine, Sildenafil

I. Introduction

1. Incidence of erectile dysfunction

The term impotence has usually been employed to indicate the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse. The preferred term is now erectile dysfunction (ED). ED is a common problem, especially among older men (1). It has been suggested that the more precise term, viz ED, be used to signify an inability of the male to achieve an erect penis as part of the overall multifaceted process of male sexual function. Such a process encompasses a variety of physical aspects with significant psychological and behavioral implications (2).

ED affects millions of men. In the U.S. alone, approximately 10 million men suffer from ED. According to the National Center for Health Statistics (1989), ED results in nearly a half-million outpatient visits. While erectile function may not be the most important indicator of sexual satisfaction, ED may contribute to mental stress that affects interactions with family and associates. Although many advances have occurred in the diagnosis and treatment of ED, other aspects remain poorly understood by the general population and even health care professionals (2). ED is frequently assumed to be a physiological event associated with the aging process, although this may not be entirely accurate.

Male sexual dysfunction is unique since it is not only non-life threatening, but it is influenced by cultural, religious and legal factors (3). Indeed, evolving changes in societal attitudes toward human sexuality have occurred along with increased awareness pertaining to ED (4). Because the U.S. is a multicultural country, it is often represented by divergent factors rendering an epidemiologic study of male sexual dysfunction rather complex.

Unlike twenty years ago when ED was attributed to being primarily a psychological disorder, it is now known that the majority of men with ED exhibit an underlying organic etiology (5, 6).

The prevalence of ED is approximately 50% in men aged 40 to 70 (6). Expectedly, the percentage is increased with increasing age. In addition to aging, other risk factors associated with ED include chronic illnesses, medications and cigarette smoking. Oftentimes, lifestyles including smok-
ing, heavy alcohol consumption, sedentary patterns and obesity are associated with the risk of erectile dysfunction (7). There are also confounding factors wherein cigarette smoking appears to predispose patients to early atherosclerotic lesions in the cavernous artery following chronic perineal trauma (8). The early adoption of health lifestyles, including physical activity, may reduce the risk of erectile dysfunction. Actually, there are a number of epidemiologic correlates associated with ED (Table 1) (9).

ED can be due to vasculogenic, neurogenic, hormonal and/or psychogenic factors (10). It can also be due to changes in the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) biochemical pathway (6). ED is associated with a host of concomitant disease states often associated with aging (7). There are correlations between ED and heart disease (11, 12), peripheral vascular disease (13), and stroke (14). Still other medical complications are associated with impotence (15) (Table 2). Severe hypogonadism is associated with the loss of libido and of erectile function (9). The majority of cases of secondary ED are usually associated with arteriosclerosis. Also, myocardial infarction is often associated with ED. Likewise, there is a prevalence of ED associated with diabetes mellitus, particularly in the older diabetic. Hypertension seems to be related to ED, and oftentimes the onset of ED is related to the initiation of anti-hypertensive therapy (9). Uremic men frequently experience ED, and this may be due to elevated prolactin, luteinizing hormone (LH) and estradiol. Neoplastic diseases, some of which may involve the prostate gland and its innervation, can contribute to ED (9, 15). Still other chronic diseases, psychogenic causes and Peyronie’s disease can be associated with ED (9). Finally, ED is associated with a high incidence of depressive symptoms, regardless of age, marital status or comorbidites (16).

Although many therapeutic agents, particularly those which affect neurotransmitter activity (both agonists and antagonists) are often associated with ED, many such reports have been anecdotal and without the benefit of well controlled clinically designed studies. Nevertheless, drug-related ED may constitute 25% of the causes (17). Hypogonadism and psychogenic reasons for ED accounted for 19% and 14% respectively. Table 3 depicts several classes of drugs that have been associated with ED (10, 15, 17). The mechanism(s) of drug-induced ED may be neural, endocrine or sometimes simply unknown. ED is perhaps most frequently associated with anti-hypertensive medications, particularly β-blockers and thiazide diuretics. Estrogen therapy and the use of anti-androgens can also lead to changes in the endocrine system causing ED. Somewhat paradoxically, selective serotonin re-uptake inhibitors (SSRIs) can be associated with ED (17), yet some of these same agents can be used for the treatment of premature

### Table 1. Epidemiologic correlates of erectile dysfunction (ED)

| Correlation with ED                                      | No correlation with ED                                                                 |
|----------------------------------------------------------|---------------------------------------------------------------------------------------|
| Age                                                      | Cigarette smoking                                                                     |
| Heart disease, hypertension, diabetes mellitus           | Depression                                                                             |
| Associated medications                                   | Indices of anger                                                                      |
| Cigarette smoking                                        |                                         |
| Depression                                               |                                         |
| Indices of anger                                         |                                         |
| No correlation with ED                                    |                                         |
| Ulcer disease                                            |                                         |
| Arthritis                                                |                                         |
| Allergies                                                |                                         |
| Alcohol intake                                           |                                         |
| Schizophrenia                                            |                                         |
| Plasma cortisol or dihydrotestosterone level             |                                         |
| Inverse correlation with ED                              |                                         |
| Dominant personality                                     |                                         |
| High plasma HDL and cholesterol level                    |                                         |
| High plasma DHEA levels                                  |                                         |

Modified from reference 9 (Korenman, 1998).

### Table 2. Medical conditions associated with impotence

| Surgical                                           | Endocrine                                            |
|-----------------------------------------------------|-------------------------------------------------------|
| Pelvic malignancy                                   | Diabetes mellitus                                     |
| Pelvic radiotherapy                                 | Hypothyroidism                                        |
| Radical pelvic surgery                              | Hypogonadism                                          |
| Lumbar disk prolapse and laminectomy                |                                         |
| Pelvic fracture                                      |                                         |
| Peyronie’s disease                                  |                                         |
| Priapism                                            |                                         |
| Bilateral orchidectomy                               |                                         |
| Iliac artery surgery                                |                                         |
| Endocrine                                           | Cardiovascular                                       |
| Diabetes mellitus                                   | Arteriosclerosis                                      |
| Hypothyroidism                                       | Peripheral vascular disease                          |
| Hypogonadism                                        | Hypertension and antihypertensive medications         |
| Neurological                                         | Neurological                                           |
| Paraplegia                                          | Arteriosclerosis                                      |
| Multiple sclerosis                                  | Peripheral vascular disease                          |
| Peripheral neuropathy                                | Hypertension and antihypertensive medications         |
| Chronic debilitating illness                         | Neurological                                           |
| Chronic renal failure and hemodialysis               | Arteriosclerosis                                      |
| Chronic hepatic failure                             | Peripheral vascular disease                          |
| Chronic alcohol abuse                               | Hypertension and antihypertensive medications         |

Modified from reference 15 (Keogh et al., 1989)
ejaculation. Erection involves a coordinated action of the autonomic nervous system (ANS) wherein certain drugs may interfere with the sympathetic division (e.g., \(\alpha_1\) receptors) and the parasympathetic division (e.g., non-cholinergic neurotransmitters). Undoubtedly, \(\beta\)-blockers are the class of antihypertensive agents most often involved in causing ED. Thiazide diuretics are essentially devoid of central nervous system (CNS) or ANS activity, yet are associated with ED, possibly due to their ability to deplete zinc (18).

It is evident that there are many disease states and surgical conditions that predispose ED. Furthermore, there are a large number of different therapeutic agents as well as social/recreational agents that can contribute to or are otherwise associated with ED.

### 2. Physiology of penile erection

Andersson (19) has provided a comprehensive review on the physiology of penile erection including the anatomical and morphological basis of erection, its hemodynamics, neurophysiology and the role of sex hormones. Penile erection involves a complex interaction between the CNS and local factors. This physical event also encompasses a component of male sexual behavior. Overall, erection is a neurovascular event modulated by psychological and hormonal factors (10).

Upon sexual stimulation, nerve impulses elicit the release of neurotransmitters from the cavernous nerve terminals and also vasoactive relaxing factors from the endothelial cells of the penis causing the relaxation of smooth muscles in the arterial system that supplies the erectile tissue, leading to a significant increase in penile blood flow. Concomitantly, relaxation of the trabecular smooth muscle increases the compliance of the sinusoids, enhancing the rapid filling and expansion of the sinusoidal system (10).

The process of erection and detumescence consists of a series of complex interactions involving the ANS and subsequent changes in local blood flow. The penis is supplied mainly by the internal pudendal artery, while there are three sets of veins that drain the penis: superficial, intermediate and deep. The pelvic nerves are mainly responsible for penile erection.

The process of erection, viz., phase 0 of the process of penile erection or the flaccid phase reveals a dominant sympathetic nervous system. In phase I, the latent or filling phase, and after sexual stimulation,
there is a local dominance of the parasympathetic nervous system. Phase 2 (tumescence), 3 (full erection) and 4 (rigid erection) are characterized more by hemodynamic changes resulting from the initial modulations in the ANS upon local blood flow. Phase 5 (transition) reveals an increase in sympathetic nervous system activity leading to increased arterial tone and contraction of the trabecular smooth muscle. In the final phases, phase 6 (initial detumescence) and 7 (fast detumescence), there is a diminished intracavernous pressure and an inactivation of the venoocclusive mechanism leading again to a flaccid state.

Vascular supply, intrinsic smooth muscle of the penis, and adjacent striated muscles are controlled by nerves arising from the thoracolumbar sympathetic, the lumbo-sacral parasympathetic and the lumbosacral somatic (19). Normal erection necessitates that all three of these systems participate. The pudendal nerve is the major somatic pathway of the male genitalia and consists of three major branches (22). In addition to the coordinated participation of these three peripheral nerve systems, there are also central neural pathways. There are at least two distinct central neural pathways involved in penile erection — psychogenic (23) and reflexogenic (24). Both these central mechanisms interact during normal sexual activity. Importantly, they require a complex coordination between the ANS and somatic outflow which occurs at the level of the spinal cord.

There appear to be several central neurotransmitters and other factors involved in the process of erection. 5-Hydroxytryptamine (5-HT), dopamine and norepinephrine play important roles as central neurotransmitters in the process of erection. Still other substances or hormones such as endorphins, oxytocin, vasopressin, adrenocorticotropin hormone (ACTH) (and related peptides) and prolactin appear to participate in this complex and coordinated process of penile erection. Pharmacologically, 5-HT pathways inhibit copulation, but it is also known to both facilitate and inhibit sexual function depending upon physiological states or conditions. Dopaminergic mechanisms are also involved in the regulation of male sexual responses, including erection. Central nonadrenergic neurons may influence male sexual behavior. The exact role of the opioids, oxytocin, ACTH, etc., while studied in animals, is less clearly understood in human sexual function.

NO released during nonadrenergic, noncholinergic neurotransmission (NANC) and from the endothelium is most likely the major neurotransmitter mediating penile erection (23–26). NO is the mediator of relaxation of the corpus cavernosum in response to NANC neurotransmission (27). NO can be synthetized as a by-product of the conversion of L-arginine by NO synthase. L-Arginine plays a role in erectile function.

Furchgott and Zawadski (28) originally described endothelium-derived relaxing factor (EDRF), recognizing its apparent endothelial origin in the peripheral vasculature and its ability to induce relaxation of smooth vascular muscle. EDRF was subsequently established to be biochemically distinct from NO (29). NO functions as EDRF in many blood vessels, and its release from the endothelial cell produces relaxation of vascular smooth muscle by activating soluble guanylate cyclase, and thereby increasing the production of intracellular messenger, cGMP. The role of NO in the physiology of male sexual function establishes its importance as the principal modulator of penile erection (30). The elevation of cGMP activates a specific protein kinase which then phosphorylates certain proteins, activates ion channels, and through intermediary biochemical events leads to a reduction in cytosolic calcium and a relaxation of smooth muscle. Following an erection or the return to the flaccid state, cGMP is hydrolyzed to GMP by phosphodiesterase type 5. While other types of phosphodiesterases are present in the corpus cavernosum, they do not appear to play any significant physiological role in erection. Selected drugs (e.g., sildenafil, and in development, cialis and vardenafil) used in the treatment of ED exert their pharmacologic mechanism of action by inhibiting the breakdown of cGMP. Sildenafil is a selective inhibitor of phosphodiesterase type 5, an enzyme that inactivates cGMP. Other drugs used in the medical management of ED exert their mechanism(s) of action through other biochemical pathways including both CNS sites and peripheral sites of action(s).

II. Pharmacologic agents

1. General

Within the past few years, there have been a number of excellent reviews on the pharmacology of drugs used for the treatment of ED (10, 31–33). Still other reviews have focused on the development of self-injection techniques (34) and the evolution treatments for ED and their classification as pharmacologic agents (35).

Heaton et al. (35) have devised a classification of pharmacologic agents based on their mode of action (Table 4). Such a classification encompasses five broad categories of treatment, and not only takes into account the mode of action, but can also be used to identify routes of administration and the means of achieving target organ selectivity (35). The primary class denotes a mode of action and not a precise mechanism of action. It has been recommended that this classification system provides a basis by which new therapies for ED could be readily assigned and that would provide a practical diagnostic tool.

Oral medication for the medical management of ED is relatively new. Earlier treatment measures often resorted to the intracavernosal injection of a vasoactive agent or
Localized injection(s) (or dermal applications) were frequently required in order to achieve sufficient pharmacologic actions upon the vascular smooth muscle of the penis. Still other pharmacologic agents with relative short durations of action were less than satisfactory in maintaining penile erection. Sometimes combinations of drugs were used to take advantage of different onsets and durations of action of the components. Both a rapid onset of action and a sufficient duration of action are desirable characteristics of drugs used in the treatment of ED. While selected pharmacologic agents that are orally effective have been available for about 20 years, the advent of sildenafil and apomorphine (buccal) have greatly improved upon the therapeutic efficacy of orally-active agents.

Mechanistically, the various agents used for the treatment of ED are different (Table 5). These agents also vary considerably in terms of their site of action, i.e., central-acting vs peripheral-acting. Some of these agents are more specific in their actions than others. Furthermore, some exert their principal actions via the autonomic nervous system, while others act through nonadrenergic noncholinergic pathways (NANC).

Generally, the side-effects associated with the various pharmacologic agents used for ED are not life-threatening, although selected drug interactions suggest caution (See Section III). Expectedly, those agents possessing \( \alpha \)-adrenergic antagonist activities might lead to postural hypotension and reflex cardiac stimulation. Excessivesmooth muscle relaxation activity caused by vasoactive agents can likewise produce hypotension. Central acting agents may produce annoying side-effects such as nausea. In some cases, although dose and agent specific, prolonged erections have been noted.

### 2. Specific agents

#### A. Alprostadil (prostaglandin E\(_1\))

Prostaglandin E\(_1\) (PGE\(_1\)) exerts a number of pharmacologic effects including systemic vasodilation, inhibitory actions on platelet aggregation and stimulation of intestinal motility. PGE\(_1\) relaxes isolated smooth muscle contracted by norepinephrine. It has become widely used in the treatment of ED. Alprostadil binds with PGE receptors, and the resultant relaxation response in the smooth muscle is mediated by cAMP. Little is known about the pharmacokinetics of PGE\(_1\) but it is believed that as much as 80% may be metabolized in one pass through the lungs (32). In all probability, this rapid degradation by the lungs accounts for

### Table 4. Classification by mode of action for treatments of erectile dysfunction

| Class | Nomenclature | Definition |
|-------|--------------|------------|
| I     | Central acting | Agents that have their primary site of action in the CNS and activate neural events that result in coordinated signaling resulting in the initiation of a penile erection (e.g., apomorphine) |
| II    | Peripheral acting | Agents that have their primary site of action in the periphery and activate events resulting in a penile erection (e.g., PGE\(_1\)) |
| III   | Central modulating | Agents that act primarily to improve the internal milieu of the CNS so that penile erection is enhanced — they do not on their own initiate an erection (e.g., trazodone) |
| IV    | Peripheral conditioner (local or systemic) | Agents that act primarily to improve the local or systemic internal milieu so that penile erection is enabled or enhanced (e.g., sildenafil) |
| V     | Other (e.g., mechanical) | Other methods (e.g., mechanical) for promoting penile rigidity including medical devices and surgery (e.g., prostheses) |

Modified from reference 35 (Heaton et al., 1997).

### Table 5. Pharmacologic agents used for the treatment of erectile dysfunction

| \( \alpha \)-Adrenergic blocking agents |
|---------------------------------------|
| moxisylyte (thymoxamine)             |
| phenoxymazenamine (Dibenzyline\(^*\)) |
| phentolamine (non-selective — \( \alpha_1\) and \( \alpha_2\) (Regitine\(^a\), Vasomax\(^a\)) yohimbine (\( \alpha_2\)-blocker) |
| Prostaglandins (PGE\(_1\))            |
| alprostadil (Edex\(^a\)) (Topiglan\(^a\)) |
| Muscle relaxants                     |
| papaverine* (Puvabid\(^a\))          |
| Serotonergic agents                  |
| trazodone (Apothecon\(^a\))          |
| Dopaminergic agents                  |
| apomorphine (Uprima\(^a\))           |
| Nitric oxide donors                  |
| linsidomine, arginine                |
| Selective inhibitors of cGMP degradation |
| sildenafil (Viagra\(^a\))            |
| Vasoactive intestinal/calcitonin-related peptides |
| Combinations**                       |
| trimix (papaverine, phentolamine and alprostadil) |

*Also has nonselective phosphodiesterase inhibitor activity. **See text for other binary mixtures/combinations. Modified from reference 33 (Meinhardt et al., 1999).
its lack of any significant cardiovascular system (CVS) side-effects when administered intracavernosally. PGE1 can also be metabolized in the penis (36).

Since PGE1 is not effective orally, its success in ED depends upon it being injected intracavernosally or administered transurethrally or intraurethrally. PGE1 has also been used in combination with other agents, such as papaverine, and the combination was superior to only PGE1 (37). Combined therapy with alprostadil and sildenafil revealed no significant differences in ED (38). PGE1 is reportedly more effective than moxisylyte in inducing full erections (39). The injection technique does not produce any long-term side-effects on penile smooth muscle (40). Transurethral therapy with alprostadil is an effective therapy (41); it is well tolerated (42). There may be a therapeutic role for transurethral administration of alprostadil in selected patients with ED (43, 44). Alprostadil is also available in a topical gel formulation (45). Finally, intracavernous alprostadil is safe and effective in patients with ED when sildenafil was ineffective (46).

Clinical studies have compared the efficacy and safety of PGE1 when administered transurethrally (e.g., alprostadil with Muse-medicated urethral system for erection) versus intracavernous injection (e.g., alprostadil alfadex-Edex/Viridal®). Muse® can also be used in conjunction with a penile constriction device (e.g., Actis®). According to Werthman and Rajfer (47) and to Shabigh et al. (48), the intracavernous injection is more efficacious. Intracavernosal injection is an effective therapy with tolerable side-effects (49).

B. Apomorphine

Apomorphine is a centrally-acting dopamine agonist that can elicit male sexual responses. Dopamine has an important role in normal erectile function (50). Apomorphine is a D1-like/D2-like dopamine receptor agonist. Apomorphine, a drug without analgesic or addicting properties, is a short-acting agonist for central and peripheral dopaminergic receptors. Apomorphine is not a new drug, and it has been used with limited success in ameliorating the symptoms of Parkinson’s disease and as an emetic. Apomorphine, like bromocriptine, can suppress prolactin release although it is not useful in treating galactorrhea or amenorrhea associated with elevated levels of prolactin. There is a paucity of information about its pharmacokinetics, but it is not orally active (except by buccal route). It can be given parenterally, usually subcutaneously (51). Apomorphine is rapidly cleared from the body due to its high lipid solubility, its large volume of distribution, and its rapid metabolism (52).

Apomorphine, along with sildenafil, is one of the few orally active (buccal route) pharmacological agents used in the treatment of ED. Several studies have demonstrated that apomorphine stimulates erection in humans (53–56). In particular, apomorphine can induce penile erection in normal men (53, 57), in men that are impotent (54, 58, 59) and in alcoholics (60, 61). Apomorphine has been used to treat ED in patients with co-existing benign prostatic hyperplasia (BPH) (62), with coronary artery disease (63), and with hypertension (64).

Apomorphine exhibits poor oral absorption, yet when formulated into a controlled release sublingual (SL) capsule, it becomes a very effective orally active drug. It possesses a relatively rapid onset of action. This agent has a narrow range of effective doses for its erectogenic actions (55). Clinical dose ranges are quite narrow (e.g., 2 to 6 mg) with the higher doses being more effective in inducing erections (65). Apomorphine SL (3 mg) was significantly more effective than placebo and comparable to a 4-mg dosage (66). Earlier investigations have noted that apomorphine can cause nausea, emesis, drowsiness and dizziness, but such side-effects are dose-related (54, 57, 59). According to Heaton et al. (55), durable erections without side-effects can be attained at a dose of 3 or 4 mg of apomorphine using a proprietary formulation. Apomorphine SL represents a new class of centrally acting oral drugs useful in the treatment of ED (67).

C. Androgens (testosterone)

Hormonal causes of ED can be due to androgen deficiency leading to decreases in nocturnal erections and libido. Hypogonadism is associated with impotence (Table 2) (15). However, erection in response to visual sexual stimulation is preserved in men with hypogonadism, indicating that androgens are not essential for erection (68). Hyperprolactinemia, regardless of etiology, inhibits central dopaminergic activity, leading to a reduction in gonadotropin secretion and hypogonadism (10). Androgens and possibly prolactin levels should be measured in the complete evaluation of men with ED (69).

While androgens can enhance male sexual function, testosterone therapy for the treatment of ED should be discouraged unless the etiology is clearly related to hypogonadism (10). Androgen therapy in normal men may enhance sexual behavior, but is without significant effects upon erectile function (70).

Oral methyltestosterone is of limited effectiveness in men with hypogonadal impotence (71). Improvement following testosterone (transdermal) may require several months of therapy (72). Androgen replacement regimens for treating male hypogonadism include long-acting i.m. injections (e.g., testosterone enanthate, testosterone cypionate, etc.) and oral preparations (e.g., methyl testosterone, fluoxymesterone). Supplements of androstenedione (100 mg/day) tend to stabilize testosterone deficiency. Transdermal patches (e.g., Testoderm®, Androderm®) and topical test-
Testosterone gel (e.g., Androgel®) are also available. In women who have undergone oopherectomy and hysterectomy, transdermal testosterone improves sexual function and psychological well-being (73).

Transdermal delivery systems may provide better consistency in serum testosterone than i.m. injection(s), but are perhaps more expensive. Generally, replacement doses of testosterone do not produce significant side-effects, but co-existing prostate cancer and hypertrophy might represent contraindications.

D. Papaverine

Papaverine is a non-specific phosphodiesterase inhibitor that increases cAMP and cGMP levels in penile erectile tissue (74). Papaverine is particularly known as a smooth muscle relaxant and vasodilator. Its principle pharmacological action is as a non-specific vasodilator of smooth muscles of the arterioles and capillaries. Various vascular beds and smooth muscles respond differently in both intensity and duration (33). Papaverine decreases the resistance to arterial inflow and increases the resistance to venous outflow (75).

Papaverine is highly effective in men with psychogenic and neurogenic ED. It is less effective in men with vasculogenic ED (10). Papaverine-phentolamine combinations have been used in self-injection procedures. Papaverine dosages may range from 15 to 60 mg. Study outcomes with respect to the efficacy of papaverine in the treatment of ED have not been consistent (31). Self-injection therapy with papaverine can be enhanced with phentolamine (76, 77). Patients with severe arterial or venous incompetence failed to successfully respond to papaverine (78). Aravena and Bustamente (79) reported that papaverine was successful in treating patients with psychogenic impotence. Despite some conflicting study results, autoinjections with papaverine using low doses sufficient to achieve erection, reportedly are safe and efficient.

A major side-effect is priapism, corporeal fibrosis, and occasional increases in serum aminotransferases. Intracorporeal scarring may be related to the low pH which is necessary in order to solubilize the drug. Attempts to buffer papaverine to render it more suitable for intracavernosal injection have not been entirely satisfactory, and may still lead to intracorporeal scarring (32).

E. Phentolamine (and other α-adrenergic blockers)

Phentolamine is a non-selective α-adrenerceptor blocking agent (Table 5). Like several other α-adrenergetic blocking agents, oral phentolamine has been used in treating ED (80 – 83). Non-selective α-adrenergetic antagonists may also provoke a reflex, increasing sympathetic outflow and release of norepinephrine. Pharmacologic studies using human erectile tissue indicate the presence of a population of membrane receptors that are predominantly of the α-adrenerceptor subtype (84). Actually, phentolamine exhibits a similar affinity for α1 and α2 adrenerceptors. However, it can also block receptors for 5-HT (32).

Phentolamine (orally) has a plasma half-life of about 30 min and a duration of action of between two to four hours. The intracavernosal injection of phentolamine reveals that the drug reaches maximum serum levels in about 20 to 30 min (32). Phentolamine is rapidly metabolized.

When phentolamine is used for the treatment of ED, it is often used in combination with other agents to enhance its efficacy. Phentolamine has been used in combination with papaverine (85), chlorpromazine (86) and vasoactive peptides (e.g., vasoactive intestinal peptide — VIP) (87 – 89). Calcitonin gene-related peptide (CGRP) induces a dose-related increase in penile arterial inflow, cavernous smooth muscle relaxlation, cavernous outflow occlusion and an erectile response (90). CGRP plus PGE1 may be an alternative to penile implants in selected patients (91). Overall, the use of vasoactive peptide, in combination with phentolamine, may have a role in treating ED; it is safe and effective.

The combination of phentolamine and papaverine for the treatment of ED has been studied extensively. Junemann and Aiken (31) have compiled and reviewed nearly 30 clinical studies comprising nearly 4,000 patients who received intracavernosal injection with papaverine/phentolamine. This Survey concluded that this combination was efficacious and induced erections sufficient for sexual intercourse in over 90% of the cases.

Phentolamine has been used orally and intracavernosally. It has also been shown to be effective buccally. These three forms of administration are not available worldwide and have not been approved by all drug regulatory agencies.

The side-effects of phentolamine are dose-related. It may cause hypotension (orthostatic) and reflex tachycardia. Cardiac arrhythmias and even rarely, myocardial infarction, have been reported (10, 32).

There are several other α-adrenergic receptor antagonists including yohimbine, phenoxybenzamine, and thymoxamine (moxisylyte). Yohimbine is an α2-adrenergic receptor antagonist. Thymoxamine is a competitive and relatively selective blocking agent for α1 adrenerceptors. Phenoxybenzamine blocks both α1 and α2 adrenerceptors, although it has been a preference for α1 adrenerceptors (10, 32). While all three of these alpha blockers can induce penile erection, they are generally inconsistent and less effective than phentolamine. Yohimbine is only moderately effective in treating patients with organic impotence (92), although it might be a reasonable therapeutic option for ED (93). All exhibit similar side-effects including postural hypotension, heart palpitation, fine tremors, and is some...
instances, cavernosal fibrosis.

**F. Sildenafil**

Sildenafil was developed over ten years ago, but as an agent that would be effective as an anti-hypertensive drug or an antianginal drug. Early clinical trials for such medical indications were unsuccessful. While sildenafil was largely ineffective upon smooth muscles in the heart, it seemed to have a propensity for affecting the vascular supply of the penis.

Sildenafil is a selective inhibitor of cGMP specific phosphodiesterase type 5. It inhibits the degradation of cGMP. Phosphodiesterase type 5 is the predominant type in the corpus cavernosa. The selective inhibition of phosphodiesterase type 5 leads to a facilitation of the release of nitric oxide and smooth muscle relaxation of the corpus cavernosa (74). Type 5 is also present in other tissues (e.g., lung, platelets and eye) (94). Sildenafil enhances erection by augmentation of nitric oxide-mediated relaxation pathways (74). The cardiovascular side-effects due to sildenafil highlight the fact that “cross-talk” between cGMP and cAMP-dependent signal transduction pathways exist in human cavernous and cardiac muscle (95).

Sildenafil has become a significant drug in the treatment of ED. It has now been evaluated in over 20 clinical studies comprised of over 3,000 men (10). Oral sildenafil is an effective well-tolerated treatment for men with ED (96). Sildenafil (oral) is well-tolerated and efficacious for treating men for ED who have diabetes mellitus (97) and in patients on chronic dialysis (98). In addition to the oral efficacy of sildenafil, it has been used as a so-called salvage therapy for intracorporeal injection for non-responders (99). Sildenafil alone or sildenafil plus intracavernosal injection reportedly is an effective salvage therapy of intracavernosal injection non-responders. Sildenafil in combination with intracavernosal injection is associated with a 33% incidence of adverse effects, including a 20% incidence of dizziness (99).

Post-marketing surveillance data following the approval of sildenafil revealed a number of serious cardiovascular side-effects, but there may have been other factors involved (100 – 103). Shabsigh et al. (46), reported that headache was the most commonly reported side-effect followed by flushing and rhinitis. More serious side-effects compiled by the U.S. FDA (through 1998) included definite or suspected myocardial infarctions, and cardiac arrest (10).

Sildenafil is readily absorbed and reaches mean plasma levels in about one hour. It undergoes hepatic metabolism, and exhibits a terminal half-life of about four hours. A starting dose of 50 mg taken about one hour prior to sexual activity has been recommended (10).

**G. Trazodone**

Trazodone is an antidepressant. It is a serotonin antagonist and a reuptake inhibitor (SSRI). It also exhibits some α-adrenoreceptor blocking actions (see Section II 2E). Thus, trazodone may have a dualistic mechanism of action (10, 33, 104).

Trazodone may cause priapism and enhance libido. It prolongs nocturnal erections. It has been used both orally and by intracavernosal injection. It has also been used alone or in combination (e.g., yohimbine) (105, 106). In a comparative study with other anti-serotonergic agents (e.g., ketaserin, manserin), trazodone was the most efficacious (107). Generally, the overall efficacy of trazodone in treating ED has not been as effective as other agents. It may be an option for selected patients, particularly those with performance anxiety or low libido (10, 33, 104).

**H. Other agents**

There are several other drugs and herbals that possess varying degrees of potency with respect to affecting penile erection. Some have undergone limited clinical trials while others are associated with anecdotal reports in humans. Generally, these agents are not overly effective nor used in the mainstream of therapeutic options for ED. Some have been investigated in animal studies only.

1-Arginine supplements (e.g., 2.8 g/day × 2 weeks) may strengthen and prolong erections. Arginine may act by providing more substrate for NO synthase and also counteract endogenous inhibitors (108).

Linsidomine (SIN-1) is an active metabolite of the antianginal drug molsidomine. Its mechanism of action upon the corpus cavernosum is through the release of nitric oxide (32). When injected intracavernously, it can produce penile erections; however, its clinical usefulness has not been fully established.

Nitroglycerin (and also isosorbide nitrate) relaxes isolated strips of human corpus cavernosum (109). Its mechanism involves the stimulation of guanylate cyclase. Clinically, nitroglycerin has met with only limited success in treating ED (32).

Minoxidil, an antihypertensive agent, produces arteriolar vasodilation by an unknown mechanism. In a limited clinical study, minoxidil increased penile rigidity, and was suggested for use in the long-term treatment of organic impotence (110).

Naltrexone, an orally active opioid receptor antagonist, restored erectile function in a small sample of patients with idiopathic ED (111).

Forskolin, an herbal, relaxes smooth muscle. Intracavernosal forskolin has been tried in the management of vasculogenic impotence (112).

There are many other herbals or so-called natural products that purportedly can enhance male sexual activity.
Some of these so-called sexual enhancement herals may contain yohimbine. Natural prosexual agents of herbal origin include Epimedium sagthatum, Tribulas terrestris and Muira puama. Their use in folk medicine in China and other countries is purportedly for their sexual stimulating properties and aphrodisiac effects. Ginkgo biloba extract has been used in the therapy of ED (113) and sexual dysfunction (114). Panax ginseng is an aphrodisiac. Ginsenosides, an active ingredient in Panax ginseng, has been shown to promote NO release (115).

III. Drug interactions

Most, but not all, drug interactions are affected by changes in gastro-intestinal absorption (116). Aging and disease can also affect a drug’s pharmacodynamics (117). Thus, the more elderly male with ED may experience a somewhat different pharmacologic effect to a particular drug. Orally active agents used in the management of ED would be more prone to modified pharmacologic actions than those injected intracavernosally, although the hepatic metabolism and/or renal clearance would still represent relative considerations. Regardless of the route of administration of the drug(s) used in the management of ED, the medical treatment for a co-existing disease could exacerbate adverse reactions. Such is the case in the concomitant use of sildenafil and nitroglycerin which is an established contraindication.

With the aforementioned exception, there is a paucity of information about drug interactions. Local injection or urethral application is less apt to produce any widespread vasodilation, which is a pharmacologic characteristic present in most drugs used in the treatment of ED.

Nitrate therapy is an absolute contraindication to sildenafil therapy (118). Other minor adverse cardiovascular effects of sildenafil (e.g., nasal congestion, headache, flushing) could also be caused by a variety of other pharmacologic agents. There are no clinically significant interactions between apomorphine (sublingual — SL) and either short-acting or long-acting nitrates (119).

Apomorphine, like sildenafil, is orally active. However, unlike sildenafil, it exerts its actions via the central nervous system. Apomorphine can produce dizziness, nausea, pallor and hypotension; side-effects that are not unique to drugs used in the treatment of ED. Apomorphine, in the presence of ethanol, purportedly increases the incidence of these aforementioned side-effects. Such a synergy caused by ethanol and apomorphine would not be unique, but would most likely be evident with other agents that induced mild hypotension. Likewise, sildenafil interacts with ethanol (120).

Grapefruit juice has the potential to modify the metabolism of testosterone (121). The concomitant intake with grapefruit juice increases the concentrations of many drugs in humans. Such actions appear to be mediated mainly by suppression of the cytochrome P450 enzyme CYP3A4 in the small intestine. The resultant diminished first pass metabolism and higher bioavailability can lead to increased drug blood levels. Since sildenafil is metabolized by CYP3A4, and to a lesser extent, CYP2C9, grapefruit juice could reduce the clearance of this drug. Other drugs can either increase or decrease serum concentrations of sildenafil. Cimetidine, erythromycin, and ritonavir can lead to increases in the serum concentration of sildenafil. Rifampin can lead to diminished blood levels of sildenafil.

Finally, an α-adrenoreceptor antagonist such as phentolamine can cause reflex tachycardia, arrhythmias and hypotension. Hypotension can be exacerbated by other vasodilatory drugs and by the ingestion of ethanol. The pharmacologic actions of trazodone can be reduced by paroxetine and possible other SSRIs (122).

IV. Concluding remarks

A comprehensive review of the pharmacology of various agents used in the treatment of ED reveals a continuing emergence of knowledge about their mechanism(s) of action and their clinical efficacy. Both systemic and locally-active agents are available. Their site(s) of action may be peripheral or central acting. Sometimes, a combination of agents is effective, but often this is determined by the etiology of the ED. Significant insight has been gained in the last decade with respect to the pharmacologic action of drugs used in the treatment of ED.

REFERENCES

1. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ and McKinlay JB: Impotence and its medical and psychosocial correlates: results at the Massachusetts Male Aging Study. J Urol 151, 54–61 (1994)

2. NIH Consensus Conference — Impotence. JAMA 270, 83 – 90 (1993)

3. Benet AE and Melman A: The epidemiology of erectile dysfunction. Urol Clin N Am 22, 699 – 709 (1995)

4. Tiefer L and Melman A: Comprehensive evaluation of erectile dysfunction and medical treatments. In Principles and Practice in Sex Therapy: Update for the 1990s, ed 2, Edited by Leiblum SR and Rosen RE, pp 207 – 236, Guildford Press, New York (1989)

5. Foreman MM and Doherty PC: Experimental approaches to the development of pharmacological therapies for erectile dysfunction. In Sexual Pharmacology, Edited by Riley AJ, Peet M and Wilson CA, pp 87 – 113, Oxford Med Publ, Oxford (1993)

6. Melman A and Gingell JC: The epidemiology and pathophysiology of erectile dysfunction. J Urol 161, 5 – 11 (1999)

7. Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB and McKinlay JB: Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 56, 302 – 306
8 Rosen MP, Greenfield AJ, Walker TG, Grant P, Dubrow J, Bettmann MA, Fried LE and Goldstein I: Cigarette smoking: an independent risk factor for arteriosclerosis in hypogastric-cavernous arterial bed of men with arterogenic impotence. J Urol 145, 759 – 763 (1991)

9 Korenman SG: Sexual function and dysfunction. In Williams Textbook of Endocrinology, 9th Edition, Edited by Wilson JD, et al, pp 927 – 938, WB Saunders, Philadelphia (1998)

10 Lue T: Erectile dysfunction. N Engl J Med 348, 1802 – 1813 (2000)

11 Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Arano AB and Mckinlay JB: Erectile dysfunction and cardiovascular risk: prospective results from the Massachusetts Male Aging Study. Prev Med 30, 328 – 338 (2000)

12 Wabrek AJ and Burchell RC: Male sexual dysfunction associated with coronary heart disease. Arch Sex Behav 9, 19 – 75 (1980)

13 Michael V: Arterial disease as a cause of impotence. Clin Endocrinol Metab 11, 725 – 748 (1982)

14 Agarwal A and Jain DC: Male sexual dysfunction after stroke. Arch Endocrinol Metab 23, 97 – 105 (1980)

15 Keogh EJ, Walters GR, Tulloch AGS, Wisniewski ZS, Lord DJ, Glancy JF, Earle CM, Carati CJ and Creede KE: Modern management of impotence. In The Testes, 2nd ed, Edited by Burger H and deKretser D, Chapter 18, pp 527 – 546, Raven Press, New York (1989)

16 Shabsigh R, Klein LT, Seidman S, Kaplan HS, Lerroff BJ and Ritter JS: Increased incidence of depressive symptoms in men with erectile dysfunction. Urology 52, 848 – 852 (1998)

17 Keene LC and Davies PH: Drug-related erectile dysfunction. Adverse Drug React Toxicol Rev 18, 5 – 24 (1999)

18 Khedun SM, Naicker T and Makarab Y: Zinc, hydrochlorothiazide and sexual function. Cent Alp J Med 41, 312 – 315 (1995)

19 Andersson KE: Pharmacology of penile dysfunction. Pharmacol Rev 53, 417 – 450 (2001)

20 Fournier GR Jr, Juemenach KP, Lue TF and Tanagho EA: Mechanisms of venous occlusion during canine penile erection: an anatomic demonstration. J Urol 137, 163 – 167 (1987)

21 Banya Y, Ushiki T, Takagane H, Aoki H, Kubo T, Ohhori T and Ide C: Two circulatory routes within the human corpus cavernosum penile scanning electron microscopic study of corrosive casts. J Urol 142, 879 – 883 (1989)

22 Uchio EM, Yang CC, Kremm BG and Bradley WE: Cortical evoked responses from the perineal nerve. J Urol 162, 1983 – 1986 (1999)

23 deGroat WC and Brath AM: Neural control of penile erection. In The Autonomic Nervous System, Vol 6, Nervous Control of the Urogenital System, Edited by Maggi CA, pp 465 – 513, Harwood, London (1993)

24 Sachs BD and Meisel RL: The physiology of male sexual behavior. In The Physiology of Reproduction, Edited by Knobil E and Neill J, pp 1393 – 1485, Raven Press, New York (1988)

25 Saenz de Tejada I, Goldstein I, Azadzoi K, Krane RJ and Cohen RA: Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med 320, 1025 – 1030 (1989)

26 Ignarro LJ, Bush PA, Buga GM, Wood KS, Fukato JM and Rajfer J: Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem Biophys Res Comm 178, 843 – 850 (1990)

27 Rajfer J, Aronson WJ, Bush PA, Dorrey FJ and Ignarro LJ: Nitric oxide as a mediator of relaxation of the corpus cavernoso-
tile dysfunction after failing in sildenafil (Viagra®). Urology 55, 477 – 480 (2000)
47 Werthman P and Rajfer J: MUSE therapy: Preliminary clinical observations. Urology 50, 809 – 811 (1997)
48 Shabsigh R, Padma-Nathan H, Gittleman M, McMurray J, Kaufman J and Goldstein I: Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional ACTIS®: a comparative randomized crossover multicenter study. Urology 55, 109 – 113 (2000)
49 Linet OI and Ogrinc FG: Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. N Engl J Med 334, 873 – 877 (1996)
50 Waddington JL: D1:D2 dopamine receptor interactions. In Neuroscience and Psychopharmacology, pp 1 – 296, Academic Press, New York (1993)
51 Heaton JP, Varrin S, Ge SP and Morales A: Preliminary studies showing erectogenic activity in an oral agent. Int J Impot Res, Suppl 2, 285 – 286 (1990)
52 Gancher ST, Woodward WR, Boucher B and Woodward WR: Peripheral pharmacokinetics of apomorphine in humans. Ann Neurol 26, 232 – 238 (1989)
53 Danjou P, Alexandre G, Warot D, Lacomblez L and Puech AJ: Assessment of ectropic properties of apomorphine and yohimbine in man. Br J Clin Pharmacol 26, 733 – 739 (1988)
54 Segraves RT, Bari M, Segraves K and Spirrak P: Effect of apomorphine on penile tumescence in men with psychogenic impotence. J Urol 149, 1174 – 1175 (1991)
55 Heaton JP, Morales A, Adams MA, Johnston B and el-Rashidy R: Recovery of erectile function of the oral administration of apomorphine. Urology 45, 200 – 206 (1995)
56 Padma-Nathan H, Fromm-Freeck S, Ruf D, McMurray JG and Rosen RC: Efficacy and safety of apomorphine SL vs. placebo for male erectile dysfunction (Abstract). J Urol 159, 241 (1998)
57 Lal S, Ackman D, Thavundayil JX, Kiely ME and Etienne P: Effect of apomorphine, a dopamine receptor agonist on penile tumescence in normal subjets. Proc Neuropsychopharmacol Biol Psychiatry 8, 695 – 699 (1984)
58 Lal S, Laryea E, Thavundayil JX, Nair NP, Negrete J, Ackman D, Blundell P and Gardiner RJ: Apomorphine-induced tumescence in impotent patient — preliminary findings. Proc Neuropsychopharmacol Biol Psychiatry 11, 235 – 242 (1987)
59 Lal S, Tesfaye Y, Thavundayil JX, Thompson TR, Kiely ME, Nair NP, Grassino A and Dubrously B: Apomorphine: clinical studies on erectile impotence and yawning. Prog Neuropsychopharmacol Biol Psychiatry 13, 329 – 339 (1989)
60 Lal S and DeLa Vega C: Apomorphine and psychopathology. J Neurol Neurosurg Psychiatry 38, 722 – 726 (1975)
61 Schlatter EK and Lal S: Treatment of alcoholism using Dent’s oral apomorphine method. J Stud Alcohol 33, 430 – 436 (1972)
62 Lewis R, Buttrler S, Ruff D and Agre K: Efficacy and safety of apomorphine SL vs. placebo for erectile dysfunction in patients with benign prostatic hyperplasia (BPH) (Abstract). J Urol 163, 310 (2000)
63 Dula E, Buttrler S, Perdok R and Agre K: Efficacy and safety of apomorphine SL vs. placebo for erectile dysfunction in patients with coronary artery disease (Abstract). J Urol 164, 200 (2000)
64 Lewis R, Agre K, Fromm S and Ruff D: Efficacy of apomorphine SL vs. placebo for erectile dysfunction in patients with hypertension (Abstract). J Urol 161, 214 (2000)
65 Padma-Nathan H, Awerbach S, Lewis R, Lewand M and Perdok R: Efficacy and safety of apomorphine SL vs. placebo for male erectile dysfunction (Abstract). J Urol 161, 214 (2000)
66 Dula E, Bukofzer S, Perdok R and George M: Double-blind, crossover comparison of 3 mg apomorphine SL with placebo and with 4 mg apomorphine SL in male erectile dysfunction. Eur Urol 39, 558 – 564 (2001)
67 Dula E: Efficacy and safety of fixed-dose and dose-optimization regimens of sublingual apomorphine versus placebo in men with erectile dysfunction. Urology 56, 130 – 135 (2000)
68 Bancroft J and Wu FC: Changes in erectile responsiveness during androgen replacement therapy. Arch Sex Behav 12, 59 – 66 (1983)
69 Guay AT: Is the measurement of serum testosterone routinely indicated in men with erectile dysfunction? BJU Int 86, 563 – 566 (2000)
70 Schiavi RC, White D, Mandeli J and Levine AC: Effect of testosterone administration on sexual behavior and mood in men with erectile dysfunction. Arch Sex Behav 26, 231 – 241 (1997)
71 Morales A, Johnson B, Heaton JWP and Clark A: Oral androgens in the treatment of hypogonadal impotent men. J Urol 152, 1115 – 1118 (1994)
72 Arver S, Dobs AS, Meikle AW, Allen RP, Sanders SW and Mazer NA: Improvement of sexual function in testosterone deficient men treated for 1 year with a permeation enhanced testosterone transdermal system. J Urol 155, 1604 – 1608 (1996)
73 Shiferen JL, Braunstein GD, Simon JA, Casson PR, Baster JE, Redmond GP, Burki RE and Ginsburg ES: Transdermal treatment in women with impaired sexual function after oophorectomy. N Engl J Med 343, 682 – 688 (2000)
74 Jeremy JY, Ballarel SA, Naylor AM, Miller MA and Angelini GD: Effects of sildenafil, a type-5 phosphodiesterase inhibitor, and papaverine and cyclic GMP and cyclic AMP levels in the rabbit corpus cavernosa in vitro. Br J Urol 79, 958 – 963 (1997)
75 Junemann KP, Rue TF, Fournier GR and Tanagho EA: Hemodynamics of papaverine- and phentolamine-induced penile erection. J Urol 136, 158 – 161 (1986)
76 Brindley GS: Maintenance treatment of erectile impotence by cavernosal unstriated muscle relaxant injection. Br J Psychiatry 149, 210 – 215 (1986)
77 Virag R: About pharmacologically induced prolonged erection. Lancet 1, 519 – 520 (1983)
78 Buvat J, Lemaire A, Marcolin G, Dehaene JL and Buvat J: Intracavernous injection of papaverine (ICIP). Assessment of its diagnostic and therapeutic value in 100 impotent patients. Wld J Urol 5, 150 – 155 (1987)
79 Aravena EP and Bustamente E: Treatment of psychogenic erectile impotence with intracavernous injection of papaverine. In Proceedings of 5th Conference of Vasculogenic Impotence and Corpus Cavernosum Revascularization. Second World Meeting on Impotence, Prague. Int Soc Impotence Res (ISIR) 11, 20 (1986)
80 Becker AJ, Stief CG, Machens S, Schultheiss D, Hartmann U, Truss MC and Jonas U: Oral phentolamine as treatment for erectile dysfunction. J Urol 159, 1214 – 1216 (1998)
81 Goldstein I: Efficacy and safety of oral phentolamine (Vasomax®) for the treatment of minimal erectile dysfunction (Abstract). J Urol 159, 240 (1998)
82 Zorgnotti AW: Experience with buccal phentolamine mesylate for impotence. Int J Impot Res 6, 37 – 41 (1994)
83 Gwinup G: Oral phentolamine in nonspecific erectile insufficiency. Ann Intern Med 109, 162 – 163 (1988)
84 Christ GJ, Maayani S, Valcic M and Melman A: Pharmacological studies of human erectile tissue: characteristics of sponta-
neous contractions and alterations in α-adrenoreceptor responsiveness with age and disease in isolated tissue. Br J Pharmacol 101, 375 – 381 (1990)
85 Zorgniotti AW and Lefleur RS: Auto-injection of the corpus cavernosum with a vasoactive drug combination for vasculogenic impotence. J Urol 133, 39 – 41 (1985)
86 Braga RS and Braga LTCM: Chlorpromazine: a good substitute drug for phentolamine-a follow-up study of 174 patients. Int J Impot Res 8, 113 (1996)
87 Gerstenberg JC, Metz P, Ottesen B and Fahrenkrug J: Intracavernous self-injection with vasoactive intestinal polypeptide and phentolamine in the management of erectile failure. J Urol 147, 1277 – 1279 (1992)
88 McMahon CG: A pilot study of the role of intracavernous injection of vasoactive substance (VIP) and phentolamine mesylate in the treatment of erectile dysfunction. Int J Impot Res 8, 233 – 236 (1996)
89 Dinsmore WW and Alderdice DK: Vasoactive intestinal polypeptide and hemotolamine mesylate administered by auto-injector in the treatment of patients with erectile dysfunction resistant to other intracavernosal agents. Br J Urol 81, 437 – 440 (1998)
90 Stief CG, Wetterbauer U, Schaebsdau F and Jonas U: Calcitonin-gene-related peptide: A possible role in human penile erection and its therapeutic application in impotent patients. J Urol 146, 1010 – 1014 (1991)
91 Truss MC, Becker AJ, Thon WF, Kuczyk M, Djamilian MH, Stief CG and Jonas U: Intracavernous calcitonin gene-related peptide plus prostaglandin E1: Possible alternative to penile implants in selected patients. Eur Urol 26, 40 – 45 (1994)
92 Morales A, Condra M, Owen JA, Surridge DH, Fenemore J and Harris C: Is yohimbine effective in the treatment of organic impotence? Results of a controlled trial. J Urol 137, 1169 – 1172 (1987)
93 Erst E and Pittler MH: Yohimbine for erectile dysfunction: A systematic review and meta-analysis of randomized clinical trials. J Urol 159, 433 – 436 (1998)
94 Thompson WJ: Cyclic nucleotide phosphodiesterases: pharmacology, biochemistry and function. Pharmacol Ther 57, 13 – 33 (1991)
95 Stief CG, Uckert S, Becker AJ, Harringer W, Truss MC, Forssmann WG and Jonas U: Effects of sildenafil on cAMP and cGMP levels in isolated human cavernous and cardiac tissue. Urology 55, 146 – 150 (2000)
96 Padma-Nathan H and Giuliano F: Oral drug therapy for erectile dysfunction. Urol Clinics N Am 28, 321 – 334 (2001)
97 Price DE, Gingell JC, Gepi-Attee S, Wareham K, Yates P and Boolell M: Sildenafil: study of a novel oral treatment for erectile dysfunction in diabetic men. Diab Med 15, 821 – 825 (1998)
98 Chen J, Mabjesh NJ, Greenstein A, Nadue A and Matzkin H: Clinical efficacy of sildenafil in patients on chronic dialysis. J Urol 165, 819 – 821 (2001)
99 McMahon CG, Samali R and Johnson H: Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy. J Urol 162, 1992 – 1998 (1999)
100 Feenstra J, Van Drie-Pierik RJ, Lacle CF and Stricker BH: Acute myocardial infarction associated with sildenafil. Lancet 352, 957 – 958 (1998)
101 Zusman RM, Morales A, Glasser DB and Osterloh IH: Overall cardiovascular profile of sildenafil citrate. Am J Cardiol 83, 35C – 44C (1999)
102 Herrmann HC, Chang G, Khugher BD and Mahoney PD: Hemodynamic effects of sildenafil in men with severe coronary artery disease. N Engl J Med 342, 1622 – 1626 (2000)
103 Cohen JS: Comparison of FDA Reports of patient deaths associated with sildenafil and with injectable alprostadil. Ann Pharmacother 35, 285 – 288 (2001)
104 Meinhardt W, Schmitz PI, Kropman RF, de la Fuente RB, Lycklama a Nijehold AA and Zwartendijk J: Trazodone, a double-blind trial for treatment of erectile dysfunction. Int J Impot Res 9, 163 – 165 (1997)
105 Lance R, Albo M, Costabile RA and Steers WD: Oral trazodone as empirical therapy for erectile dysfunction: a retrospective review. Urology 46, 117 – 120 (1995)
106 Montorsi F, Strambi LF and Guazzoni G: Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study. Urology 44, 732 – 736 (1994)
107 Kurt U, Ozkardes H, Altug U, Germiyanoğlu C, Gurdal M and Erol D: The efficacy of anti-serotonergic agents in the treatment of erectile dysfunction. J Urol 152, 407 – 409 (1994)
108 Fried R and Merrill WC: The Arginine Solution. Warner Books, (1999)
109 Heaton JPW: Synthetic nitrovasodilators are effective, in vitro, in relaxing penile tissue from impotent men: the findings and their implications. Can J Physiol Pharmacol 67, 78 – 81 (1989)
110 Cavallini G: Minoxidil versus nitroglycerin: a prospective double-blind controlled trial in transcutaneous erection facilitation for organic impotence. J Urol 146, 50 – 53 (1991)
111 Goldstein JA: Erectile function and naltrexone. Ann Intern Med 105, 799 (1988)
112 Mulhall J, Daller M and Traish A: Intracavernosal forskolin: role in the management of vasculogenic impotence resistant to standard 3-agent pharmacotherapy. J Urol 158, 1752 – 1758 (1997)
113 Sikora R, Sohn M and Deutz F-J: Ginkgo biloba extract in the therapy of erectile dysfunction. J Urol 141, 188A (1989)
114 Cohen AJ and Bartik B: Ginkgo biloba for anti-depressant-induced sexual dysfunction. J Sex Marital Ther 24, 139 – 143 (1988)
115 Chen X and Lee TJJ: Ginsenosides-induced nitric oxide-mediated relaxation of the rabbit corpus cavernosum. Brit J Pharmacol 115, 15 – 18 (1995)
116 Charman WN, Porter CJH, Mithani S and Dressman JB: Physiological and chemical mechanisms for the effects of food on drug absorption: The role of lipids and pH. J Pharm Sci 86, 269 – 282 (1997)
117 Thomas JA and Burns RA: Important drug-nutrient interactions in the elderly. Drugs Aging 13, 199 – 209 (1998)
118 Cheitlin MD, Hutter AM and Brindis RG: Use of sildenafil (Viagra®) in patients with cardiovascular disease. Circulation 99, 168 – 177 (1999)
119 Fagan TC, Butler S, Schultz C and Edmonds A: Pharmacodynamic interactions of sublingual amorphophine with oral anti-hypertensive agents and nitrates (Abstract). Am J Hypertens 13, 116 (2000)
120 D’Arcy PF: Drug reactions and interactions. Internet Pharm J 13, 16 – 17 (1999)
121 Fuhr U: Drug interactions with grapefruit juice. Drug Saf 18, 251 – 272 (1998)
122 Landrum Michalets E: Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy 18, 84 – 112 (1998)