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EFFECTIVE THERAPY FOR THE MANAGEMENT OF ERECTILE DYSFUNCTION IN MEN WITH DIABETES MELLITUS: A REVIEW

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ABSTRACT

Diabetes is a significant cause of erectile and sexual dysfunction. The pathologic processes in diabetes that particularly compromise the responsivity of vascular systems preferentially impact on the vulnerable vascular bed of the penis. About 36% of men with diabetes will experience some degree of erectile dysfunction. Unfortunately, this high-risk population is also difficult to treat. All of the pharmacologic therapies for erectile dysfunction have shown a decrease in efficacy in diabetic patients in comparison with non-diabetic patients. The many strategies for the treatment of erectile dysfunction share an important distinction from most other medical conditions in that the treatment is directed by the choice of the patient and partner. Alprostadil by intracavernous injection has been shown to benefit up to 94% of men with erectile dysfunction and diabetes. Sildenafil will restore the capacity for intercourse in>40% of diabetic patients. More recently two other agents, vardenafil and tadalafil, have been introduced. All the drugs have been shown to be effective across a wide range of aetiologies of erectile dysfunction (ED), including diabetes. The drugs have been shown to improve EF domain scores, penetration and maintenance of erection, resulting in more successful intercourse. Other pharmacologic treatments are available and in development. Ultimately, penile rigidity may be created surgically if the sexual needs of the couple require it.

KEYWORDS

Diabetes, Erectile dysfunction, Sildenafil, Pharmacotherapy.

INTRODUCTON

Diabetes mellitus is an extremely common, complex, and serious chronic disease. It is a metabolic disorder characterized by hyperglycemia, which is associated with a high subsequent risk of eye and kidney disease, although it is also associated with a

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high subsequent risk of neurologic, cardiovascular, and other health adverse health outcomes. Diabetes mellitus is characterized by fasting plasma glucose ≥ 7.0 mmol/l or a 2-hour plasma glucose level ≥11.1 mmol/L. [1]

The last 10 years have been a momentous period of time for health care professionals and patients concerned with erectile dysfunction (ED). The understanding of the condition has progressed scientifically and socially, the pharmacotherapy has expanded dramatically, and the responsibility for care is shifting. Sexual function is an important component of the life of most people who anticipate keeping active into their later years, even in the face of chronic disease. It is how often possible to restore function medically in a large proportion of men. The most recent step is the introduction of vardenafil and tadalafil and of course previously introduced drug sildenafil (Viagra, Pfizer, NY) and its adoption by a wider range of patients and prescribers than could ever have been suspected even 3years ago. The compounds currently under review, such as apomorphine SL and new (second) generation phosphodiesterase inhibitors will further broaden the range of therapies and herald a phase of maturation of therapeutics in ED.

Erectile dysfunction is particularly frequent in men with diabetes, who constitute a prime population to benefit from single or multiple agents. Indeed, diabetes mellitus (DM) is one of the most common causes of ED. It constitutes a special subset of ED and one that is receiving increasing attention since the world is facing a pandemic of DM.

WHAT IS ERECTILE DYSFUNCTION?

Erectile dysfunction is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis sufficient for satisfactory sexual performance.[2]

An erection occurs as a hydraulic effect due to blood entering and being retained in sponge-like bodies within the penis. The process is most often initiated as a result of sexual arousal, when signals are transmitted from the brain to nerves in the pelvis. Erectile dysfunction is indicated when an erection is consistently difficult or impossible to produce, despite arousal. There are various and often multiple underlying causes, some of which are treatable medical conditions. The most important organic causes are cardiovascular disease and diabetes, neurological problems (for example, trauma from prostatectomy surgery), hormonal insufficiencies (hypogonadism) and drug side effects. It is important to realize that erectile dysfunction can signal underlying risk for cardiovascular disease.

There is often a contributing and complicating and sometimes a primary psychological or relational problem. Psychological impotence is where erection or penetration fails due to thoughts or feelings (psychological reasons) rather than physical impossibility; this can often be helped. Notably in psychological impotence, there is a strong response to placebo treatment. Erectile dysfunction, tied closely as it is to cultural notions of potency, success and masculinity, can have severe psychological consequences. There is a strong culture of silence and inability to discuss the matter. In reality, it has been estimated that around 1 in 10 men will experience recurring impotence problems at some point in their lives. Erectile dysfunction is the preferred term for impotence as a result of the deliberations at the Consensus Conference in Impotence held by the US National Institutes of Health in 1992.The definition for ED provided as a

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result of this conference is "inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance." [3] This term is less demeaning for patients than the term "impotence" and provides a framework for defining a diagnostic basis for identifying patients with ED. Still missing from this is the concept of time (continuous or for the last 3 months). Resolutions to this and many other issues are expected as a result of ongoing study. [4]

The sub classification of ED into clinically useful groups has not yet provided a basis for predicting therapy or outcomes, although much effort to this end has been expended. [5.] In fact, useful sub classifications almost certainly will follow the development of a range of good therapies for ED. As long as therapeutic choice is restricted to one effective oral compound and patient preference, there is little need for a classification to help select therapy or predict success.

HOW COMMON IS ERECTILE DYSFUNCTION IN MEN WITH DIABETES?

There are few published sources of incidence data on erectile dysfunction, despite the many studies that have been designed to assess the epidemiology of ED in a number of countries. The general obstacles of proving a diagnosis of Ed create difficulties in standardizing methodology, recruitment, question interpretation, and reporting accuracy. True incidence data can only be collected when the same group of patients is reassessed after a period of time has elapsed. Currently, the best estimate is that, in Caucasian man 40 to 69 pears old, a rate of ED of 26 cases per 1,000 man-years can be expected. [6] This study also confirms all other studies in finding significant associations between age, diabetes, hypertension, cardiovascular disease, and ED. In this study, the age-adjusted relative risk (RR) of incident ED from diabetes was 1.83, which is higher than that documented for untreated heart disease or hypertension.

WHY DOES ERSCTILE DYSFUNCTION OCCUR?

A brief review of the physiology of erections and the etiology of ED is provided below to facilitate understanding of the various therapeutic options.

Normal Physiology of Erections

Erections occur as a result of an orchestrated cascade of neural, cellular, and vascular events spanning brain initiation to penile rigidification. Reproductive systems have a very fundamental position in the survival of the species, and it is no surprise to discover the important role of ancient parts of the brain (the limbic system) [7] and the availability of multiple and overlapping pathways (redundancy). [8] These pathways balance proerectile and antierectile signals, with the central pathways providing overriding control and the spinal cord functional coordination and peripheral erectile reflex capability. Dopaminergic receptors have an important role in this signal transmission pathway [9] and provide an opportunity for centrally acting pharmacotherapy of erection, such as apomorphine. [10] Other neurotransmitters, such as serotonin and oxytocin, also play critical roles. [11] Spinal cord centers integrate central and local pelvic neural inputs, resulting in coordinated vasodilation (smooth muscle relaxation) in pelvic arteries, the cavernous arteries, and the smooth muscle of the penile trabecular tissue itself. In addition, there is some supportive somatic stimulation, and detumescence occurs through adrenergic signaling. The observation that reflex

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erections are possible, and may involve only spinal cord circuits, highlights the importance of reducing inhibition in these spinal cord centers as a means of causing an erection.

Etiology of Erectile Dysfunction

From the foregoing, it is clear that any neural problems that affect the brain, midbrain, or spinal cord involved (eg, multiple sclerosis or spinal cord injury) may cause ED. Central biochemical disturbances or neurotransmitter disorders (eg, depression), surgical procedures to parts of the erectile system (pelvic nerves or penis), and diseases that directly affect the penis (cancer and Peyronie's disease) may all cause ED. Moreover, diseases of the vascular system, including hypertension and atherosclerosis, clearly increase the risk of ED. Finally, anatomic obliteration of smooth muscle in the cavernosa (or excess fibrosis) precludes achievement of normal erections. The fact that diabetes is a strong risk factor for many of these diseases likely accounts for the association of diabetes with ED.

Most men with ED have both functional impairment and structural damage. [12] For example, small defects in endothelial function, plus excessive adrenergic or rennin angiotensin system (inhibitory) activity, may cause overwhelming vasoconstriction that is not reversed by normal proerectile signals. These considerations are the basis for the success of different pharmacotherapeutic approaches to treating ED.

Establishing the etiology of ED in an individual patient is based largely on the presentation and on clinical judgment. However, although risk factors may be identified, they are seldom the sole cause. Fortunately, effective therapy does not require identification of the cause; the clinical response to a drug and the choice of the patient ("goal-directed" therapy) [13] are the dominant in selecting therapy today.

WHAT ARE THE RISK FACTORS FOR ERECTILE DYSFUNCTION IN MEN WITH DIABETES?

The prevalence of ED in a large group of diabetic men has been estimated at about 36%.The percentage increased with age, the need for insulin, the historical quality of control, and the duration of diabetes. [14]

Neurodegeneration and neuropathic problems, and even a possible "central neuropathy," may lead to ED in diabetic men. [15] Autonomic assessment may have a particular role in people with diabetes, although the consequences of the findings for changing or improving therapy have not been established. Evidence of peripheral neuropathy increases the likelihood of ED. [16]

HOW IS ERECTILE DYSFUNCTION ASSESSED?

The best way of identifying ED is through a careful history and physical examination (Table 1). Because they are at high risk, men with diabetes should be routinely asked about ED. No accepted measurement (eg, blood test or imaging study) can determine the amount of erectile failure; specifically, the routine use of ultrasound, intracavernous injection, nocturnal testing, or any other invasive study in the primary assessment of the patient has no support in the literature. Although there are validated psychometric scales, such as the International Index of Erectile Function (or its short forms) [17] or the Brief Sexual Function Inventiry, [18] these are best suited to trials, not to clinical practice. These instruments cannot

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replace an interactive clinical history. Erectile dysfunction should be clinically distinguished from premature ejaculation or desire disorders; there should be a thorough psychosexual history taken, and partner status needs to be evaluated. Erectile dysfunction risk factors such as diabetes should also be identified; the importance of a proper medication history is key, as various medications may cause ED (hydrochlorothiazide, beta-blockers, antiandrogens) and may have important drug interactions with potential therapies (eg, nitrates and phosphodiesterase inhibitors). The clinical assessment should clearly include the cardiovascular system (including heart rate and blood pressure); the genital exam should include the prostate.

Laboratory investigation is then guided by the presentation. For example, if there are no other known medical problems, a search for these and risk factors for vascular disease (such as hypertension, hyerlipidemia, and DM), is indicated. If there are known risk factors and Ed is a new complaint, serum androgens (usually a bioavailable or free testosterone between 8:00am and 10:00am), serum prolactin, and a serum prostate-specific androgen may be indicated. It should be remembered that hypogonadism is difficult to diagnose in adults on a purely clinical basis and that biochemical confirmation is mandatory prior to onset of therapy.[19]

Neurologic testing may be useful in people with diabetes. [20] Nerve conduction studies may provide information regarding future therapeutic strategies, but a specific focus on these in the diabetic patient with ED is unlikely to change the approach to therapy.

Table 1. Assessment of Patients with Erectile Dysfunction

History and physical examination
Education
Medication factors
Reversible factors
Lifestyle changes
Laboratory tests

HOW ERECTILE DYSFUNCTION IS BEST MANAGED?

Most men developing erectile dysfunction will experience a period where they will have significant fluctuation in their erectile ability. At such tines, education, counseling, and stopping or altering any suspected drugs may be all that is required. If ineffective, medical therapy should be considered to avoid possible deterioration in self-esteem and the relationship.

Nonmedical Management

Current therapy of ED in people with diabetes is the same as it is in other individuals. This includes

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patient education, attention to medications, and cessation of any potentially causal agents including smoking, reversal of particular risk factors, and lifestyle modification (including regular exercise and dietary changes) where appropriate. Optimal therapy of diabetes together with any coexisting conditions (hypertension and dyslipidemia), should underlie any management of patients with ED.

Pharmacotherapy for Erectile Dysfunction

The natural state of the penis is detumescence (inhibitor dominance), and the opportunity for disruption of proerectile mechanisms is great. The many neural and biochemical pathways involved in an erection provide as many opportunities as do pathophysiologic vulnerabilities.

There are a number of current and proposed therapeutic strategies for treating ED, which can be classified according to their site and mode of action.[21] Central initiators with clinical data include apomorphine SL, other dopamine agonists, and melanocyte-stimulating hormone (MSH) analogues.[22] The central mode of action takes advantage of the natural amplification that occurs between the central nervous system (CNS) and the effector systems in the periphery.

Peripheral initiators cause vasodilation through direct action in vascular tissue. The penis is highly accessible to the direct introduction of agents, so almost anything that will cause vasodilation has been tested for intracavernous injection (ICI) or transdermal (penile skin) application. These vasoactive agents act directly on vascular smooth muscle cells or indirectly, leading to the release of vasoactive agents such as NO from vascular endothelial cells or neurons.[23] Currently, prostaglandin E1 (PGE1) is the basic component of the most common forms of peripheral initiator treatment. Other agents in this class or under consideration include triple therapy,[24] new forms of PGE1, SIN (3-morpholino-syndomimin)-1,[25] VIP (vasoactive intestinal polypeptide),[26] CGRP (calcitonin gene-related peptide),[27] and potassium-channel openers.[28]

Central conditioners that enable or enhance erectile function centrally may overlap with drugs that affect libido and orgasm. Testosterone[29] is the best example of such an agent, although it is not a primary therapy for ED. Peripheral conditioners increase the activity of peripheral systems that support or cause erections. They are best typified by the first of the type 5 phosphodiesterase inhibitors, sildenafil (Viagra, Pfizer, NY) and of course newly introduced drugs like vardenafil and tadalafil[30, 31, 32]. Phentolamine (Vasomax, Schering-Plough, Madison, NJ), an α-adrenoceptor blocker, is another peripheral conditioner when prepared for use as a therapy for ED.

Sildenafil and related drugs.

Sildenafil is a peripheral conditioner. It acts as a type 5 phosphodiesterase inhibitor (inhibiting the degradation of cGMP by phosphodiesterase type 5 enzymes), thereby enhancing the availability of cGMP and promoting vasodilation; the specificity of action of sildenafil for erectile smooth muscle is based on the relative preponderance of type 5 phosphodiesterase isozymes in penile smooth muscle. In the many published trials and in clinical use, sildenafil has shown a clear dose response relationship and significant efficacy. The definitive article on sildenafil is the report of two studies published by Goldstein and colleagues.[33] At doses of

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100 mg, 69% of patients indicated that sildenafil had improved their erections. A number of subsequent publications have confirmed the safety and efficacy of the drug in general and in specific ED populations.[34]

Apomorphine

Apomorphine HCI is the first centrally active agent ED drug; the sublingual tablet has been tested in phase III trials.[35] It is an aporphine (not an opiate) that acts as a dopaminergic agonist effective at nanogram concentrations, working in the midbrain (para ventricular and supraoptic nuclei).[36] Since apomorphine acts centrally, any prosexual signaling is enhanced, and following the natural pathways, it generates an erectile response. The action on nuclei affecting erection is highly specific and sensitive, and there is little discernable direct action on cells outside the central nervous system at the doses used.

Phentolamine

Phentolamine mesylate is a peripheral conditioner delivered as Vasomax. It is an α-adrenoceptor blocker and acts to limit the vasoconstrictive effects of α- adrenoceptor activation as typified by stress response.[37] The preparation undergoing phase III trials is designed for oral administration at doses between 40 and 80 mg. Peak plasma levels are achieved within 60 minutes. At 40 and 80 mg, 55% and 59% of men, respectively, were able to achieve penetration at some time.[38] There are no data yet available on the specific efficacy of phentolamine on ED in diabetic patients.

Yohimbine

There has been a continuing interest in the use of yohimbine in the treatment of ED.[39] Yohimbine is a presynaptic α-2 adrenoceptor agonist, although its precise mechanism and location of action in ED is not know. Yohimbine is not approved for use in ED, although sporadic ad hoc use continues.

Prostaglandin E1

Prostaglandin E1 for Ed has been available since 1996 for intracavernous use (Caverject, Edex) and since 1998 as an intraurethral preparation (MUSE). Caverject has been assessed in an international multicenter study in diabetic men. Overall, 94% of men were able to find an effective dose (average 20 µg).Direct application of powerful vasodilators has great appeal in the management of ED; however, the nonoral routes have proved to be a significant deterrent to widespread use. Nevertheless, the efficacy of intracavernous injections with PGE1 and the freedom to titrate doses to suit an individual have proven to be two persuasive factors in using it to treat people with diabetes.

Vacuum Erection Devices

Vacuum erection devices (VED), create erections by drawing blood into the penis under negative pressure, where it is trapped by means of a customized rubber ring at the base of the penis. These devices are well accepted by some patients and are a good example of the relevance of patient choice and good patient support. They are clumsy to use, however, and should be prescribed and supported by a knowledgeable team. Studies in diabetic men suggest that 75% of men may be able to have intercourse using the vacuum devices.[40]

Prostheses

People with diabetes constitute some of the most challenging populations for pharmacotherapy of ED.

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The insertion of penile prostheses avoids the need for functional cavernosal tissue and is therefore a universal, if invasive, option. Prosthesis implantation carries specific potential problems as well. Perioperative precautions regarding infectious disease need special attention although there is no increase in risk depending on the value of glycosylated hemoglobin.[41] Diabetic patients are more prone to develop wound infections,[42] and in the case of a prosthetic device, an infection may have devastating effects.[43] In a large-scale study, 13% of patients were diabetic, and overall, 87% had erections suitable for intercourse. [44]

Testosterone

In diabetes, as in other chronic diseases, levels of testosterone and sex hormone-binding globulin may be decreased.[45] This phenomenon may theorectically result in an insufficient amount of bioavailable testosterone for sexual performance in some men. However, the efficacy of providing testosterone as a primary therapy of ED in mildly hypogonadal men is approximately 60%,[46] but when this condition is coincident with diabetes, there are no data to guide us. A recent meta-analysis of testosterone therapy for ED suggested an improvement over placebo, "implying a role for supplementation in select groups."[47] The issue is not clarified by reports of low testosterone levels in elderly men with Type 2 diabetes because in this population other comorbidities may contribute more than the mild diabetic condition.[48] In general, the use of testosterone one speculative basis in the management of ED is attended by risks and discouraged in the absence of clear hormonal indications.

New Agents

There are other new agents for ED in clinical trials, and developing specific preventive and management strategies for people with diabetes and ED is recognized as a priority. Most of the new drugs currently under consideration are phosphodiesterase inhibitors. Other interesting possibilities are being studied using endothelin-receptor antagonists, potassium-channel openers, and protein-kinase modulators.

CONCLUSION

Future generations of treatments for ED will incorporate a variety of mechanistic strategies, some of which may be especially suited to ED patients with diabetes. The field of hypertension has shown how improvements in pharmacotherapy naturally incorporate new classes of agents and variations within those classes. The therapy of ED will probably expand from monotherapy to combination therapy, and this should be based on suitable studies documenting real gains in efficacy, continuing safety, and better understanding of the characteristics of appropriate patient populations. Diabetic patients have been shown to be particularly susceptible to the development of ED and more resistant to the treatments that have found their way into clinical practice. For patients, rapid expansion of the therapy available for ED means that they now have a choice of effective medications; in the next 5 years, that choice will expand further. The medical choices and disease evaluation are now within the scope of a wide range of physicians, which will further enhance the management of this increasingly common problem. One would expect that prevention should be possible and that treatment, nearing the status of a cure, would eventually be available for many ED victims. For

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many people with diabetes, such a resolution may best be achieved in the form of successful management of the diabetes and prevention of the ED.

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