

Erectile Dysfunction

What is erectile dysfunction?

Erectile dysfunction or impotence is the term to describe the inability of a man to attain or sustain an erection satisfactory for coitus. The erection of the penis involves an integration of complex physiological processes involving the central nervous system, the peripheral nervous system, and hormonal and vascular factors. Any abnormality involving these systems, whether from medication or disease, has a significant impact on the ability to develop and sustain an erection. Tumescence, the vascular filling of the cavernous bodies of the penis, relies on neural and hormonal mechanisms. This is unique among visceral functions, because it requires central neurological input. Detumescence results from the cessation of neurotransmitter release, the breakdown of secondary messengers by phosphodiesterases (PDEs), and sympathetic nerve excitation during ejaculation.



Erectile dysfunction (ED) or impotence is when a man cannot get or maintain an erection. This can seriously affect quality of life for millions of men. The development of medicines to treat ED has been a considerable advance in recent years.

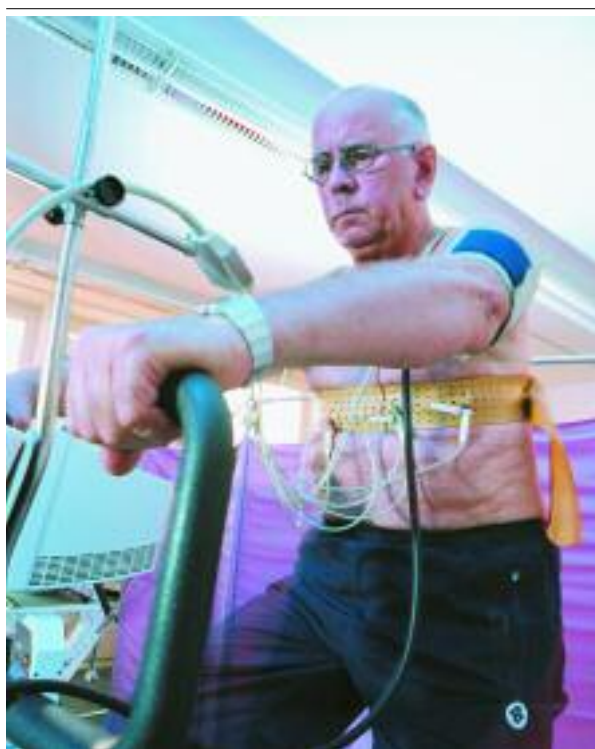
Rarely, erectile dysfunction is primary, which signifies that a man has never been able to attain or sustain erections. Such cases are almost always due to psychological factors and only rarely due to biogenic factors such as low testosterone levels and reflecting disorders of the hypothalamic-pituitary-gonadal axis. Secondary erectile dysfunction occurs when a man who could previously attain and sustain erections no longer can. More than 90 per cent of these cases are organic in nature. The major cause of secondary erectile dysfunction is vascular; other pathogenic categories include hormonal disorders, use of certain medicines, a situation arising after surgery affecting the genito-urinary tract, and other neurological disorders.

Vascular problems include atherosclerosis of penile arteries, inadequate regulation of venous outflow, or a combination of both. With age and underlying diseases, dilation

of arterial blood vessels decreases, diminishing the amount of blood entering the penis. Venous leaks may make it difficult for blood to remain in the penis during erection. Diseases that accelerate atherosclerosis such as diabetes and hypertension increase the prevalence of erectile dysfunction. Hormonal disorders, e.g. hypogonadism and malfunctioning of the thyroid, may cause erectile dysfunction. Forty per cent of men undergoing transurethral resection of the prostate experience problems with erections. Neurological diseases such as stroke, multiple sclerosis, and spinal cord injuries are often causally related to the disorder.

Who does erectile dysfunction affect?

An estimated 25 to 35 million men over the age of 18 are affected in Europe. The prevalence is more than 50 per cent in individuals aged 40 to 70. There is a strong correlation between increasing prevalence and age. The independent association with ageing suggests that vascular changes in the vessels of the corpora cavernosa of the penis, similar to those found elsewhere in the body, are contributing factors. However, men in general can engage in sexual activity throughout life; although the amount and force of ejaculate and muscular tension decrease, erectile dysfunction is not inevitable with ageing.



Long-term predictions based on an ageing population and an increase in risk factors such as hypertension, diabetes, peripheral vascular disease, prostate surgery, benign prostatic hyperplasia, lower urinary tract symptoms suggest a large future increase in the number of men with erectile dysfunction. Studies conducted around the world report similar risk factors and similar prevalence rates for the disorder.

Present treatments:

In cases in which a cause is found, e.g. hypothyroidism or a malfunctioning of the hypothalamic-pituitary-gonadal axis, treatment will be directed toward the underlying disorder.

Since the late 1990s, a special class of oral medicines known as phosphodiesterase 5 (PDE 5) inhibitors have been made available as a first line therapy for secondary erectile dysfunction. PDE 5 is the enzyme located in the corpora cavernosa to break down cyclic guanosyl monophosphate (GMP). This action is mediated by the secondary neurotransmitter nitric oxide (NO), which is primarily responsible for vascular smooth muscle relaxation within the corpora cavernosa. The inhibition of PDE 5 slows the degradation of NO, which enhances the effect of more blood flow to the penis. This permits the development of an improved and sustainable erection. Additionally, PDE 5 inhibitors create a more normal erectile response because they only work with concomitant sexual arousal. In general, the medicines are taken 30 to 60 minutes before sex. Increased sensitivity for erections may last for a day up to 36 hours.

There are groups of men for whom PDE 5 inhibitors are contraindicated, for example, if the patient is taking nitrates or derivatives for a heart condition. Some patients simply do not respond to the products. In such cases, injectable products are available. Penile injection therapy using prostaglandin compounds (PGE1), which act as vasodilators, usually result in erections with an average duration of about 60 minutes. For men who dislike injection therapy, PGE1 has been formulated into a small suppository that can be inserted into the urethra. Other injectables include a mixture of PGE1 with papaverine and another alpha receptor blocker. A further product for injection consists of an alpha receptor blocker and a vasoactive intestinal polypeptide. The effectiveness of alpha receptor blockers is based on the fact, that detumescence is influenced by alpha-adrenergic tone. Alpha-1 receptors predominate in the smooth

muscle cells of the corpora cavernosa, alpha-2 receptors are the predominant receptors in the cavernosal arteries, and both alpha-1 and alpha-2 receptors are present in the cavernosal veins.

Another option may be the sublingual use of a D1/D2 dopamine receptor agonist from the apomorphine (nonopioid) medicine class. The compound has a central effect on certain areas of the hypothalamus which are known to be involved with penile erections. A new slow-release sublingual formulation has demonstrated erectile function with a significant reduction in unwanted effects.

What's in the development pipeline?

An approach to an entirely new way of treating erectile dysfunction would be therapy of the disorder with medicines that function as an antagonist of advanced glycation end-product (AGE) crosslinks. First results in a preclinical model of diabetes have shown their effectiveness. About 30 to 40 per cent of diabetic and elderly patients with erectile dysfunction cannot benefit from available medicines, and those with diabetes or severe vascular disease are among the most refractory to such treatments. AGEs are known to impair erectile function in men with diabetes. They cause the corpus cavernosum to become glycosylated and fibrotic, impairing its ability to expand and fill with blood. AGEs also interfere with the production of the natural penile vasodilating agents, endothelial and neuronal NO.

Researchers are also pursuing the biochemical pathway of selective activation of dopamine D4 receptors, alone or in combination with PDE 5 inhibiting compounds. Scientists have reported results of preclinical studies showing that molecules which act as dopamine D4 receptor agonists induce penile erection in animals. Further investigation showed that combining low doses of D4 receptor agonist with non-effective doses of PDE 5 inhibitors increase the incidence of erection. The compound is now in Phase 2 clinical trials for erectile dysfunction.

The longer-term future:

Sexual health and function are important determinants of quality of life. A disorder such as erectile dysfunction is becoming increasingly important as a result of the ageing European population.

The exciting new knowledge of some of the regulators of vascular tone will lead to future treatments. Increasing evidence indicates that NO acts centrally in the brain to modulate sexual behaviour and to exert its effects on the penis. NO is thought to act in the hypothalamus, preferably in the medial preoptic area and the paraventricular nucleus. Factors that mediate contraction in the penis include noradrenalin, endothelin-1, neuropeptide Y, angiotensin II, and other factors not yet identified. Mediators of relaxation include acetylcholine, NO, vasoactive intestinal polypeptide, pituitary adenylyl cyclase-activating peptide, calcitonin gene-related peptide, adrenomedullin, adenosine triphosphate, and adenosine prostanoids. There are still various options for scientists to have a deeper look into the details of these biochemical mechanisms.

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