

# Viagra and cardiology?

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During my year in the US, one of the things that struck me was that 'erectile dysfunction' seemed to be much more common there than in England, where I had previously worked, and in Ireland where my experience had been (and still is) that it is quite rare. The likelihood is however that American men were more likely to discuss the issue with their doctor, and perhaps as importantly, the doctors were more likely to consider and discuss the issues with patients. Erectile dysfunction is still to a certain extent a taboo subject, perhaps seen as a 'weakness' by afflicted persons or patients, and perhaps seen as a subject best avoided by healthcare professionals.

## What causes erectile dysfunction?

Erectile dysfunction is the inability to achieve or maintain an erection sufficient for satisfactory sexual activity. Normal function requires the coordination of psychological, hormonal, neurological and vascular factors. Various organic factors that may be implicated include chronic disorders such as diabetes and heart disease, where it is reported that there is a 28% and a 39% probability respectively of complete erectile dysfunction. Also implicated are medications, cigarette smoking and excessive alcohol. Incidence increases with age, with approximately 50% of men between 68-73 years having moderate dysfunction. Prostatic surgery, spinal cord injury and penile disorders can also result in dysfunction.

Features suggesting primary psychogenic dysfunction include acute onset and normal erections on waking. As the central and peripheral nervous systems play a fundamental role in the physiology of an erection, psychogenic influences may result from anything from anxiety about sexual performance to depression. In some cases, no cause will be evident for erectile dysfunction.

## How does an erection occur?

Penile erection is controlled by central and peripheral nervous systems. Various stimuli (i.e. visual, imaginative) produce impulses that pass from the brain to the spinal cord, where they are coordinated with somatic pathways of the peripheral nervous system within the penis. In the flaccid state, sympathetic innervation produces contraction of arterial and corporal smooth muscle, minimising blood flow into the cavernous spaces.

Sexual stimulation increases parasympathetic activity resulting in vasodilation and increased blood flow through the cavernous and helicine arteries, with blood filling the erectile tissue due to simultaneous relaxation of penile smooth muscle. The increased blood volume compresses veins in the subtunical space, reducing venous outflow and maintaining the erection.

The most important chemical mechanism appears to involve cGMP. Its formation is mediated by nitrous oxide, which itself is released in response to sexual stimuli, and diffuses into the smooth muscle cells of the corpora cavernosa. This results ultimately in the formation of cyclic guanosine monophosphate (cGMP), which relaxes the smooth muscle of the corpora cavernosa, with increased blood flow and an erection. An erection is lost when cGMP is broken down by another enzyme, phosphodiesterase type 5, mainly present in the corpora cavernosa.

## How does Viagra help?

Viagra (sildenafil) is a selective inhibitor of phosphodiesterase type 5, the main enzyme responsible for breaking down cGMP, thereby regulating levels of cGMP within the corpus cavernosum. Clearly therefore Viagra will not cause an erection to happen, but will restore natural erectile function in response to sexual stimulation. Viagra is rapidly absorbed with maximum concentrations occurring within an hour, but acting within a mean of 19 minutes post-dosing and allowing for erections to be achieved up to four hours post-dosing.

The drug appears very efficacious in all groups, both with organic problems and those with no defined organic cause and has a clear dose response relationship, at least to 100mg. Amongst others, patients with diabetes and hypertension get significant benefit in terms of improved erectile function from Viagra. Viagra is as effective in those above 65 years, as below.

## Side effects and contraindications

The main side effects are headache, flushing and dyspepsia, most being mild. Prolonged erections appear rare, with no case of priapism. The overall rate of dropout from studies due to side effects was 2.5%. The major contraindication to Viagra is the episodic or continuous use of nitrates. This is because Viagra potentiates the hypotensive effects of organic

nitrates, resulting in sudden falls in blood pressure.

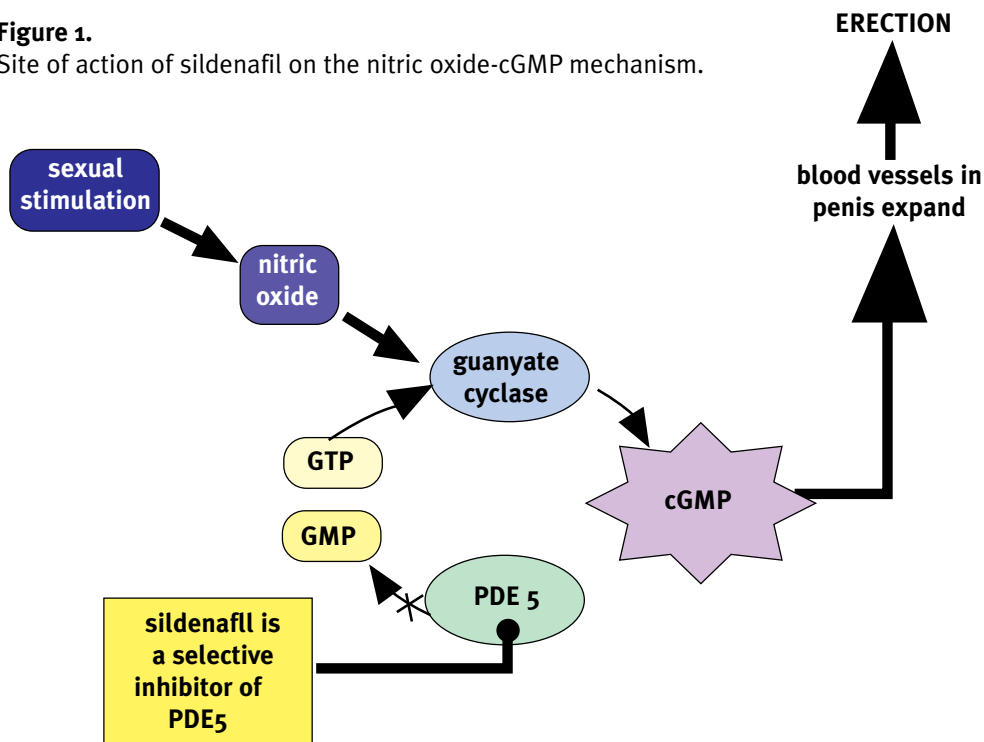
The company state: "There is a degree of cardiac risk associated with sexual activity, and physicians should consider the cardiovascular status of their patients before initiating any treatment for erectile dysfunction." This seems sensible, practical advice. The agent is also contraindicated with severe hepatic impairment, hypotension (<90/50), recent history of CVA or MI and retinitis pigmentosa.

### Conclusion

So we have a problem which is all too often not established or discussed and we have a good treatment for it. Although we cannot use Viagra in patients taking nitrates, or in those considered at risk from sexual intercourse because of severity of heart disease, we can use it in hypertensive or diabetic patients who are not on nitrates.

We will only establish the scale of the problem of erectile

**Figure 1.** Site of action of sildenafil on the nitric oxide-cGMP mechanism.



dysfunction by incorporating relevant questions within our history taking, especially in those considered more at risk. Hopefully with sensible investigating and safe prescribing we can significantly improve the quality of life of many patients with cardiovascular risk factors who have erectile dysfunction.

# Study Report

## Nicorandil Ire-401

Nicorandil, a nicotinamide ester, is a vasodilator agent that has been marketed in Japan since 1984. Its vasodilatory activities, acting on both venous and arterial systemic circulations and leading to a balanced decrease in cardiac pre- and afterload, combined with coronary spasmolytic properties, stimulated clinical development in this drug in ischaemic heart disease. It compares well with established anti-anginal drugs if required. Nicorandil has a favourable risk/benefit ratio, which makes it a promising treatment for a wide range of subjects with ischaemic heart disease and justifies further clinical research.

Nicorandil Ire-401 is a multicentre, double-blind, randomised, crossover study to compare the frequency of anginal episodes, safety and tolerability of nicorandil vs placebo in patients with stable angina following a one-week, single-blind, placebo, baseline period. The study is designed to evaluate the benefit of the addition of nicorandil in Irish patients with stable angina, but comparing the frequency of anginal episodes, exercise tolerance, safety and tolerability of nicorandil vs placebo.

The study is being performed in 100 patients in Ireland in various hospitals throughout the country. Patients will be asked to visit the hospital five times over a six week period. All patients will have a one week run-in period in which placebo will be given (in addition to baseline medication). They will then be entered into arm A or arm B.

Arm A: nicorandil for 14 days followed by a seven day wash-out period, followed by placebo for 14 days.

Arm B: placebo for 14 days followed by a seven day wash-out, followed by nicorandil for 14 days.

The patients will be asked to keep a diary to record all anginal episodes and the amount of nitrates used to relieve each episode. They will have regular exercise stress tests to compare progress.

*The national coordinator for this study is Dr David Mulcahy, consultant cardiologist at AMNC Hospital. If there are any queries regarding this study, he can be contacted at (01) 414 3054.*