ED Drugs:
Seeing Clearly the Cardiac & Visual Risks of PDE-5 Inhibitors

Stephen Holzapfel, MD, CCFP, FCFP
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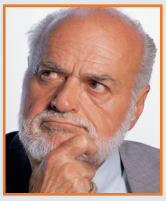
About Matthew



- Matthew, 65, has been taking a PDE-5 inhibitor for his ED.
- He and his partner have been pleased with his treatment.
- He is also taking warfarin for his atrial fibrillation, atenolol for his hypertension and he manages his diabetes with diet and exercise with reasonable success.
- He comes to your office with a print out from the Internet and is concerned that the PDE-5 inhibitor will make him go blind.

How can you help Matthew? Go to page 90 to find out.

FAQ 1

My patient had angina, which was treated with nitroglycerine. Since his stent was put in four months ago, he hasn't needed any nitroglycerine. Can he use tadalafil?

Yes, the patient can use tadalafil because his risk for needing nitroglycerin has dropped. However, he needs to know that if he gets angina in temporal association with having taken a PDE-5, that he cannot take nitroglycerin.

The treatment of male erectile dysfunction (ED) became a primary care issue with the revolutionary development of the phosphodiesterase-5(PDE-5) inhibitors sildenafil, tadalafil and vardenafil.[1] The prevalence of ED is such, that millions of these tablets have been prescribed over the last decade.

Most side-effects of the PDE-5s are relatively mild and transient in nature and commonly cause headache, flushing, dyspepsia, rhinitis, back pain, or visual abnormalities.

Safety concerns about adverse effects of PDE-5's have generally been rare. However, some of the issues relating to the use of PDE-5s in patients with cardiac risk factors and emerging evidence about a possible temporal association of PDE-5 inhibitors with non-arteritic ischemic optic neuropathy (NAION) causing visual loss, are important to address.

PDE-5 inhibitors and the risk of cardiac events

Most physicians are aware of the contraindication of using PDE-5s for a patient who is actively taking nitrates. However, the contraindications for other heart disease patients are not yet known. The Heart and Stroke Foundation and the Canadian Cardiovascular Society[2] have made this more clear. Their consensus statement classified patients into three risk categories (Table 1).

As judged by the Princeton consensus conference, most patients with ED and heart disease fall into low risk categories.[3] These include those with atrial fibrillation and a completed MI, even with mild angina (Table 2).

The risk of treatment must be weighed against

the risk of not treating a man who is concerned about his ED. For many men, having ED leads to a loss of self-esteem, a distancing from their partner and an increase in stress and anxiety, which contribute to an increase in cardiac risk.

NAION

Non-arteritic anterior ischemic optic neuropathy (NAION) is caused by an ischemic injury to the optic nerve. It results in sudden, painless vision loss and visual field defect. It needs to be differentiated from inflammatory processes, such as temporal arteritis. It is the most common cause of acute visual loss in adults over the age of 50, with an incidence in the US of 2.3-10.3:100,000 per year resulting in an estimated 7,000 new cases per year. More than half are left with permanent visual damage.[4] The other eye is affect-

Table 1

Which ED patients with heart disease should be considered for PDE-5 Treatment?[2]

No	Maybe	Yes
Nitrate therapy prescribed & used	Asymptomatic hypotension	All others
Symptomatic hypotension	Severe aortic stenosis or LVOT obstruction	
Patients who may need nitrates for active ischemia,	NYHA Class II or III (acute coronary syndromes, angina with intercourse)	

LVOT: Left ventricular outflow tract obstruction
NYHA: New York Heart Association
ED: Erectile dysfunction

Table 2

Management of sexual dysfunction in patients with cardiovascular disease: The Princeton Consensus Panel

Low risk for cardiac disease
- Asymptomatic < 3 major CAD risk factors
- Controlled BP/ mild, stable angina
- Post Asymtomatic < 3 major CAD Risk Factors
- Controlled increase inBP/ mild, stable angina
- Post-successful CABG or stent
- Uncomplicated MI after six to eight weeks
- Mild valvular disease or atrial fibrillation
- NYHA Class I

Management
- Primary care
- Consider all therapeutic options
- Follow regularly every six to 12 months

Intermediate risk for cardiac disease
- 3 major CAD risk factors (exclude)
- Moderate, stable angina
- Recent MI (> 2, < 6 weeks)
- Noncardiac sequellae (stroke, PVD, *etc*.)
- NYHA Class II

Management
- Cardiac testing: GXT, ECHO, possible consultation
- Re-stratify according to the above info

High risk for cardiac disease
- Unstable-refractory angina
- Uncontrolled increase in BP
- Recent MI (< 2 weeks), or stroke
- High risk arrhythmias
- Hypertrophic and other cardiomyopathies
- Moderate/severe valvular disease
- NYHA Class III-IV

Management
- Urgent referral specialized CV care
- Defer sexual dysfunction therapy until cardiac condition stabilizes

CAD: coronary artery disease
GXT: exercise stress test
CABG: coronary artery bypass graft
ECHO: echocardiogram
NYHA: New York Heat Association
CV: cardiovascular
PVD: peripheral vascular disease

ed in 12% to 19% of patients within five years of onset. The vast majority of these are not associated with PDE-5 use.

On July 26, 2005, Health Canada released an advisory[5] about vision problems possibly associated with sildenafil, tadalafil and vardenafil based on a report by Pomeranz, *et al.*[6] This report summarized 14 cases of NAION associated with PDE-5 use. The men were aged 42 to 69 years, with the majority over the age of 50 and showing multiple vascular risk factors. Eight of these men had permanent visual loss in the affected eye with an accuracy of less than 20/80. In one case, both eyes were affected.

By the Spring of 2005, the American Food and Drug Administration (FDA) recorded 43 cases of ischemic optic neuropathy, with most being NAION, that were associated with all three PDE-5 inhibitors.[7]

NAION is associated with vascular risk factors similar to those clustering with ED (see Table 3).

It is not possible to estimate the absolute risk that PDE-5 inhibitors pose for NAION. Given that over 100 million doses have been used, the individual risk would appear to be very small at this point. Furthermore, the Health Canada Advisory did not make any specific recommendations and stated, "It is difficult to determine whether the use of sildenafil, tadalafil and vardenafil is causing NAION, as individuals who have erectile problems often have high BP, diabetes or other conditions that put them at increased risk."

Pomeranz, *et al.* felt it prudent "that patients with a history of monocular NAION be cautioned that sildenafil may increase the risk of NAION in the fellow eye".

The FDA in the US went further to recommend product labeling reflecting that "physicians should advise patients to stop use of all PDE-5 inhibitors and seek medical attention in the event of a sudden loss of vision in one or both eyes."

The challenge for the primary care physician is to put this information into a clinical context for a particular patient. While it may be important to warn patients, especially those with pre-disposing eye conditions, about a potential adverse event with possible serious consequences; this conversation must also balance the significant benefit

FAQ 2

My patient had cataract surgery and heard that vardenafil might make him go blind. Does the eye surgery increase his risk of optic neuropathy with his PDE-5?

No. Medical risk factors associated with non-arteritic anterior ischemic optic neuropathy (NAION) include, cardiac disease, hypertension, hyperlipidemia, and smoking.

Table 3

Risk factors for NAION and ED

- Age greater than 50 years
- Heart disease
- High BP
- High cholesterol
- Diabetes
- Smoking

FAQ 3

A patient has asthma, diabetes and hypertension. He does not have angina. Is sildenafil harmful to him?

There is no evidence that any PDE-5 causes more heart attacks compared to placebo. There is also no evidence of any increased all-cause mortality for PDE-5s over placebo.

that the patient may derive from the treatment.

Myths about PDE-5 inhibitors often scare patients and their partners. These myths include the fear of suffering from a heart attack and the fear of "too much sex (with PDE-5's) will make you go blind." The clinician's role is to assess and explain the real risks and the benefits of taking a PDE-5 inhibitor to the patient wanting to deal with his ED and to help him and his partner make informed choices.

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Responding to Matthew

You explain to Matthew that he is at increased risk of blindness from a number of factors:

1) His greatest risk is from diabetic retinopathy and he should have his retina checked on an annual basis to rule out neovascularity.
2) His atrial fibrillation is not a contraindication for using a PDE-5 inhibitor. Even though he is appropriately anticoagulated, he is still at an increased risk of having a stroke, including a retinal artery occlusion.
3) Non-arteritic anterior ischemic optic neuropathy (NAION) has, in rare cases, found to be correlated with the use of PDE-5s. While this is a possible risk for him, the chances are profoundly less than those listed above.

- Matthew does have risks associated with NAION (*i.e.*, his age, hypertension and diabetes), but whether his PDE-5 increases his risk is not yet known.
- Should he experience any visual loss, he should discontinue use of any PDE-5 inhibitors until he can have his case properly assessed.

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