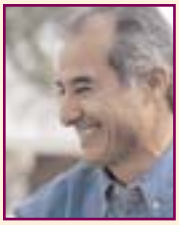
Erectile Dysfunction

Assessing the New Drugs

Richard Ward, MD, CCFP, FCFP

As presented at the University of Calgary's
Evening Course CME Program (March 2004)

Ron's case



Ron, 64, has had Type 2 diabetes for 15 years. He has multiple complications from his diabetes, including:

- neuropathy,
- proteinuria, and
- early diabetic retinopathy.

On a visit to your office last fall, he complained of impotence. You prescribed sildenafil, 50 mg.

Ron presents today for a complete exam. You ask him how the sildenafil worked. He replies, "Nothing happened, Doc. Could I try one of these new medications for erections?"

For the answer to Ron's question, go to page 75.

The management of male sexual problems has changed dramatically since the release of sildenafil. A safe and effective therapy, combined with unprecedented publicity, resulted in more men approaching their physicians for treatment.

Two new therapies have been approved for the treatment of erectile dysfunction (ED) in the past six months. But how do all of these agents compare?

What are the two new medications? How are they different?

All three ED treatments are isoenzyme phosphodiesterase type 5 (PDE-5) inhibitors. The two new therapies, tadalafil and vardenafil, differ mostly in their pharmacodynamics. Vardenafil has a similar half-life to sildenafil, but tadalafil's is longer. Clinically, this means tadalafil will last longer for patients; it remains effective for up to 36 hours post-ingestion.

Vardenafil is a more potent and selective PDE-5 inhibitor. It is unclear whether this means vardenafil is more effective or has fewer overall side-effects than the other PDE-5s. There is evidence of good efficacy with vardenafil in difficult-to-treat populations (*i.e.*, those who have undergone radical prostatectomy for localized prostate cancer and/or those with diabetes). However, sildenafil and tadalafil have also shown efficacy in these populations.

Food, particularly high-fat meals, delay the absorption of sildenafil. The absorption of tadalafil is not affected by food. Vardenafil's absorption is delayed only with high-fat meals.

None of the PDE-5 inhibitors interact with alcohol.

Table 1

Causes of apparent treatment failure of PDE-5 inhibitors

1. Inadequate dosing
2. Not enough trials using the medication
3. Timing of sexual activity after taking the medication
4. No sexual stimulation
5. Incorrect diagnosis
6. Androgen deficiency resulting in inadequate response to therapy
7. True treatment failure—most often in men with severe and long-standing erectile dysfunction occurring as a result of significant vascular disease or neuropathy

What are the starting doses of the two new medications?

Vardenafil should be started at 10 mg, while tadalafil's starting dose is 20 mg. Lower doses should be considered in:

- the elderly,
- patients with severe hepatic dysfunction, or
- those on medications that inhibit the P450 3A4 enzymes.

Inadequate dosing is one of the reasons the PDE-5 inhibitors may fail. Other causes of apparent treatment failure are listed in Table 1.

Are the side-effects the same?

The side-effects of the three PDE-5 inhibitors are similar. All can cause:

- headache,
- nasal congestion,
- facial flushing, and
- dyspepsia.

Furthermore, tadalafil has uniquely been associated with a small incidence of back pain.

These side-effects are infrequent, temporary, and rarely result in discontinuation of the drug.

Dr. Ward is a clinical associate professor, department of family medicine, and a senior educational consultant, office of CME and professional development, University of Calgary, Calgary, Alberta

Are the medications safe in patients with cardiovascular disease?

The evidence from the Phase III data submitted for tadalafil and vardenafil indicate these are very safe drugs for patients with stable cardiovascular disease. There were no increases in cardiovascular side-effects or mortality among patients with existing coronary artery disease treated with tadalafil or vardenafil, as compared to those who received placebo.

This data, combined with the extensive post-launch safety experience from sildenafil, strongly support the notion that the PDE-5 class of medications is safe in patients with existing cardiovascular disease.

Can patients take nitroglycerine with either of the two new PDE-5 inhibitors?

No. The concurrent use of nitroglycerine in any form is an absolute contraindication to all the PDE-5 inhibitors. This is due to the potential for significant hypotension when the two agents are combined.

Nitrates must not be given for 24 hours after taking either sildenafil or vardenafil. Because of its longer half life, tadalafil should not be combined with nitroglycerine for 48 hours after ingestion .

A followup on Ron

While it would be reasonable to try one of the newer agents, it is most likely there are other reasons for Ron's lack of success with sildenafil.

Many of the reasons for apparent treatment failure apply to all the isoenzyme phosphodiesterase type 5 (PDE-5) inhibitors. Treatment failures can be minimized by:

- taking a good sexual history,
- providing adequate counselling to patients when prescribing a PDE-5 inhibitor, and
- booking a followup appointment to ensure efficacy.

Take-home message

Which ED drug should I prescribe?

- The three ED drugs on the market are sildenafil, tadalafil, and vardenafil; all three are PDE-5 inhibitors.
- All three drugs are probably equally effective. Tadalafil lasts longer and its absorption is unaffected by food. The absorption of vardenafil is only influenced by high-fat meals.
- All three are safe for patients with cardiovascular disease and contraindicated in patients taking nitroglycerine.
- Deciding which ED agent to prescribe depends on the response of individual patients; there are no head-to-head comparisons.

Which drug is the most effective?

There are no head-to-head trials comparing the effectiveness of the three PDE-5 inhibitors. Efficacy data comparing one trial to another should not be used as a basis for comparison, as the end points, inclusion criteria, and protocols differ.

Efficacy is probably similar between all three compounds. However, it is likely that individual patients may show a different response to different agents. Similar to other classes of drugs which we prescribe, patients will often report differences in efficacy and side-effects that are unique to the individual and not predicted based on pharmacology or clinical trial experience.

Physicians should be comfortable and familiar with prescribing all three therapies to patients with ED.

Which drug is best for my patient?

The choice of therapies is probably best made by explaining the differences in pharmacology to patients. It takes a short amount of time to highlight the key differences between the three existing oral therapies and let the patient decide which medication best suits his lifestyle. Dx