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Erectile dysfunction (ED), once a taboo issue, has received a lot of attention by consumers and healthcare professionals in recent years. Did you know that 1 in 5 men have erectile dysfunction? [1] For obvious reasons, drug companies have jumped on the bandwagon to find a treatment for this medical condition.

Tadalafil (Cialis ® - Eli-Lilly™) has just hit the Canadian market. Vardenafil (Levitra® - GlaxoSmithKline™) is in the pipeline waiting for its ticket to be on the market. Where does Sildenafil (Viagra® - Pfizer™) fit into this picture of new and exciting things? Here's what you need to know….

**Q: Which one is more effective?[1-4]**
Comparative trials between the PDE5 agents are lacking. Sildenafil achieves near maximal inhibition of PDE5 already suggesting there isn't much room for improvement with tadalafil or vardenafil. The onset of action varies among the PDE5 inhibitors (sildenafil → 30-60 minutes; vardenafil → within 60 minutes; tadalafil → 30-45 minutes). Unpublished data suggests tadalafil might be effective as early as 16 minutes post dose. Tadalafil has the longest duration of action (36 hours) followed by sildenafil (up to 4 hours) then vardenafil (1 hour).

**Q: What side effects should we watch for with the new agents?[1]**
Current data suggests the PDE5 inhibitors are similar in terms of the severity and frequency of side effects. Most commonly reported side effects in clinical trials were headache, facial flushing, nasal congestion and dyspepsia. Sildenafil and vardenafil, but not tadalafil have a slight hypotensive effect. Change in vision is a rare, dose dependant adverse effect reported in sildenafil and vardenafil users due to weak inhibition of PDE6. Tadalafil is a weak inhibitor of PDE11, which is distributed in various tissues including skeletal muscles, heart and vascular muscles. Back pain has been reported with tadalafil, possibly related to inhibition of PDE11. The clinical significance of PDE11 inhibition on other tissues remains to be seen. More study is required to better assess the adverse effect profile of the newer agents particularly in long-term use and the high-risk population.

**Q: Who should not use the new PDE5 inhibitors?[1,5,6]**
The PDE5 inhibitors should not be used in patients for whom sexual activity is not recommended (i.e. severe cardiovascular disease). In addition, it is not advisable to use in those patients who have had a recent heart attack or stroke or are on concurrent nitrate therapy. Sildenafil and vardenafil should not be used in those with marked arterial or orthostatic hypotension. This does not appear to be a problem in tadalafil users however the data is scarce. Sildenafil, the first PDE5

inhibitor to be marketed, included a wide range of patients in clinical trials. Investigators exercised more caution for scientific and ethical reasons in the vardenafil and tadalafil trials. Those who experienced cardiac effects within the last six months and had a history of proliferative retinopathy or retinitis pigmentosa were not included in vardenafil trials. Similarly, patients with CNS disturbances, liver, kidney or heart disease were excluded from tadalafil studies. As a result, this translates into insufficient data in the high-risk population.

**Q: Are there any special concerns about drug interactions?[1,5,6]**

All three agents are metabolized by CYP 3A4 suggesting possible pharmacokinetic interactions with CYP 3A4 inhibitors. As with sildenafil, exacerbation of the hypotensive effect of nitrates is possible with the newer agents. Vardenafil is associated with QT prolongation. Caution should be exercised in those on QT drugs or who have congenital QT prolongation.

**Q: What is the bottom line?[1,5,6]**

The differences between these agents are minimal. Unlike sildenafil, and for that matter vardenafil, tadalafil may increase the spontaneity of sexual activity due to its rapid onset and longer duration of action. Whether this translates into therapeutic benefit or increased adverse effects remains to be seen with further study. Vardenafil is very similar to sildenafil with the exception of a lower incidence of vision changes, an already rare adverse effect. The bottom line is they all appear to be effective for erectile dysfunction. Further study is needed to determine whether one agent is superior to the others.

***Prepared by Zahra Hirji, Drug Information Consultant***

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