CME Drug Treatments for Erectile Dysfunction: An Update

Sildenafil was introduced in Canada in 1998 as the first effective oral therapy for erectile dysfunction (ED). Since its release, sidenafil has been proven to be an effective and safe treatment for ED in older patients with multiple medical problems. In the last year, two new PDE5 inhibitors have been approved for ED treatment: vardenafil and tadalafil. There are subtle differences between the three phosphodiesterase type 5 (PDE5) inhibitors with respect to efficacy, dosing instructions, and adverse event profiles. All three PDE5 inhibitors have exhibited efficacy and safety in the cardiac patient as long as he is not reliant upon the regular use of nitroglycerine. This article reviews the similarities and differences between the three PDE5 inhibitors, and refers to patient attitudes in Canada towards sexual activity and its treatment with these agents, as discussed in the Canadian Sexual Satisfaction Survey (CSSS).

Key words: Erectile dysfunction, phosphodiesterase inhibitor, sildenafil, vardenafil, tadalafil

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Introduction

Physicians in Canada are treating an increasingly aging population, and coupled with this is an increase in the incidence of specific diseases that may arise as a result of the breakdown of biological mechanisms (e.g., endothelial dysfunction leading to cardiovascular disease or diabetes). While it is now routine for older male patients to be screened for cardiovascular-related diseases such as hypertension and hyperlipidemia, there still exists a significant level of discomfort in discussing the topic of erectile dysfunction during patient consultations.

Erectile dysfunction is known to increase with age[1] and is, to a large degree, a consequence of impaired vasculature. The diffidence surrounding this issue has been documented in a recent survey designed and endorsed by the Canadian Male Sexual Health Council, conducted in Canada in 2003.[2] In this Canadian Sexual Satisfaction Survey (CSSS), approximately 1,000 men with ED, age 40 years and older, and 200 physicians were surveyed as to whether sexual health was discussed during visits. The perceptions of each group differed vastly, as 65% of physicians responded that they asked their patients about sexual health often or very often, whereas 72% of men with ED said that their physicians rarely or never asked about ED. Is this gap due to a lack of knowledge about or discomfort with discussing sexual dysfunction, a concern about the time required to correctly diagnose and treat the condition, or a lack of awareness of the medications that are available and their use in an older population? This article presents an update on the three available phosphodiesterase type 5 (PDE5) inhibitors, including recent information on the new additions to the Canadian market, vardenafil and tadalafil.

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 inhibitors work by increasing blood flow to the penis during sexual stimulation and, as a result, restoring the potential to achieve and sustain an erection (Figure 1). Sildenafil, which has been on the market in Canada for approximately five years, afforded men with ED the first oral treatment option. The efficacy and safety of sildenafil has been shown in a number of studies.[2,3] The question remains whether this drug the ideal treatment for ED. While sildenafil has answered a large need among patients, there is still a gap in general acceptance. An indication is provided in the CSSS, where 45% of men who demonstrated aided awareness of sildenafil (n=938) expressed concerns such as the potential for as-yet unidentified side effects, heart problems, and drug interactions.[5] Of those men who had taken sildenafil (n=186), 60% reported that it allowed them to attain and maintain a satisfactory erection for at least some of the time. However, up to 45% of men overall were dissatisfied to some degree, and the major reason was lack of efficacy (77%). In fact, 88% of men who had taken sildenafil indicated that they would be interested in trying a new medication if it were available.

Efficacy

The approvals of vardenafil and tadalafil for prescription sale in Canada now provide physicians and patients with first-line treatment options to sildenafil. Both vardenafil and tadalafil are effective in the broad population of men with ED.[6,7,8] Retrospective analyses of the vardenafil broad population studies show that, compared to placebo, vardenafil provides good reliability in terms of first-time success and subsequent success rates for vaginal penetration, successful completion of intercourse, and overall patient satisfaction with the sexual experience.[9] In addition, a separate study found that the efficacy of vardenafil was maintained in ED patients over a two-year period.[10]

Patients with diabetes or those who have had radical

Figure 1.
Physiology and Drug Therapy in Erectile Dysfunction

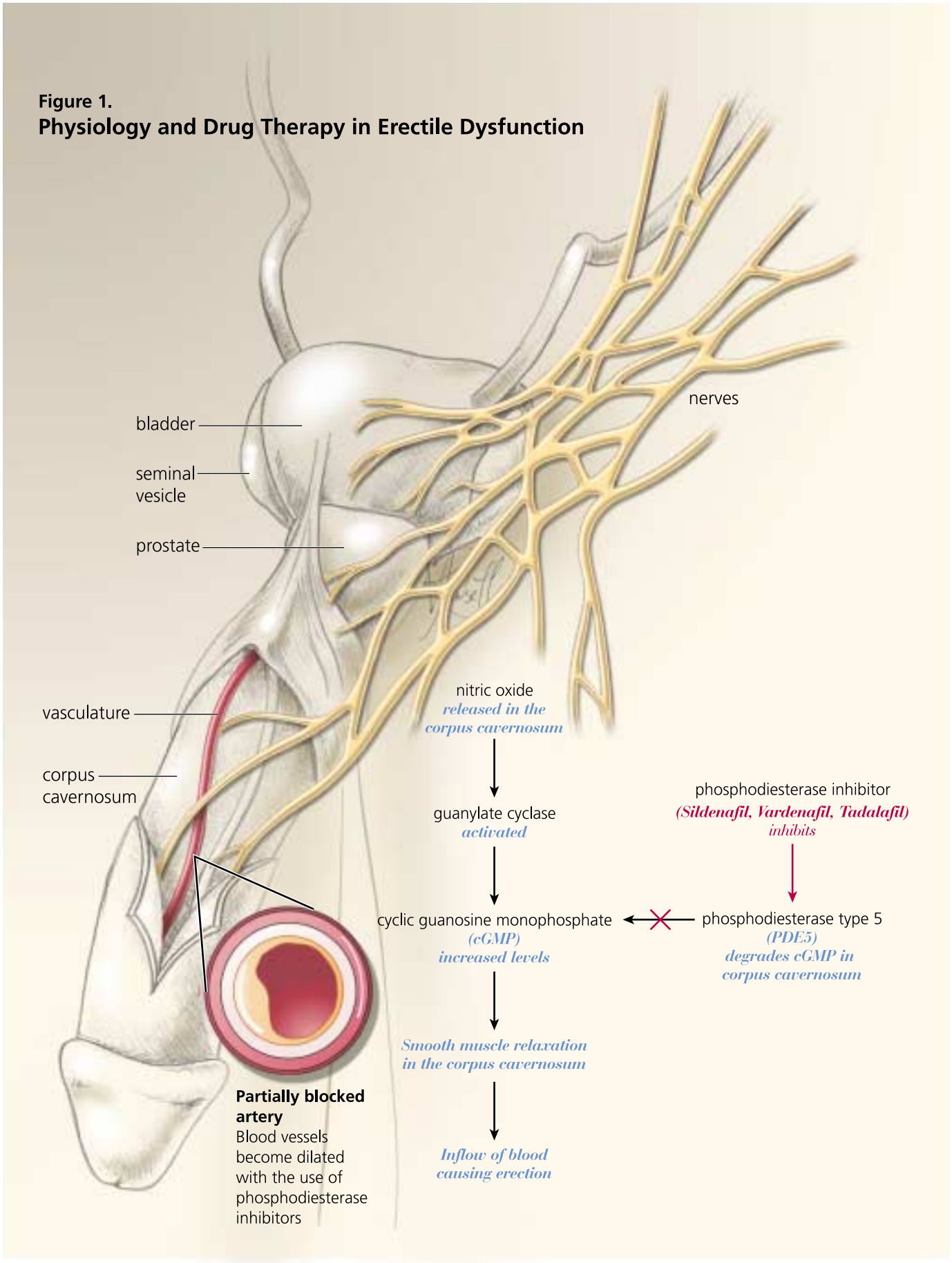

Table 1: Available Doses and Suggested Starting Doses of the Three Available PDE5 Inhibitors in Canada

PDE5 Inhibitor	Available oral doses	Starting dose	Starting dose in older men (≥65 years)
Sildenafil	25mg, 50mg, 100mg	50mg	Consider 25mg (reduce dose in cases of renal impairment)
Vardenafil	5mg, 10mg, 20mg	10mg	Consider 5mg
Tadalafil	10mg, 20mg	20mg	20mg (reduce dose in cases of renal impairment)

Source: Viagra Canadian product monograph, Levitra Canadian product monograph, Cialis Canadian product monograph

prostatectomy surgery have ED that is considered difficult to treat. All three PDE5 inhibitors have shown efficacy in patients with diabetes.[11,12,13] Both sildenafil and vardenafil show efficacy in patients post-prostatectomy. In the former, single-centre studies were done,[14] and with vardenafil, a large-scale North American multicentre trial was conducted.[15] Vardenafil has also been shown to be effective in other challenging ED patients as in those patients who, by history, are unresponsive to sildenafil.[16]

Table 2A: Adverse Events Reported by ≥2% of Patients Treated with Sildenafil (PRN flexible-dose Phase II/III studies)

	Percent of patients	
Adverse event	**Sildenafil (n=734)**	**Placebo (n=725)**
Headache	15.8	3.9
Flushing	10.5	0.7
Dyspepsia	6.5	1.7
Nasal Congestion	4.2	1.5
Respiratory Tract Infection	4.2	5.4
Flu Syndrome	3.3	2.9
Urinary Tract Infection	3.1	1.5
Abnormal Vision*	2.7	0.4
Diarrhea	2.6	1.0
Dizziness	2.2	1.2
Rash	2.2	1.4
Back Pain	2.2	1.7
Arthralgia	2.0	1.5

*__Abnormal vision__: mild and transient changes, predominantly impairment of colour discrimination (blue/green), but also increased perception to light or blurred vision.
Source: Viagra Canadian Product Monograph; with permission from Pfizer

Dosing Instructions

The available doses of sildenafil, vardenafil and tadalafil are provided in Table 1.

The rate of drug metabolism in older patients (≥65 years of age) is usually reduced in comparison to younger individuals. It is for this reason that a lower starting dose should be considered when prescribing vardenafil or sildenafil to this patient population (5mg and 25mg as needed, respectively). This can be titrated up depending on efficacy and tolerability. While there is a reduced rate of metabolism of tadalafil in the aging, no dose adjustment is required. In patients with renal impairment, which is more frequent in older men, a reduced starting dose is recommended with sildenafil and tadalafil. For tadalafil, reduced frequency of dosing is also advised in these patients. In patients with hepatic impairment, dose adjustments are required with all three drugs, depending on the degree of hepatic impairment.

In the CSSS, men with ED (n=1,000) were asked to rate preferred characteristics of an ideal oral ED medication.[5] As many as 58% rated no food interactions as important, and close to half the group (49%) preferred a 25-minute onset of action, while the drug's ability to last 24 or 48 hours was ranked low. Both vardenafil and tadalafil can be taken with or without meals, and while all three are effective at 30 minutes to one hour after dosing, sexual activity can be initiated as early as 15 minutes after ingestion of vandenafil. The long half-life of tadalafil (17.5 hours) allows patients and their partners to have sexual intercourse within 36 hours of taking the medication.[17] Post-hoc analyses of data from the broad population trials of vardenafil have shown that successful attempts at intercourse can be achieved within an extended time window from 15 minutes to 8 to 12 hours.[18]

Adverse Event Profiles

For the most part, the adverse event profiles of the three PDE5 inhibitors are fairly similar, relate to the mechanism of action, and are transient. The discontinuation rates due to adverse events as reported in clinical trials fall well below 5% and are

generally similar to placebo. Table 2 summarizes the adverse events reported with each of the PDE5 inhibitors and the associated placebo rates. There are certain adverse events that occur at a higher frequency with specific inhibitors, and these are noted in the table with shaded boxes. The abnormal vision reported with sildenafil may be attributed to non-selective inhibition of PDE6, which is found in the retina. The reason for increased incidence of back pain and myalgia that is associated with tadalafil is not known. In treating older patients, it is important to determine their tolerability to adverse events before choosing a medication. Patients who have arthritis may have less tolerance for back and associated muscle pain.

Cardiovascular Issues

A question that is frequently asked by patients, their partners, and physicians is whether it is safe for men with CV disease to take PDE5 inhibitors and engage in sexual activity. In the older male, this may take on particular significance as age, gender and sedentary lifestyle, in addition to hypertension, dyslipidemia, and diabetes, contribute to the overall CV risk. In light of the observations of increased incidence of ED in patients with CV disease and the potential cardiac risk associated with sexual activity itself, the Princeton Consensus recommendations were developed to aid in patient management.[19]

As a small but definite risk of a cardiac event exists for patients with CV disease, physicians need to do an initial stratification of patients for cardiac risk. This is based on a number of elements including but not limited to hypertension (controlled/uncontrolled), history of myocardial infarction, valvular disease and angina (severity and stability to determine existing or potential need for nitrates). Low-risk patients can initiate or continue sexual activity and use treatments for erectile dysfunction, including PDE5 inhibitors. High-risk patients should first stabilize their cardiovascular condition before initiating sexual activity or using PDE5 inhibitors, and those with intermediate risk should be reassessed and stratified into high or low risk. It is important to emphasize that the use of any form of nitrate with a PDE5 inhibitor is contraindicated because of the increased likelihood of hypotension. Controlled safety studies have been done to investigate, for emergency purposes, the effects of elapsed time between administration of a PDE5 inhibitor and a nitrate on heart rate (HR) and blood pressure (BP). Because of the long half-life of tadalafil, at least 48 hours should have elapsed after the last dose before nitrate administration can be considered administration in a life-threatening situation (Cialis product monograph). With vardenafil, at least 24 hours should have elapsed after the last dose of vardenafil before nitrate administration is considered, with appropriate monitoring and close medical supervision (Levitra Canadian Product Monograph).

Table 2B: Vardenafil (all placebo controlled trials of 5mg, 10mg, and 20mg more frequent on drug)

	Percent of patients	
Adverse event	**Vardenafil (n=3,3103)**	**Placebo (n=1,502)**
Headache	13	4
Flushing	12	1
Rhinitis	9	3
Dyspepsia	3	1
Accidental Injury	2	2
Flu Syndrome	2	2
Increased Creatine Kinase	2	2

Source: Levitra Canadian Product Monograph; with permission from Bayer-GlaxoSmithKline Inc.

Conclusion

In 2004, the aging male patient with medical comorbidities who wishes to be sexually active can be afforded that opportunity. The old saying "You're only as old as you feel" seems to be appropriate when referring to this group of male patients. The discovery of safe and effective first-line oral therapy has not only revolutionized the management of ED but has also changed Canadian men's and their partners' attitudes concerning this disease entity. The CSSS suggested that not all patients are satisfied with sildenafil and would like to try new therapies for treatment of their ED.

The three PDE5 inhibitors currently on the market, sildenafil, vardenafil, and tadalafil, have similarities but also subtle differences that physicians should be cognizant of

Table 2C: Tadalafil (Phase 2/3 clinical trials, more frequent on drug than placebo)

	Percent of patients	
Adverse event	**Tadalafil (n=1,561)**	**Placebo (n=758)**
Headache	11	4
Dyspepsia	7	1
Back pain	4	3
Myalgia	4	1
Nasal congestion	4	2
Flushing	4	1

Source: Modified from Cialis Canadian Product Monograph; with permission from Eli Lilly Inc.

when prescribing them to the aging male patient.

Furthermore, the CSSS has demonstrated that the aging Canadian male and his partner are anxious to discuss ED with their physicians and would prefer that their physicians initiate the discussion. ED in Canada is still underdiagnosed and undertreated despite the publicity surrounding this disease and the effective oral therapies now available. Physicians can now offer their patients a choice in PDE5 inhibitor and improved quality of life. ◆

Dr. Pommerville serves on the advisory boards of Pfizer, Eli Lilly, and Bayer/GSK.

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