Tadalafil: a new agent for erectile dysfunction

Gerald B. Brock, MD

Department of Surgery, Division of Urology, St. Joseph's Health Centre, London, Ontario, Canada

BROCK GB. Tadalafil: a new agent for erectile dysfunction. Supplement of The Canadian Journal of Urology. 2003;10(Supp. 1):17-22.

Oral phosphodiesterase 5 (PDE5) inhibitors for the treatment of erectile dysfunction are preferred by most men, and are recommended in guidelines as first-line therapy, because of convenience, high efficacy, and low rates of side effects. Tadalafil (Cialis™) is a new agent that has been studied in different patient populations. It has a different molecular structure than other PDE5 inhibitors, and a different pharmacologic profile that provides a longer period of effectiveness than other agents. This article will review clinical trials on tadalafil, to provide a comprehensive overview of its efficacy and safety.

Key Words: erectile dysfunction, tadalafil, efficacy, pharmacology

Introduction

In the search for an ideal agent for the management of erectile dysfunction (ED), the oral inhibitors of phosphodiesterase type 5 (PDE5) appear to be the best choice currently available. The combination of a high degree of efficacy (regardless of the underlying etiology of ED), with excellent safety and convenience, have made these oral agents the first-line therapy as recommended by the current Canadian Urological Association guidelines.[1] The only agent in this class available in 2002 in Canada is sildenafil, which has been very widely studied and prescribed. New members of this family currently undergoing regulatory review are vardenafil (Levitra™) and tadalafil (Cialis™), previously studied as IC351. In this report we will focus on tadalafil, providing a comprehensive review of pharmacological and clinical information summarized from recently published studies (including four Canadian trials) and current abstracts.

Address correspondence to Dr. Gerald B. Brock, St. Joseph's Health Centre, 268 Grosvenor Street, Urology Department, London, ON N6A 4V2 Canada

Pharmacology of tadalafil

The pharmacology of sildenafil, vardenafil, and tadalafil are presented (by Dr. Serge Carrier) in the third article of this supplement. Although all agents target PDE5, their chemical structures and pharmacologic properties are distinct.

The time to maximum serum concentration for tadalafil, after oral administration of a single dose, is 2 hours,[2] compared with that of sildenafil (1 h),[3] or another new agent, vardenafil (0.7 h to 0.9 h).[4] Tadalafil has been shown to have an onset of action

as early as 16 minutes, which can be related to the minimal inhibitory concentration of this agent required to have a clinical effect.

The serum half-life ($t_{1/2}$) is 4 hours for sildenafil,[3] 4 to 5 hours for vardenafil,[4] and 17.5 hours for tadalafil.[2] This difference in half-life is the most significant pharmacologic characteristic differentiating the three agents.

Another pharmacological feature of tadalafil is that its absorption and pharmacodynamic properties are not affected by either food or alcohol,[5] in distinction to sildenafil whose absorption can be blunted by fatty food.[3]

Outcome measures

Many trials of new drugs for ED use standardized, validated questionnaires as the major outcome measures. The most commonly used is the International Index of Erectile Function (IIEF), a questionnaire that is available in at least 57 different languages, and has been validated in different cultures.[6] The self-administered IIEF consists of 15 questions, six of which make up the erectile function domain.[7] These six questions are shown in Table 1. Each is scored from 1 to 5, so that a maximum score is 30: normal erectile function is defined as a score of 26 or greater.[8]

Another scale that is frequently used is the Sexual Encounter Profile (SEP), a patient diary used to record sexual experiences. In this scale, the most commonly analyzed questions are question 2 (SEP-Q2), "Were you able to insert your penis into your partner's vagina?" and question 3 (SEP-Q3), "Did your erection last long enough to have successful intercourse?"[9]

A summary question that was asked in all of these studies is a global assessment question (GAQ), which uses wording such as, "Has the treatment you have been taking improved your erections?" The GAQ provides good insight into the subjective clinical response to a therapeutic agent and provides the

TABLE 1. **Questions making up the IIEF erectile function domain.[7] Reprinted with permission from Elsevier Science**

Question*	**Response options**
Q1: How often were you able to get an erection during sexual activity? Q2: When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q5: During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q15: How do you rate your confidence that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

* All questions are preceded by the phrase "Over the past 4 weeks"

clinician with an indirect estimate of patient satisfaction.

Efficacy

Integrated analysis

The most important data supporting the efficacy of tadalafil for ED come from an integrated analysis of five randomized, double-blind, placebo-controlled, multicentre trials, four of which enrolled patients from Canada.[6] The trials shared common elements of design, including inclusion and exclusion criteria, which facilitated pooling of their results for analysis. Conducted in a total of 74 centres, the trials enrolled 1112 patients with ED of varying etiologies, and varying severities (41% mild, 23% moderate, 36% severe). The mean age of the patients was 59 years: 30% had hypertension, 21% were diabetic.[6]

Doses of tadalafil in the studies ranged from 2.5 mg to 20 mg at a time, with patients instructed to take a tablet before sexual intercourse.[6] One of the major strengths of the tadalafil data is that this agent can be taken without restrictions on food or alcohol, as shown by its pharmacokinetic and pharmacodynamic data. All of the studies were analyzed over a 12-week period.[6] The major outcome measures were change from baseline in the IIEF erectile function domain questions and the SEP questions 2 and 3.

At all doses, tadalafil gave statistically significant improvements from baseline in erectile function compared to placebo. Figure 1 shows responses to SEP question 3, "Did your erection last long enough to have successful intercourse?" Figure 2 displays changes from baseline in the total IIEF erectile function domain scores, analyzed by baseline severity of ED; tadalafil was effective regardless of baseline severity.[6]

Men were asked to record the time from taking the medication, until intercourse. Rates of successful intercourse (SEP-Q3) at different time intervals, for men taking 20 mg tadalafil, are shown in Figure 3.[6]

Other outcome measures showed similar improvements with tadalafil. One of the most clinically relevant was the proportion of men who achieved normal erectile function (an IIEF erectile function domain score of 26 or better). Scores increased in a dose-related manner from 11% with placebo to 21% with tadalafil 2.5 mg. For men taking tadalafil 20 mg, 59% achieved a score of 26 points or greater, placing them within the "normal" range.[6] As well, in response to the most commonly quoted number on ED, the GAQ, 81% of men taking tadalafil 20 mg reported overall improvement in their erections Figure 4.[6]

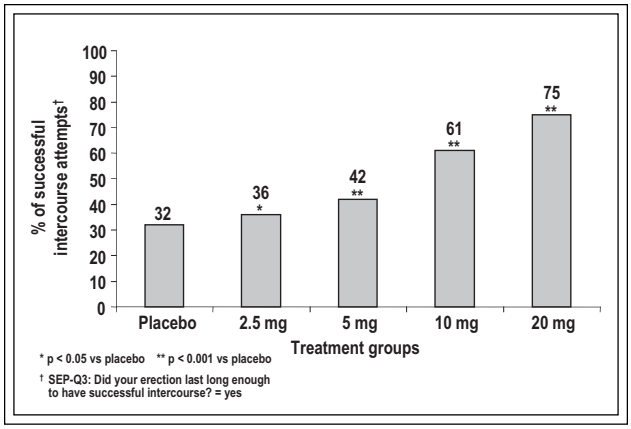

Figure 1. Effect of tadalafil on rate of successful intercourse (SEP-Q3) (integrated analysis).[6] Reprinted with permission from Lippincott Williams and Wilkins.

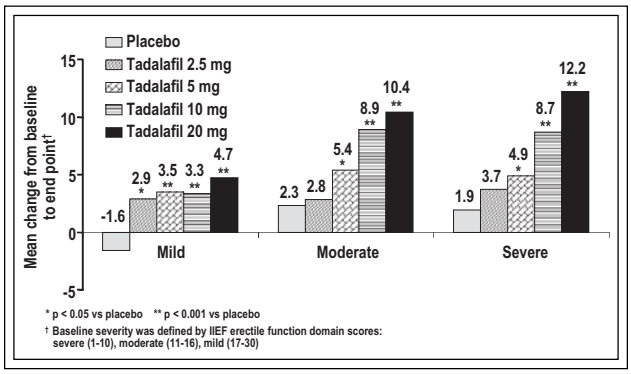

Figure 2. Changes from baseline in IIEF erectile function domain scores, by baseline severity (integrated analysis).[6] Reprinted with permission from Lippincott Williams and Wilkins.

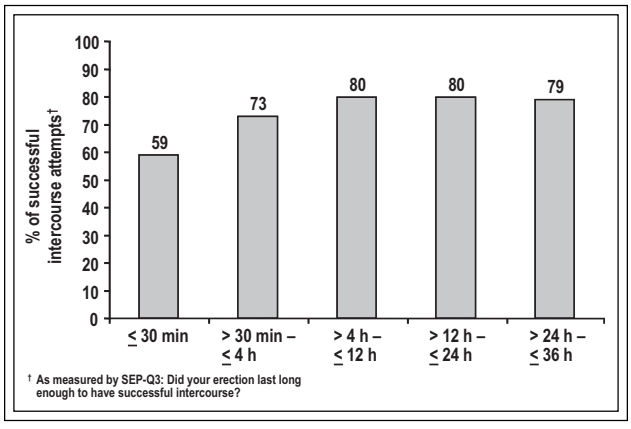

Figure 3. Effect of tadalafil on rate of successful intercourse, over time after dosing (integrated analysis).[6] Reprinted with permission from Lippincott Williams and Wilkins.

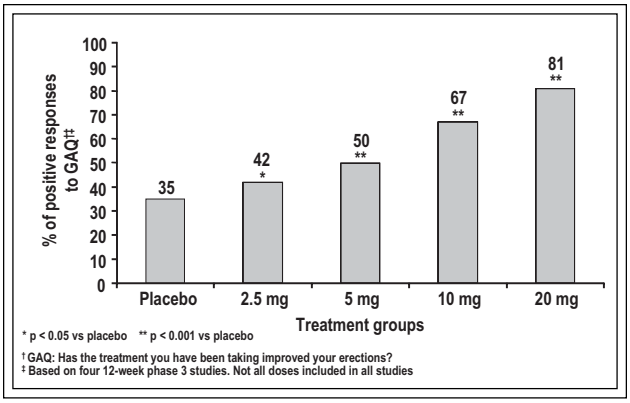

Figure 4. Global assessment of tadalafil (integrated analysis).[6]

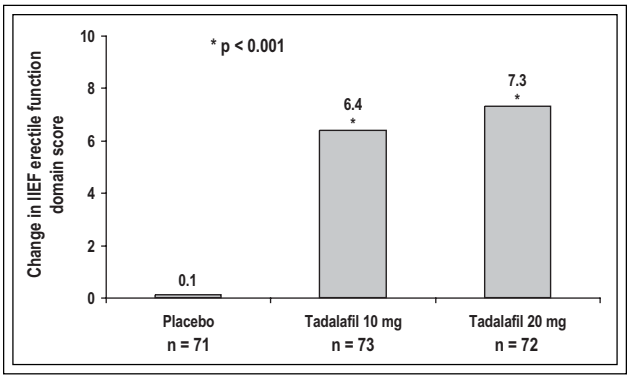

Figure 5. Effect of tadalafil on IIEF erectile function domain scores (Spanish study of diabetic men).[9]

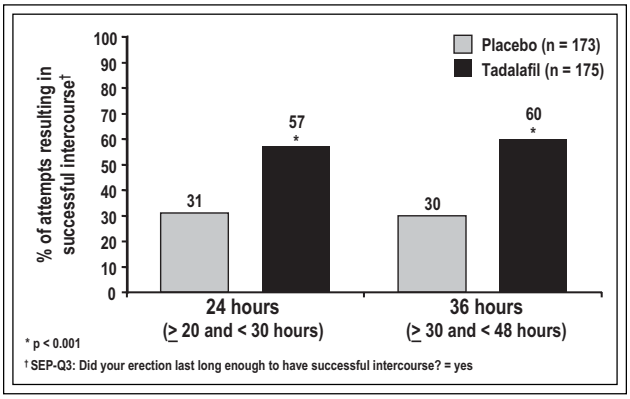

Figure 6. Effect of tadalafil over time (period of effectiveness study).[10]

Efficacy in men with diabetes

The integrated analysis included men with diabetes, making up 21% of the study population. Results showed significant improvements from baseline in all outcome measures in men with diabetes.[6]

More specific information is available, however, from a recently published Spanish trial of 216 men with diabetes.[9] This randomized, double-blind, placebo-controlled trial was conducted at 18 sites in Spain. The average duration of diabetes was 11.7 years, 90.7% of men had type 2 diabetes, and only 18.5% were well controlled (HbA_{1c} < 7%). Hypertension was diagnosed in 39% of the men, and hypercholesterolemia in 19%. Once enrolled, men were randomly assigned to treatment with placebo or tadalafil 10 mg or 20 mg taken once daily as needed. As in the integrated analysis, there was no restriction on timing with respect to food or alcohol consumption.[9]

Treatment with tadalafil significantly improved erectile function in these diabetic men. Figure 5 shows the change from baseline in IIEF erectile function domain scores. Men taking placebo showed a 4.1% decline over the study period in positive responses to SEP-Q2 (attaining an erection), while those taking tadalafil 10 mg showed a 22.2% improvement, and those taking 20 mg showed a 22.6% improvement (both comparisons to placebo $p < 0.001$).[9]

In response to the GAQ question, 25% of men taking placebo felt that the treatment improved their erections, compared with 56% of those taking 10 mg of tadalafil, and 64% of those taking 20 mg (both comparisons to placebo $p < 0.001$).[9]

Period of effectiveness

The period of effectiveness of tadalafil was assessed in a trial of 348 men with varying severity of ED.[10] Men in this double-blind, placebo-controlled trial were instructed to attempt intercourse on four occasions, twice roughly 24 hours after a dose of either placebo or tadalafil 20 mg, then on two other occasions roughly 36 hours after either placebo or tadalafil.

At both 24 hours and 36 hours after the medication, men who took tadalafil were much more likely to be successful in intercourse attempts than men who received placebo ($p < 0.001$) Figure 6.[10] Other secondary measures of erectile function and overall satisfaction showed similar improvements with tadalafil.[10]

These results confirm the findings from the integrated analysis Figure 3,[6] showing a prolonged period of effectiveness after the use of tadalafil.

Safety

In all studies published to date, tadalafil has been generally well tolerated, with side effects comparable to those seen with other PDE5 inhibitors. The most

TABLE 2. **Summary of most commonly reported adverse events and discontinuations from treatment.[6] Reprinted with permission from Lippincott Williams and Wilkins**

Safety variable	Placebo	All tadalafil	Tadalafil (mg)			
			2.5	5	10	20
No. patients	308	804	74	151	321	258
No. overall safety (%):						
Subjects with greater than 1 treatment emergency adverse events	159 (52)	479 (60)	38 (51)	68 (45)	185 (58)	188 (73)
Discontinuations from adverse events	4 (1.3)	17 (2.1)	3 (4.1)	1 (0.7)	5 (1.6)	8 (3.1)
No. most common treatment emergency adverse events (%):						
Headache	19 (6)	114 (14)	5 (7)	17 (11)	37 (12)	55 (21)
Dyspepsia	7 (2)	81 (10)	1 (1)	7 (5)	28 (9)	45 (17)
Back pain	15 (5)	50 (6)	3 (4)	5 (3)	20 (6)	22 (9)
Rhinitis (nasal congestion)	12 (4)	40 (5)	4 (5)	6 (4)	18 (6)	12 (5)
Myalgia	6 (2)	38 (5)	2 (3)	2 (1)	16 (5)	18 (7)
Vasodilatation (flushing)	6 (2)	30 (4)	1 (1)	4 (3)	11 (3)	14 (5)

common side effects have been dyspepsia and headache. Table 2 shows the rate of side effects noted in the integrated analysis of 1112 men.[6] The side effects tended to occur maximally with initial doses of tadalafil, and generally became less frequent and less severe with repeated dosing. The duration of side effects was similar to placebo and tended to occur shortly after administration and diminish thereafter. No life-threatening or cumulative side effects have been seen, and most side effects have become less noticeable with ongoing use of tadalafil. Figure 7 illustrates this attenuation of side effects with continued use.[11,12]

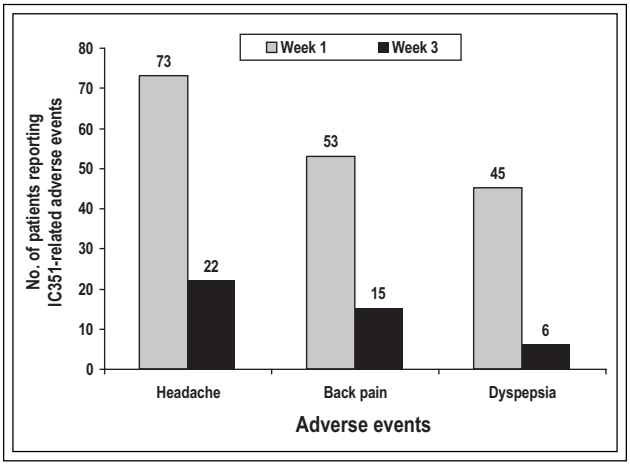

Figure 7. Attenuation of side effects due to tadalafil over time (European phase 2 study).[11,12]

The rates of adverse events in the Spanish study of diabetic men were comparable, with dyspepsia in 11% of men taking tadalafil, headache in 9%, back pain in 3.4%, myalgia in 4.8%, and flushing in 3.4%. Of these, only dyspepsia was reported at a rate statistically significantly different from that seen with placebo ($p = 0.005$).[9]

Conclusion

Clinical trial evidence currently available on tadalafil has shown it to be an effective and well-tolerated agent for the oral treatment of ED. The absence of instructions with food and alcohol should simplify administration. Its extended period of effectiveness may offer clinical benefits to patients, allowing added freedom to choose when intercourse will take place. A reduction in time pressure may help to decrease performance anxiety in some men. □

References

1. Erectile dysfunction practice guidelines. *Can J Urol* 2002;9:1583-1587.
2. Eardley I, Cartledge J. Tadalafil (Cialis) for men with erectile dysfunction. *Int J Clin Pract* 2002;56:300-304.

3. Krane R, Brock G, Eardley I, Fourcroy J, Giuliano F, Hutter A, et al. Oral non-endocrine treatment. In: Jardin A, Wagner G, Khoury S, Giuliano F, Padma-Nathan H, Rosen R, editors. Erectile dysfunction. Plymouth UK; Health Publication Ltd; 2000. p. 241-278.
4. Pryor J. Vardenafil: update on clinical experience. *Int J Impot Res* 2002;14 Suppl 1:S65-S69.
5. Patterson B, Bedding A, Jewell H, Payne C, Mitchell M. The effect of intrinsic and extrinsic factors on the pharmacokinetic properties of tadalafil (IC351). 4th Congress of the European Society for Sexual and Impotence Research; 2001 Sep 30-Oct 3; Rome, Italy.
6. Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, Watkins V, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002;168:1332-1336.
7. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822-830.
8. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology* 1999;54:346-351.
9. Saenz de Tejada I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care* 2002;25:2159-2164.
10. Porst H, Rosen RC, Padma-Nathan H, Varanese L, Anglin G, Giuliano F. Tadalafil allows men with erectile dysfunction to have successful intercourse up to 36 hours postdose. Presented at the 97th Annual Meeting of the American Urological Association; 2002 May 25-30; Orlando, USA.
11. Porst H, Giuliano F, Meuleman E, Saoud J, Ferguson K, Whitaker S. Daily IC351 treatment of ED. *Int J Impot Res* 2000; 12 Suppl 3:S76.
12. Porst H. IC351 (tadalafil, Cialis): update on clinical experience. *Int J Impot Res* 2002;14 Suppl 1:S57-S64.