ORIGINAL ARTICLE UDC: 616.69–008.14:616.379–008.64]–085

Effect of tadalafil on erectile dysfunction in male patients with diabetes mellitus

Efekat tadalafila na erektilnu disfunkciju kod muškaraca sa dijabetes melitusom

Srđan Popović*, Đorđe Nale[†], Marija Dabetić*, Dragana Matanović[‡], Vesna Dimitrijević-Srećković*, Gordana Milić*, Draško Gostiljac*, Svetlana Vujović*, Nebojša Antonijević[§], Tanja Nišić*, Predrag Đorđević*

Clinical Center of Serbia, *Institute of Endocrinology, Diabetes and Metabolism Diseases, [†]Institute of Urology and Nephrology, [‡]Institute of Physical Medicine and Rehabilitation, [§]Institute of Cardiovascular Diseases, **Belgrade**

Abstract

Background/Aim. During the first 10 years over 50% of diabetes patients develop erectile dysfunction (ED). It is more severe and resistant to therapy than in male patients with normal glucoregulation. The purpose of this pilot study was to estimate the tadalafil (Cialis) efficacy and safety in male patients with diabetes mellitus (DM), together with moderate to severe ED. **Methods.** The study included 30 male patients with diagnozed type 1 or type 2 DM together with ED. ED was estimated through the International Index of Erectile Function (IIEF-6), Sexual Encounter Profile (SEP) questionnaire and prostaglandin test, at the beginning of the research and three months after the 20 mg tadalafil therapy initiation, once a week (on Fridays). Glycosylated haemoglobin in blood (HbA1c) values were also monitored. According to the ED severity (IIEF values at the beginning of the therapy) the patients were divided into 2 groups. The previous experience with sildenafil citrate (Viagra) and prostaglandin E1 intracavernous therapy was recorded. **Results.** Tadalafil significantly improved ED ($p < 0.001$) for 7.40 points of the IIEF score, i.e. for 58% and 60% towards SEP2 and SEP3 questionnaire, respectively. Compared to the previous ED therapy subjectively better tadalafil experience was recorded. Each group experienced a significant improvement in IIEF score ($p < 0.001$), more significantly in the group 2 (8.26±1.49 points) compared with the medium improvement in the group 1 (6.27±1.35 points). After three months HbA1c values decreased for 2.26±1.62 ($p < 0.001$). **Conclusion.** Tadalafil is an effective tool for treating ED in diabetes patients. In some situations tadalafil application could replace prostaglandin test. The sexual sphere motivation leads to the improvement of glucoregulation in DM patients.

Key words:
diabetes mellitus; impotence; phosphodiesterase inhibitors; drug therapy.

Apstrakt

Uvod/Cilj. Više od 50% obolelih od dijabetes melitusa (DM) razvije erektilnu disfunkciju (ED) tokom prvih 10 godina od početka bolesti. Ona je mnogo teža i rezistentnija na terapiju nego kod muškaraca sa normalnom glikoregulacijom. Cilj rada bio je da se proceni efikasnost i bezbednost tadalafila (Cialis) kod muškaraca sa DM i pridruženom umerenom do teškom ED. **Metode.** Studijom je obuvaćeno 30 muškaraca sa dijagnozom DM tip I ili tip II i pridruženom ED. Procena ED vršena je pomoću Internacionalnog indeksa erektilne funkcije (IIEF-6), *Sexual Encounter Profile* (SEP) upitnika i prostaglandinskog testa, na početku istraživanja i nakon tri meseca od početka terapije tadalafilom 20 mg, jedan put nedeljno (petak). Praćene su i vrednosti glikoliziranog hemoglobina u krvi (HbA1c). Prema težini ED (vrednostima IIEF skora na početku studije) bolesnici su bili podeljeni u dve grupe. Beleženo je prethodno iskustvo sa sildenafil citratom (Viagra) i intrakavernoznom terapijom prostaglandinom E1. **Rezultati.** Tadalafil je značajno popravio erektilnu funkciju ($p < 0,001$) za 7,40 poena IIEF skora, odnosno za 58% kod SEP2 i 60% kod SEP3 upitnika. Zabeleženo je subjektivno bolje iskustvo sa tadalafilom u odnosu na prethodnu terapiju za ED. U svakoj grupi došlo je do značajnog poboljšanja IIEF skora ($p < 0,001$), značajnije u grupi 2 (8,26±1,49 poena) u odnosu na srednje poboljšanje u grupi 1 (6,27±1,35 poena). Vrednosti HbA1c nakon tri meseca su se smanjile za 2,26±1,62% ($p < 0,001$). **Zaključak.** Tadalafil je efikasno sredstvo za lečenje ED kod obolelih od DM. Davanje tadalafila bi moglo da zameni prostaglandinski test u nekim situacijama. Motivacija u seksualnoj sferi dovodi do poboljšanja glikoregulacije kod bolesnika sa DM.

Ključne reči:
dijabetes melitus; impotencija; fosfodiesteraze, inhibitori; lečenje lekovima.

Correspondence to: Srđan Popović, Clinical Center of Serbia, Institute of Endocrinology, Diabetes and Metabolism Diseases, Varvarinska 33, 11 000 Belgrade, Serbia. Tel.: +381 11 28 505 44, +381 63 7726 353. E-mail: drzokpop@eunet.yu

Introduction

One of the most perfidious diabetes mellitus (DM) complications is autonomic neuropathy. The most dangerous autonomic neuropathy complications are 'mute infarction' and a sudden death. However, the first symptoms to occur are most commonly on the part of the urinary tract. In male patients this is erectile dysfunction (ED), and in female patients reduced vagina lubrication and the absence of orgasm. Due to common retrograde ejaculation (RE) complications of ED male population is more exposed, which significantly affects the quality of life and leads to sterility. That suggests to the importance of an adequately taken anamnesis and the application of sexology questionnaire in the prevention of severe complications.

Diabetes patients are exposed to 4.1 times greater risk of developing ED than non-diabetics of the same age, whereas the risk in hyperlipoproteinemia patients is only 1.7 times greater, and in hypertonic patients the risk is 1.6 times greater versus healthy population [1]. During the first 10 years from the onset of the disease more than 50% of diabetes patients develop ED [1]. ED in DM male patients is more severe and resistant to treatment than in male population with normal glycoregulation [2]. DM duration, therapy type and its adequate application, age, dyslipidemia, hypertension and risk factors, firstly nicotine, to a great extent define the ED severity.

Both ED and DM strike more than 150 million people worldwide, and according to the estimations by the year 2025 the number will doubled [3–5].

The initial event for the normal erectile function is sexual stimulation. As an answer to the sexual stimulation in potent men nitrogen oxide (NO) is set off. NO actives guanylin cyclase enzyme that further activates guanosine 3 phosphate (GTP) and creates cyclic 3'5' guanosine monophosphate (cGMP). cGMP leads to relaxed smooth artery muscles, arterioles and sinusoidal corpus cavernous. Distended sinusoids comprise venulas on *tunica albuginea* and in this way the blood stays trapped in the penis corpus cavernous. Combination of the enhanced blood flow into the penis along with the labored discharge increases the intracavernous pressure that quickly moves up to the systolic blood pressure. With these pressure values the penis attains satisfactory hardness for penetrating the vagina. The main phosphodiesterasis (PDE) that unbinds cGMP of the smooth penis blood vessel muscles is PDE5. PDE5 inhibitors (tadalafil, sildenafil citrate, vardenafil, etc.) block cGMP degradation thus enhancing NO effect. Although these drugs are effective in men with different etiology and ED degree, their effect depends on the quality of pudendal bloodstream and endothelial cells and pudendal nerves to free NO during the sexual stimulation [6–8]. In patients with DM hyperglycemia it aggravates NO discharge from these structures [9–11]. Accordingly, the combination of vascular insufficiency, autonomic neuropathy and endothelial dysfunction leads to more severe ED in men with DM, and these patients have a weaker response to PDE5 inhibitors than the patients of the same age and without DM [2].

Numerous researches [12–15] show that PDE5 oral inhibitors are effective and well tolerated in male patients with DM and ED. Tadalafil is potent, reversible and selective PDE5 inhibitor. It is used as an oral pharmacotherapy in ED, psychogenic, organic or mixed etiology [16]. The aim of this pilot study was to determine the tadalafil efficacy and safety in male patients with DM together with moderate to severe ED.

Methods

This pilot study was conducted in the Institute of Endocrinology, Diabetes and Metabolism Diseases, Clinical Center of Serbia in cooperation with the Institute of Urology (urodyname researches), Institute of Physical Medicine (electromyography researches) and Institute of Cardiovascular Diseases. The study involved 30 male patients over 18 years of age, clinically diagnozed with type 1 or type 2 DM together with ED during the minimum period of 6 months.

The first examination included anamnesis, laboratory tests with the glycaemia profile assessment and glycosylated haemoglobin in blood (HbA1c), EKG, sexology questionnaire with 6 standardized questions – International Index of Erectile Function (IIEF-6 score), physical examination and the lower extremities polyneuropathy electromyography tests. In all patients the ED severity was estimated through IIEF score, Sexual Encounter Profile (SEP) questionnaire, and in 20 patients also through the prostaglandin test (10–20 μg Prostaglandin E1 intracavernous) and the artificial erection 1–3 response was graduated. IIEF is a 15-question-questionnaire divided into 5 sections related to erectile function (6 questions), orgasm (2 questions), sexual desire (2 questions), pleasure gained from sexual intercourse (3 questions), and general sexual satisfaction (2 questions).

The study used IIEF-6 score relating to the erection frequency, the erection hardness, penetrating ability, preserving frequency and the ability to maintain erection and the certainty of achieving erection, with the score of 1 to 30 points.

SEP questionnaire assumed 2 questions to which patients answered with YES/NO. SEP Q2: Were you able to place your penis into the partner's vagina? SEP question 3: Did your erection last long enough for having a successful sexual intercourse?

Patients were asked to compare tadalafil with the previous ED therapy (if applied) and to say if the erection achieved with the help of tadalafil feels as natural or as artificially caused.

Patients agreed not to apply another ED therapy during the study. They all gave their assent to the research and they were all very motivated.

All the patients who had been using nitrates as well as those who recently suffered a severe cardiovascular event, stroke or the spinal cord injury were excluded from the study. Patients with HbA1c values > 13% were also excluded. The study included male patients with microvascular complications, including retinopathy.

For checking possible therapy joint effects and glucoregulation monitoring controls were carried out every

month, and every third month IIEF-6 test, SEP 2,3 questions and HbA1c were repeated.

According to the ED severity (IIEF score values at the beginning of the study) patients were divided into 2 groups.

Differences in the IIEF score values and the number of a YES responds of the SEP questionnaire at the beginning of the research and at the end of the study were taken as a leading parameter in evaluating the treatment efficacy.

The therapy side-effects were also monitored.

The drug study

The 20 mg tadalafil (Cialis) was used in this study. The patients were given instructions to take the drug with water once a week, on Fridays, and no more than 1 pill. They were also explained that their sexual activity should not necessarily be of a limited duration.

Statistic analysis

The results were presented as individual or medium values with standard deviation. The obtained data were processed through the SPSS 13.0 software package. Chi-square test, Independent sample *t*-test, 2 sample paired *t*-test with the Bonferini's correction were used.

Results

The study included 30 male patients of the average 46.27±11.09 age group (Table 1). Totally 14 (46.7%) patients were diagnozed with type 1 DM, whereas 16 (53.3%) patients were diagnosed with type 2 DM.

Twenty (66.7%) patients experienced retrograde ejaculation. Twelve patients experienced the complete absence of ejaculation, whereas 8 patients had the reduced amount of ejaculate. Except for 4 patients (13.3%), all others (25-86.7%) were smokers of the long standing. The most common complications were polyneuropathy 30 (100%), retinopathy (11 patients–36.6%), cardiac autonomic neuropathy (4 patients–13.3%) and in 2 cases incipient nephropathy.

All the patients were on an antidiabetic therapy (Table 2).

Twenty-seven (90%) patients tried sildenafil (Viagra), whereas 3 (10%) patients experienced intra-cavernous therapy (prostaglandin E1, standard dosage) of limited duration. Twenty five patients stated that compared with the previous therapy they had had a more favorable experience with tadalafil (Cialis), whereas 2 patients hadn't noticed any difference. These favorable experiences were firstly explained by the erection duration (and on the following day), and 5 out of 8 patients with reduced ejaculate said that there had been a real improvement in the amount of ejaculate.

Tadalafil improved erectile function in all the patients. The medium improvement in the IIEF score was 7.40 points (41.67%). A significant improvement has also been recorded in SEP 2, i.e. SEP 3 question, for 58% and 60% respectively. It also come to a significant glucoregulation improvement (Table 3).

Table 1

General characteristics of the patients with diabetes mellitus and erectile dysfunction (ED)

Patients characteristics	$\bar{x}$ ±SD
Age (years)	46.27±11.09
BMI (kg/m^2)	27.27±4.27
Diabetes duration (years)	13.33±6.96
ED duration (years)	2.46±0.89

BMI–Body Mass Index

Table 2

Number/percentage of diabetics treated with insulin and/or oral antidiabetics

Antidiabetic therapy	Patients	
	number	%
Oral antidiabetics	9	30
Insulin	16	53.3
Insulin + oral antidiabetics	5	16.7

Table 3

Erectile function and glucoregulation improvement tendency in patients with erectile dysfunction and diabetes mellitus treated with tadalafil (together with antidiabetic therapy)

Parameter	Beginning	3rd month	Difference	Statistical significance
IIEF score (points)	10.53±3.49	18.07±4.42	7.53±1.71	$p < 0.001$
HbA1c (%)	9.51±1.95	7.25±0.89	2.26±1.62	$p < 0.001$

IIEF–International Index of erectile function; HbA1c–glycosylated haemoglobin

According to the values of the basic IIEF score the patients were subsequently divided into groups. Of all the patients, 36.7% diabetes patients had the severe ED (Table 4).

The group 1 included 11 patients who according to the IIEF score had the most severe ED (Table 5). Six (54.5%) of the patients were diagnozed with type 1 DM, and 5 (45.5%) with type 2 DM. Only 1 (9%) patient didn't have RE and all the others had been previously using sildenafil citrate (Viagra).

In the group 1 tadalafil improved the erectile function in all the patients. Medium improvement of the IIEF score was 6.27±1.35 points compared with the basic values. HbA1c values were also significantly reduced for 2.03±1.50% (Table 6).

Erectile function and glucoregulation improvement tendency in the patients with severe ED treated with tadalafil.

The goup 2 included 19 patients with moderate ED according to the IIEF score (Table 7). Eight patients (42.1%) were diagnozed with type 1 DM, and 11 (57.9%) with type 2 DM. Ten patients (52.6%) had already developed RE and apart from 2 patients all others had been using sildenafil citrate.

Ten patients had RE lasting for at least 6 months.

Table 4

Severity of erectile dysfunction (ED) according to the International Index of Erectile Function (IIEF) score

Severity of ED	IIEF score	Number of examinees	%
Severe	1-10	11	36.7
Moderate	11-16	19	63.3
Mild	17-25	0	0
Normal	26-30	0	0

Table 5

General characteristics of the patients with severe erectile dysfunction (ED) and diabetes mellitus

Patients characteristics	x̄±SD
Age (years)	41±10.05
BMI (kg/m^2)	27.8±5.61
Diabetes duration (years)	16.27±8.02
ED duration (years)	4.91±4.43

BMI–Body Mass Index

Table 6

Erectile function and glucoregulation improvement tendency in the patients with severe erectile dysfunction treated with tadalafil

Parameter	Beginning	3rd month	Difference	Statistical significance
IIEF score (points)	6.45±2.07	12.73±1.85	6.27±1.35	$p < 0.001$
HbA1c (%)	9.26±1.51	7.23±0.94	2.03±1.50	$p < 0.001$

IIEF–International Index of Erectile Function; HbA1c–glycosylated haemoglobin in blood

Table 7

General characteristics of the patients with moderate erectile dysfunction (ED) and diabetes mellitus

Patients characteristics	x̄±SD
Age (years)	44.95±11.49
BMI (kg/m^2)	27.26±3.45
Diabetes duration (years)	11.63±5.82
ED duration (years)	1.82±0.87

BMI–Body Mass Index

In all the patients tadalafil led to the IIEF score improvement of 8.26±1.49 points of the erectile function. A significant HbA1c values reduction was also detected (Table 8).

Table 8

Erectile function and glucoregulation improvement tendency in the patients with moderate erectile dysfunction

Parameter	Beginning	3rd month	Difference	Statistical significance
IIEF score (points)	12.89±1.10	20.95±11.74	8.26±1.49	$p < 0.001$
HbA1c (%)	9.66<±2.20	7.26±0.90	2.40±1.71	$p < 0.001$

IIEF–International Index of Erectile Function; HbA1c–glycosylated haemoglobin in blood

There hasn't been any statistically important age and BMI difference between groups 1 and 2 and the HbA1c values. A statistically significant difference was detected in the number of the IIEF score points that had improved after the 3-month-use of tadalafil in each group ($p < 0.01$) (Table 9).

After the 3-month-follow-up HbA1c values were significantly lower. Judging from our experience with diabetes patients we can say that the more attention they are given the better discipline they show and the satisfactory glucoregulation is achieved, which is obvious from the HbA1c values

Table 9

Better effects of tadalafil in the patients with moderate erectile dysfunction (ED) and diabetes mellitus

Parameter	Group 1 (severe ED)	Group 2 (moderate ED)	Statistical significance
Age (years)	41.55±10.05	44.95±11.49	NS
BMI (kg/m^2)	27.28±5.62	27.26±3.45	NS
IIEF score difference (points)	6.27±1.35	8.26±1.49	$p < 0.01$
HbA1c difference (%)	2.03±1.50	2.40±1.71	NS

IIEF–International Index of Erectile Function; HbA1c–glycosylated haemoglobin in blood; BMI–Body Mass Index; NS–not significant

According to expectations and considering the fact that their ED was of less severe form, the increase was more significant in the group 2.

Side-effects

Tadalafil was well tolerated. The most common side-effects were headaches in 2 patients (6.7%), nausea in 2 patients (6.7%), backache (6.7%), and myalgia (3.3%). Due to side-effects none of the patients discontinued the treatment.

There were no cases of myocardial infraction or myocardial ischemia, as well as no significant changes in laboratory values, EKG parameters or internist examinations.

Discussion

PDE5 inhibitors, which include tadalafil, by cGMP blockade degradation enhance the NO effect and in this way provide successful erection.

What separates tadalafil from the rest of PDE5 inhibitors is the ability of acquiring the active drug concentration 2 hours after the intake, with the 17.5 h half-life and the effect lasting up to 36 h. Drug absorption is not affected by food or alcohol intake. As with other drugs from this group there is the possibility of developing hypertension and when combined with nitrates the risk of undesirable cardiovascular events [17].

Tadalafil improved the erectile function of both diabetes groups even more significantly in the group with the less severe ED. Medium improvement of 6.27±1.35 points of the IIEF score was achieved in the group 1, and 8.26±1.49 in the group 2 ($p < 0.01$).

that improved for 2.03% after 3 months bearing the statistical significance ($p < 0.01$). Normoglycaemia in diabetes patients affects the improvement of the endothelial function, enhanced NO bioavailability, and therefore a better reaction to the PDE5 inhibitor treatment. If diabetes patients understand that the erectile function and diabetes control are connected, they are then more motivated to improve the disease control. It is necessary to continue examining good diabetes control effect on the erectile function and, due to the fact that the male population is seriously exposed to the disease with the better patient motivation purpose. In the Fonseca et al. [15] study the patients were divided according to their HbA1c values, into the patients with good glucoregulation (HbA1c <7%), bad (HbA1c 7.0–9.5%) and distinctly bad (HbA1c >9.5%) glucoregulation, which showed that the IIEF score was lower in the group with the bad glucoregulation that only points to the ED development glucoregulation significance. In our study the drug efficacy was certainly affected by a tendency to improve glucoregulation. Considering the ED development etiology, organic factors (the existence of neurogenic and vasculogenic components), but the psychogenic upgrade as well, compared to diabetes type as well as the oral, combined or insulin therapy application no significant difference in ED patients was detected.

Tadalafil improved erectile function in our patients and, compared to the previously used preparations proved more effective primarily regarding erection duration. A new moment is a subjective detection of the patients with scarce

ejaculate, which is a tendency to increase ejaculate amount that has not yet been recorded. In addition, the authors found interesting a statement given by 27 patients who had previously been using sildenafil citrate, that while using tadalafil most of them (20–74%) had a subjective sensation of a natural erection.

The patients who had experienced intracavernous ED therapy experienced erection as artificial, whereas all 3 patients with that experience characterized tadalafil application as having a more natural erection sensation.

Regarding side-effects, our study is not different from the Fonseca et al. [15] study. In no case the therapy was discontinued, and the stated changes (headaches, nausea) were of a transitive nature, and backache was attributed to the increased physical activity and previously known polyneuropathic discomforts.

Conclusion

Tadalafil proved to be an effective tool for treating ED in diabetes patients. According to the expectations, the drug efficacy was better in the patients with less severe ED. Compared with the previously applied PDE5 inhibitors tadalafil also proved to be more effective. Considering the prostaglandin test procedure complexity, we are of the opinion that the application of this drug could in some cases replace the prostaglandin test (difficulties in the intracavernous injection application, the patients' fear, side-effects, etc.). Tadafil side-effects are very mild, almost negligible and no one has discontinued the therapy. Sexuality is an inalienable part of a good quality life, and in this case the sexual sphere motivation proved to have a good effect on achieving satisfactory glucoregulation in DM patients.

R E F E R E N C E S

1. *Buvat J, Lemaire A, Buvat-Herbaut M, Fourlinnie JC, Racadot A, Fossati P.* Hyperprolactinemia and sexual function in men. Horm Res 1985; 22(3): 196–203.
2. *Penson DF, Latini DM, Lubeck DP, Wallace KL, Henning JM, Lue TF,* et al. Do impotent men with diabetes have more severe erectile dysfunction and worse quality of life than the general population of impotent patients? Results from the Exploratory Comprehensive Evaluation of Erectile Dysfunction (ExCEED) database. Diabetes Care 2003; 26(4): 1093–9.
3. Diabetes estimates: 2025 [article online]. Geneve: World Health Organization; 2001. Available from: http://www.who.int/ncd/dia/databasesO.htm
4. *McKinlay JB.* The worldwide prevalence and epidemiology of erectile dysfunction. Int J Impot Res 2000; 12 Suppl 4: S6–S11.
5. *Ayta IA, McKinlay JB, Krane RJ.* The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int 1999; 84(1): 50–6.
6. *Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA.* Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 1998; 338(20): 1397–404.
7. *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(4 Pt 1): 1332–6.
8. *Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T,* et al. Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 2002; 23(6): 763–71.
9. *Noyman I, Marikovsky M, Sasson S, Stark AH, Bernath K, Seger R,* et al. Hyperglycemia reduces nitric oxide synthase and glycogen synthase activity in endothelial cells. Nitric Oxide 2002; 7(3): 187–93.
10. *Booth G, Stalker TJ, Lefer AM, Scalia R.* Elevated ambient glucose induces acute inflammatory events in the microvasculature: effects of insulin. Am J Physiol Endocrinol Metab 2001; 280(6): E848–56.
11. *Graier WF, Posch K, Fleischhacker E, Wascher TC, Kostner GM.* Increased superoxide anion formation in endothelial cells during hyperglycemia: an adaptive response or initial step of vascular dysfunction? Diabetes Res Clin Pract 1999; 45(2–3): 153–60.
12. *Rendell MS, Rajfer J, Wicker PA, Smith MD.* Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA 1999; 281(5): 421–6.
13. *Price DE, Gingell JC, Gepi-Attee S, Wareham K, Yates P, Boolell M.* Sildenafil: study of a novel oral treatment for erectile dysfunction in diabetic men. Diabet Med 1998; 15(10): 821–5.
14. *Buvat J, van Ahlen H, Schmitt H, Chan M, Kuepfer C, Varanese L.* Efficacy and safety of two dosing regimens of tadalafil and patterns of sexual activity in men with diabetes mellitus and erectile dysfunction: Scheduled use vs. on-demand regimen evaluation (SURE) study in 14 European countries. J Sex Med 2006; 3(3): 512–20.
15. *Fonseca V, Seftel A, Denne J, Fredlund P.* Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. Diabetologia 2004; 47(11): 1914–23.
16. *Padma-Nathan H, McMurray JG, Pullman WE, Whitaker JS, Saoud JB, Ferguson KM,* et al. On-demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. Int J Impot Res 2001; 13(1): 2–9.
17. *Broderick GA.* Oral pharmacotherapy and the contemporary evaluation and management of erectile dysfunction. Rev Urol 2003; 5 Suppl 7: S9–S20.

Tha paper was received on March 14, 2007.