

EFFECTIVENESS OF SILDENAFIL CITRATE (VIAGRATM) AND TADALAFIL (CIALISTM) ON SEXUAL RESPONSES IN SAUDI MEN WITH ERECTILE DYSFUNCTION IN ROUTINE CLINICAL PRACTICE

SYED TABREZ ALI

*Department of Physiology, Faculty of Medicine
P.O. Box 7607, Umm-Al-Qura University, Makkah, Saudi Arabia*

ABSTRACT

Satisfaction with the sexual experience is considered important when evaluating the impact of treatments for erectile dysfunction, yet enhanced satisfaction has been infrequently assessed in the sexual trials. We evaluated the efficacy of sildenafil versus tadalafil, in Saudi men with erectile dysfunction and determined the self-based rating of medicinal preference.

Sildenafil citrate (ViagraTM) is a potent inhibitor of the electrolytic enzyme type V phosphodiesterase (PDE5), in the corpus cavernosum and therefore increases the penile response to sexual stimulation.

Tadalafil (CialisTM) is also a PDE5 inhibitor that increases the level of cyclic guanosine monophosphate (cGMP) in cavernous smooth muscle cells. Whereas cGMP is a second messenger for the vasodilator effects of nitric oxide causing smooth muscle relaxation, which in turn leads to penile erection; however the mechanism by which cGMP stimulates relaxation of the smooth muscles remains to be elucidated.

Both sildenafil and tadalafil have a rapid onset with the effectiveness up to 4 hours and 36 hours respectively.

In this study subjects treated with 100 mg oral dose of sildenafil / 20 mg tadalafil were found to be associated with higher mean scores for the questions of the International Index of Erectile Function (IIEF). Frequency of penetration and maintenance of erection after sexual penetration and/or during masturbation were found to be enhanced significantly ($p < 0.001$) in both sildenafil/tadalafil treated men. Similarly mean domain of erectile function, orgasmic function, and intercourse satisfaction also showed a significantly positive improvement ($p < 0.001$) in both the treated groups in comparison with their age matched untreated controls. Interestingly in all the cases, tadalafil group showed considerably greater positive responses than the sildenafil group but within the same significant levels. Strikingly the sexual-desire domain in sildenafil treated men with respect to their age matched controls showed a non-significant difference, where as this difference was found to be highly significant in tadalafil treated group. Similarly mean scores for the overall satisfaction domains of the IIEF in comparison with the untreated subjects showed a significant positive response in the sildenafil treated group ($p < 0.001$), where as tadalafil treated group showed a highly significant positive response ($p < 0.005$). These findings suggest that both sildenafil and tadalafil may assist an individual in extending/enhancing the excitement phase or prolonging the sexual interaction. These studies further conclude that there is a major point of difference between the short-acting agent sildenafil and the longer acting tadalafil. This probably allows more choice about the onset of sexual responses with tadalafil than with sildenafil.

Keywords: Erectile dysfunction; sexual responses; sildenafil; tadalafil; clinical trials.

INTRODUCTION

There has recently been an explosion of interest in sexual dysfunction. Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity. The causes of erectile dysfunction are many. Endocrine disorders, neuropathy, vascular disease, diabetes, control nutrition, psychogenic factors, as well as drugs used in the treatment of these complications all play a role (Saenz *et al.*, 2005).

The National Institute of Health Consensus Panel reported that ED affects as many as 30 million men in the United

States (NIH, 1993). The prevalence of ED in the United States was evaluated more extensively in the Massachusetts Male Aging Study (MMAS). The MAAS evaluated nearly 1,300 men found that there is some degree of erectile dysfunction in 52% of men aged 40-70 years (Feldman *et al.*, 1994).

Based on questionnaire responses by 1709 men, 35% of men reported moderate-to-complete ED. Overall prevalence rates were 39% in men 40 years of age, 48% in those 50 years of age, 57% in those 60 years of age, and 67% in those 70 years of age (Brock *et al.*, 2007).

One interesting new breakthrough in the treatment of ED using oral drugs lies in the substance phosphodiesterase

Corresponding author : e-mail: shazali_2004@hotmail.com

type-5 inhibitor (PDE5i), for example sildenafil citrate (Viagra) or tadalafil (Cialis).

In response to sexual stimuli, these drugs potently enhance the release of nitric oxide (NO) through cavernous nerves and endothelial cells resulting an increased levels of cGMP in corpus cavernosum. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE-5 causes smooth muscle relaxation, which in turn leads to penile erection, however the mechanism by which cGMP stimulates relaxation of the smooth muscles remains to be elucidated (Rajfer., 1992 and Blount, 2004).

The recommended dose of sildenafil (Viagra) is 50mg once per day approximately 60 minutes before sexual activity with the lasting effects up to 4 hours. Based on efficacy and tolerability the minimum and maximum recommended doses are 25 and 100 mg. respectively (Padma *et al.*, 2003 and Saftel, 2005).

The first major trial of the effects of tadalafil (Cialis) in ED was published in 2001 (Padma *et al.*, 2001). In a trial of 220 Western European men with ED, tadalafil 20 mg provided successful sexual intercourse to 74%, compared to 30% of those treated with placebo (Eardley *et al.*, 2004). Improved sexual satisfaction with tadalafil 10 and 20 mg has also been reported in men with mild, moderate and severe ED (Rosen *et al.*, 2005; Goldstein *et al.*, 2007).

In comparison with short-acting agent sildenafil, the major differences, which are evident from comparing trials with either sildenafil or tadalafil, are that there is no requirement to take tadalafil one hour before sexual intercourse, and sexual activity can be initiated between 30 minutes and 24 hours after dosing (Doggrell, 2007). This probably allows more choice about the onset of sexual intercourse with tadalafil than sildenafil.

From the above described literature information it is now clear that these PDE-5 inhibitors are effective, well tolerated and safe in most patients, with adverse effects limited as previously noted (Waldkirch *et al.*, 2005).

The present study has been therefore designed to evaluate a comparison between the effectiveness of sildenafil and tadalafil on sexual responses in men with ED in routine clinical practice.

MATERIALS AND METHODS

A total of 150 Saudi men, age ranging from 25 to 65 years (average age of 45 years) with a minimum 3-months ED history (including all ED severities and ED of psychogenic, organic, or mixed origin) were selected for

the study. Potential subjects were examined for general poor health, nitrate use, any history of sexual dysfunction associated with diabetes mellitus, a history of cigarette smoking, peptic ulcer disease, obesity, hypertension, high blood pressure, or cardiac disease. Men were excluded if they had penile anatomical defects, a primary diagnosis of another sexual disorder (premature ejaculation) or any psychiatric sexual disorder.

Informed consent was obtained from the institutional ethical committee, as well as 50 screened subjects (Group-I, untreated), who were not using either sildenafil or tadalafil along with 50 screened subjects (Group-II) using 100 mg (recommended dose) tablets of ViagraTM (Sildenafil citrate-Pfizer, USA) and another 50 screened subjects (Group-III) who were using 20 mg (recommended dose) tablets of CialisTM (Tadalafil-Ell Lilly, UK) with standard instruction on its use on regular bases to enhance their sexual performance. Other erectile therapies (if any) were discontinued at the time of screening (four weeks before the subjects received the study medication).

All the 50 Group-II, subjects were instructed to take one tablet of sildenafil citrate (100 mg orally), but not more than once daily for 3 months, one hour before sexual activity, 2-3 hours after a meal.

Group-III subjects were instructed to take one tablet of tadalafil (20 mg orally), not more than once a day for 3 months like group-I, but 20 minutes before the sexual activity irrespective of the food intake.

Subject's response to treatment with sildenafil / tadalafil were evaluated using the International Index of Erectile Function (IIEF)-5, a validated, multidimensional, self administered questionnaire (15-questions) used for the clinical assessment of erectile dysfunction and treatment outcomes in clinical studies (Rosen *et al.*, 1997).

Based on scores of (IIEF)-5 efficacy was assessed for the five separate response domains of male sexual functions including erectile function (questions 1 through 5 and 15), orgasmic function (question 9 and 10), sexual desire (questions 11 and 12), intercourse/masturbation satisfaction (questions 6, 7, and 8), and overall satisfaction (questions 13 and 14). The efficacy to the responses of question 3 and 4 was also assessed and rated on a scale of 1 (almost never and never) to 5 (almost always or always).

The mean frequency of response to questions 3 and 4 and the mean domain scores of male sexual functions from IIEF were calculated. An analysis-of-covariance model was fitted for each question and the treatment effects were analyzed with the base line score. A *p*-value of less than 0.05 was considered to indicate statistical significant.

RESULTS

Mean scores of response to question 3 and 4 of the IIEF for the men receiving sildenafil citrate/tadalafil in comparison with their age matched controls are presented in tables 1 and 2. In this study, subjects with the dose of sildenafil/tadalafil were found to be associated with higher mean scores for the questions of the IIEF assessing frequency of penetration (Question-3), and maintenance of erection after sexual penetration or during masturbation (Question-4).

The mean scores for these questions (3 and 4) in respect to achieving erections hard enough for sexual intercourse showed a significantly greater response for sildenafil treated group, which was about 88%, and about 124% respectively ($p < 0.001$), where as this score for tadalafil treated group was found to be slightly greater than the Sildenafil, but with in the same significant levels.

The mean ($\pm$ SE) scores for domain of the erectile function (five questions; possible total score, 1 to 30) and orgasmic function domain score (two questions; possible total score, 0-12) for 50 men in the sildenafil verses tadalafil group in comparison with their age matched

controls is presented in figs. 1 and 2.

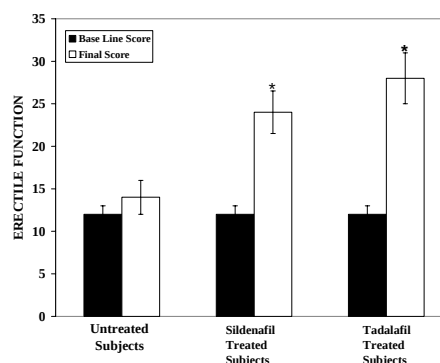


Fig. 1: Mean ($\pm$ SE) scores for the Erectile Function Domains of the International Index of Erectile Function for untreated and sildenafil/tadalafil treated men. Treatment effects are analyzed with the base line scores. (* = $p < 0.001$)

Both the groups showed a significant and positive response in erectile function ($p < 0.001$) than the control group with considerably higher values in tadalafil treated group but within the similar significant levels as sildenafil group.

Table 1: Mean scores of responses to Question-3 of The International Index of Erectile Function for the untreated men and the men treated with sildenafil citrate/tadalafil. Values are Mean $\pm$ Standard Errors (SE).

Subjects	Base-line score	Final score	Percent change from base line
Untreated Group N = 50	2.0 $\pm$ 0.1	2.1 $\pm$ 0.2	5
Sildenafil Treated Group N = 50	1.8 $\pm$ 0.2	3.4 $\pm$ 0.25	88*
Tadalafil Treated Group N = 50	1.85 $\pm$ 0.25	3.5 $\pm$ 0.3	89*

N = Number of the subjects examined.

Base line and final scores of untreated and sildenafil/tadalafil treated groups are compared for t-test. * = $p < 0.001$

Question 3: When you attempted sexual intercourse; how often were you able to penetrate your partner? (*Modified with the attempts of successful masturbation in some cases*).

Table 2: Mean scores of responses to Question 4 of the International Index of Erectile Function for the untreated men and the men treated with sildenafil citrate/tadalafil. Values are Mean $\pm$ Standard Errors (SE).

Subjects	Base-line score	Final score	Percent change from base line
Untreated Group N = 50	1.8 $\pm$ 0.1	2.2 $\pm$ 0.2	22
Sildenafil Treated Group N = 50	1.7 $\pm$ 0.1	3.8 $\pm$ 0.2	123.5*
Tadalafil Treated Group N = 50	1.75 $\pm$ 0.2	3.95 $\pm$ 0.25	125.7*

N = Number of the subjects examined.

Base line and final scores of untreated and sildenafil/tadalafil treated groups are compared for t-test. * = $p < 0.001$

Question 4: During the sexual intercourse; how often were you able to maintain your erection after you had penetrated your partner? (*Modified with the attempts of successful masturbation in some cases*).

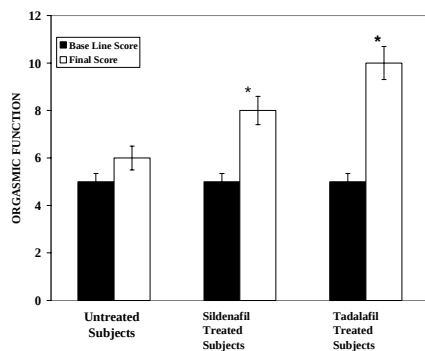


Fig. 2: Mean (±SE) scores for the orgasmic function domains of the international index of erectile function for untreated and sildenafil/tadalafil treated men. Treatment effects are analyzed with the base line scores. (*= $p < 0.001$)

A comparison regarding the sexual desire domain (two questions; possible total score, 0 to 12); for 50 men each in the sildenafil versus tadalafil group in comparison with their age matched controls is presented in fig. 3.

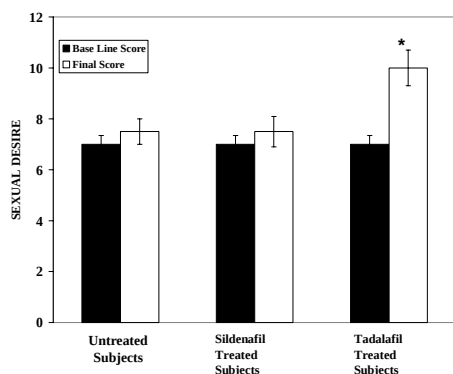


Fig. 3: Mean (±SE) scores for the Sexual Desire Domains of the international index of erectile function for untreated and sildenafil/tadalafil treated men. Treatment effects are analyzed with the base line scores. (*= $p < 0.001$)

This comparison revealed striking results. In all the cases, sildenafil treated men with respect to their aged matched controls showed a non-significant difference, whereas tadalafil group showed a significant positive response ($p < 0.001$) to sexual desire than the controls.

The mean domain scores for the intercourse satisfaction (three questions; possible total score, 0 to 12), and overall satisfaction (two questions; possible total score, 0-12) for the sildenafil versus tadalafil group and the control group is presented in figs. 4 and 5 respectively.

These results indicated a significant and positive response for both sildenafil and tadalafil treated group ($p < 0.001$), for intercourse satisfaction domain, where as tadalafil

treated group showed highly significant positive responses ($p < 0.005$) for the overall satisfaction domain when compared with the sildenafil and the control groups.

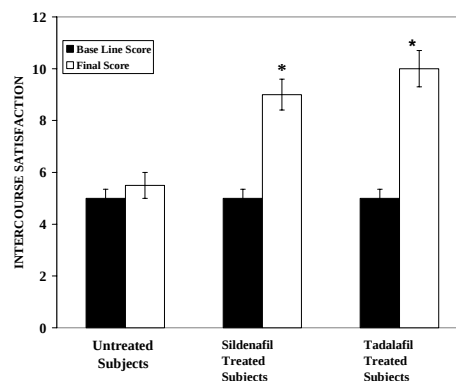


Fig. 4: Mean (±SE) scores for the intercourse satisfaction domains of the international index of erectile function for untreated and sildenafil/tadalafil treated men. Treatment effects are analyzed with the base line scores. (*= $p < 0.001$)

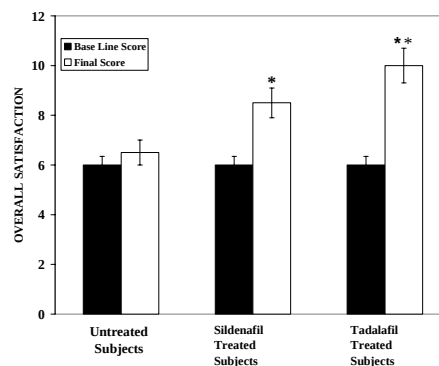


Fig. 5: Mean (±SE) scores for the overall satisfaction domains of the international index of erectile function for untreated and sildenafil/tadalafil treated men. Treatment effects are analyzed with the base line scores. (*= $p < 0.001$; ** = $p < 0.005$)

DISCUSSION

Sildenafil citrate is the first oral agent for the treatment of erectile dysfunction, since its introduction in 1998, and demonstrated an excellent efficacy as well as safety profile across age groups, racial groups, ethnicities and ED etiologies (Morals *et al.*, 1998; Goldstein *et al.*, 1998; Saftel, 2005; Goldstein *et al.*, 2007).

The first major trial of the effects of tadalafil in ED was published in 2001 (Padma *et al.*, 2001) and the long term safety and tolerability of tadalafil was confirmed by Montorsi *et al.* (2004).

Sildenafil and tadalafil both are selective inhibitors of PDE5 (Daugan *et al.*, 2003). These are rapidly absorbed

after oral administration. The absolute bio-availability for sildenafil is about 40%, whereas the absolute bioavailability of tadalafil has not been reported to date.

Both the phosphodiesterase inhibitors have a rapid onset of action. In men who respond to sildenafil, within 20 minutes of sildenafil dosing, 51% had an erection that led to successful intercourse (placebo, 30%) (Padma *et al.*, 2003). Also, in the home setting, 51% of men taking tadalafil 20 mg had at least one successful intercourse attempt within 30 minutes (placebo, 35%) (Rosen *et al.*, 2004; Mirone *et al.*, 2007).

The maximum plasma concentration is obtained after 60 minutes with sildenafil but later with tadalafil (2 hours). The half-life of tadalafil is 17.5 hours, compared to 3.8 hours for sildenafil (Porst *et al.*, 2002). Consequently, tadalafil would be expected to have a longer duration of action than sildenafil. In accord with the half-life and directions given with tadalafil, many men do attempt successful intercourse in the 12-36 hours window after administration (Shabsigh *et al.*, 2005, Segraves *et al.*, 2007). Another study showed that tadalafil 10 mg was nearly as effective as tadalafil 20 mg after 24 and 36 hours. The successful intercourse attempts at 24 hours were 42, 56 and 67%, and at 36 hours, 33, 56 and 62%, for placebo, tadalafil 10 and 20 mg, respectively (Young *et al.*, 2005, Wespes *et al.*, 2007).

Of the 190 evaluable patients, 66% preferred tadalafil compared with 34% who preferred sildenafil (Govier *et al.*, 2003). Headache (tadalafil, 11.2%; sildenafil, 8.8%), dyspepsia (6.0 and 4.2%), nasopharyngitis (4.7 and 2.8%) and flushing (2.8 and 4.7%) were the most common adverse effects (Govier *et al.*, 2003). In a second trial of sildenafil and tadalafil, ED patients who were taking sildenafil were switched to tadalafil and then asked which they preferred, and most preferred tadalafil (Stroberg *et al.*, 2003). Most of the men selected tadalafil (90%), and the proportions preferring tadalafil were similar irrespective of age, severity of ED, and etiology of ED (Stroberg *et al.*, 2003).

When a blinded trial was undertaken to evaluate patient preference between 20 mg tadalafil and 50-100 mg sildenafil, most ED patients preferred tadalafil. Thus, 73% of 181 ED patients chose to receive tadalafil during the extension period (Von Keitz *et al.*, 2004).

A more recent study has reduced the bias towards tadalafil by allowing the men with ED to titrate to find their optimum dose (for sildenafil 25, 50 or 100 mg; for tadalafil 10 or 20 mg) (Eardley *et al.*, 2005). After the crossover between the drugs, the 367 men with ED were given the choice of sildenafil or tadalafil and 29% chose sildenafil and 71% chose tadalafil (Goldstein *et al.*, 2007).

The present study relied on self-report, looked at different aspects of male sexual act in response to oral sildenafil/tadalafil administration in Saudi men (aged 25-65 years) with ED of various etiologies. In keeping with sildenafil/tadalafil mode of action (i.e. the drug causes erection only in response to sexual stimulation), the studies were performed entirely in a natural environment, which meant that we had to rely on men's own reports of efficacy. However, the self-administered International Index of Erectile Function has a higher degree of sensitivity and specificity for detecting treatment-related changes in men with ED (Rosen *et al.*, 1997, Doggrell *et al.*, 2007). The questionnaire provided a comprehensive assessment of erectile function.

We found most recognized improvement with both sildenafil and tadalafil in the frequency of penetration and the maintenance of erections after penetration, the mean score for the erectile-function domain of International Index, and the percentage of men reporting better erection, although in all the cases, men treated with tadalafil showed greater sexual responses than the sildenafil treated men in comparison with the controls. These results are in conformity with the above described tadalafil responses in the patients of different ED etiologies.

Surprisingly the men treated with tadalafil showed a significantly greater sexual desire than the sildenafil treated men who had a normal level of sexual desire, as might be expected with reference to another study with the men having ED who enter a clinical trial (Akira *et al.*, 2002; Sandner *et al.*, 2007) and sildenafil did not alter that level. A greater sexual desire in the tadalafil treated men may be interpreted as its long acting mode of action and excess accumulation in the plasma. Similar can be applied to the overall satisfaction domains in our results, where sildenafil treated men showed a significant response ($p < 0.001$), where as response with tadalafil treated men was more significant ($p < 0.005$).

Sildenafil/tadalafil treatment in all the cases was found to be well tolerated. Mild adverse effects were headache, flushing, dyspepsia and rare visual disturbances (pharmacological nature of sildenafil/tadalafil as a phosphodiesterase-type-5 inhibitor and as a weak phosphodiesterase-type-6 inhibitor respectively). No men had priapism after the treatment thus suggesting a relatively high level of drug tolerability and acceptance in these men (data not shown).

Overall, the results of the efficacy assessments demonstrated that both sildenafil and tadalafil significantly enhanced erectile function, quadrupled the success of intercourse/ masturbation and sexual performance without altering the sex desire in case of sildenafil and a greater sexual derive in case of tadalafil

treatment in these men. Both sildenafil citrate and tadalafil may assist an individual or couple in extending the excitement phase or prolonging the sexual interaction. They may restore men's confidence in obtaining an erection.

These studies further conclude that there is a major point of difference between the short-acting agent sildenafil and the longer acting tadalafil. This probably allows more choice about the onset of sexual intercourse with tadalafil than with sildenafil. The dosing instructions for sildenafil are that patients take sildenafil one hour before sexual activity, whereas those for tadalafil suggest that sexual activity can be initiated between 30 minutes and 24 hour after dosing. Tadalafil has a longer half-life than sildenafil and therefore may be recommended as the choice of preference.

REFERENCES

- Akira T, Masaki Y, Toru T and Akihiko O (2002). The clinical studies of sildenafil for the aging male. *Int. J. Androl.*, **25**: 28-33.
- Blount MA, Beasley A, Zoraghi R, Sekhar KR, Bessay EP and Francis SH *et al* (2004). Binding of tritiated sildenafil, tadalafil or vardenafil to the phosphodiesterase-5 catalytic site displays potency, specificity, heterogeneity, and cGMP stimulation. *Mol. Pharmacol.*, **66**: 144-152.
- Brock G, Chan J, Carrier S, Chan M, Salgado L, Klein AH, Lang C, Horner R, Gutkin S and Dickson R (2007). The treatment of erectile dysfunction study: focus on treatment satisfaction of patients and partners. *B.J.U. Int.*, **99** (2): 3, 76-82.
- Daugan A, Grondin P, Ruault C, Le Monnier de Gouville AC, Coste H *et al* (2003). The discovery of tadalafil: a novel and highly selective PDE5 inhibitor. 2: 2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione analogues. *J. Med. Chem.*, **46**: 4533-4542.
- Doggrell S. (2007). Do vardenafil and tadalafil have advantages over sildenafil in the treatment of erectile dysfunction? *Int. J. Impot. Res.*, **19** (3):281-95.
- Eardley I, Gentle V, Austoni E, Hackett G, Lembo D, Wang C, and Beardsworth A (2004). Efficacy and safety of tadalafil in a Western European population of men with erectile dysfunction. *B.J.U. Int.*, **94**: 871-877.
- Eardley I, Mirone V, Montorsi F, Ralph D, Kell P and Warner MR *et al* (2005). An open-label, multicentre, randomized, crossover study comparing sildenafil citrate and tadalafil for treating erectile dysfunction in men naive to phosphodiesterase 5 inhibitor therapy. *B.J.U. Int.*, **96**: 1323-1332.
- Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ and McKinlay JB (1994). Impotence and its medical and psychological correlates: Results of the Massachusetts male aging study. *J. Urol.*, **151**: 54-61.
- Goldstein I, Lue TF, Padma NH, Rosen RC, Steers WD and Wicker PA (1998). Oral sildenafil in the treatment of erectile dysfunction. *N.E.J.M.*, **338**: 1397-1404.
- Goldstein I, Kirn E, Steers WD, Pryor JL, Wilde DW, Natanegara F, Wong DG and Ahuja S. (2007). Efficacy and safety of tadalafil in men with erectile dysfunction with a high prevalence of comorbid conditions: results from MOMENTUS: multiple observations in men with erectile dysfunction in National Tadalafil Study in the US. *J. Sex. Med.*, **4**(1): 166-175.
- Govier F, Potempa AJ, Kaufman J, Denne J, Kovalenko P and Ahuja SA (2003). Multicenter, randomized, double-blind, crossover study of patient preference for tadalafil 20mg or sildenafil citrate 50 mg during initiation of treatment for erectile dysfunction. *Clin. Ther.*, **25**: 2709-2723.
- Mirone V, Imbimbo C, Rossi A, Sicuteri R, Valle D, Longo N and Fusco F (Italian Sure Study Group) (2007). Evaluation of an alternative dosing regimen with tadalafil, three times per week, for men with erectile dysfunction: SURE study in Italy. *Asian. J. Androl.*, **9**(3): 395-402.
- Montorsi F, Nathan HP, McCullough A, Brock GB, Broderick G and Ahuja S *et al* (2004). Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retro-pubic prostatectomy: a randomized, double-blind, placebo controlled trial. *Urology*, **172**: 1036-1041.
- Montorsi F, Padman-Nathan H, Buvat J, Schwaibold H, Beneke M and Ulbrich E *et al* (2004). Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind placebo-controlled trial. *J. Sex. Med.*, **1**: 168-178.
- Morales A, Gingell C, Collins M, Wicker PA and Osterloh IH (1998). Clinical safety of oral sildenafil citrate in the treatment of erectile dysfunction. *Int. J. Impot. Res.*, **10**: 69-74.
- NIH consensus development panel on impotence (1993). *J.A.M.A.*, **270**: 83-90.
- Padma-Nathan H, McMurray JG, Pullman WE, Whitaker JS, Saoud JB and Ferguson KM *et al* (2001). On demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. *Int. J. Impot. Res.*, **13**: 2-9.
- Padma-Nathan H, Stecher VJ, Sweeney M, Orazem J, Tseng LJ and Deriesthal H (2003). Minimal time to successful intercourse after sildenafil citrate: results of a randomized, double-blind placebo-controlled trial. *Urology*, **62**: 400-403.
- Porst H. (2002). IC351 (tadalafil, Cialis): update on clinical experience. *Int. J. Impot. Res.*, **14**(Suppl 1): S57-S64.
- Rajfer J, Aronson W, Bush P, Dorey F and Ignarro L (1992). Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic,

- noncholinergic neurotransmission. *N. Engl. J. Med.*, **326**: 90-94.
- Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J and Mishra A (1997). The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*, **49**: 822-830.
- Rosen RC, Padma-Nathan H, Shabish R, Saikali K, Watkins V and Pullman W (2004). Determining the earliest time within 30min to erectogenic effect after tadalafil 10 and 20 mg: a multicenter, randomized, double-blind, placebo-controlled, at-home study. *J. Sex. Med.*, **1**: 193-200.
- Rosen RC, Shabsigh R, Kuritzky L, Wang WC and Sides GD (2005). The efficacy of tadalafil in improving sexual satisfaction and overall satisfaction in men with mild, moderate, and severe erectile dysfunction: a retrospective pooled analysis of data from randomized, placebo-controlled clinical trials. *Curr. Med. Res. Opin.*, **21**: 1701-1709.
- Saenz de Tajada I, Angulo J, Celtek S, Gonzalez C, Heaton J, Pickard R and Simonsen U (2005). Pathophysiology of erectile function. *J. Sex. Med.*, **2**: 26-39.
- Sandner P, Hutter J, Tinel H, Ziegelbauer K and Bischoff E (2007). PDE5 inhibitors beyond erectile dysfunction. *Int. J. Impot. Res.*, Jul 12; [Epub ahead of print]
- Seftel AD (2005). From aspiration to achievement: assessment and noninvasive treatment of erectile dysfunction in aging men. *J. Am. Geriatr. Soc.*, **53**: 119-130.
- Segraves RT, Lee J, Stevenson R, Walker DJ, Wang WC and Dickson RA. (2007). Tadalafil for treatment of erectile dysfunction in men on antidepressants. *J. Clin. Psychopharmacol.*, **27**(1): 62-66.
- Shabsigh R, Burnett AL, Eardley I, Sharlip ID, Ellsworth PI, Garcia CS *et al* (2005). Time from dosing to sexual intercourse attempts in men taking tadalafil in clinical trials. *B.J.U. Int.*, **96**: 857-863.
- Stroberg P, Murphy A and Costigan T (2003). Switching patients with erectile dysfunction from sildenafil citrate to tadalafil: results of European multicenter, open-label study of patient preference. *Clin. Ther.*, **25**: 2724-2737.
- Von Keitz A, Rajfer J, Segal S, Murphy A, Denne J and Costigan T *et al* (2004). A multicenter, randomized, double-blind, crossover study to evaluate patient preference between tadalafil and sildenafil. *Eur. Urol.*, **45**: 499-507.
- Waldkirch E, Uckert S, Yildirim H, Sohn M, Jons U, Andersson KE and Hedlur P (2005). Cyclic AMP-specific and cyclic GMP-specific phosphodiesterase isoenzyme significance. *World. J. Urol.*, **23**: 405-410.
- Wespes E, Moncada I, Schmitt H, Jungwirth A, Chan M and Varanese L (2007). The influence of age on treatment outcomes in men with erectile dysfunction treated with two regimens of tadalafil: results of the SURE study. *B.J.U. Int.*, **99**: 121-126.
- Young JM, Feldman RA, Auerback SM, Kaufman JM, Garcia CS and Shen W *et al* (2005). Tadalafil improved erectile function at twenty-four and thirty-six hours after dosing in men with erectile dysfunction: US Trial. *J. Androl.*, **26**: 310-318.