Lebda Medical Journal
Vol. 4, Jun. 2018, p.148-153

Salem Hasan Abukres,
Received 13 Mar. 2018; accepted in revised form 3 May. 2018

Comparison between the efficacy and tolerability of On Demand Sildenafil citrate and Tadalafil in Treatment of Erectile Dysfunction in Type 2 Diabetic Patients

Salem Hasan Abukres[(1)], Noradeen Hamza[(2)], Kaled Attomy[(2)], Sedki Abdasalam Erwimi[(2)]
[(1)] Faculty of pharmacy, Elmergib University.
[(2)] Faculty of medicine, Tripoli University

Key ward: Sildenafil, Tadalafil, Erectile Dysfunction, Diabetes

ABSTRACT:

Introduction: Data from head-to-head clinical trials of phosphodiesterase type 5 inhibitors are scarce, making it difficult for clinicians to select the most appropriate treatment for their patients with erectile dysfunction.
Aim: To compare efficacy and tolerability of Sildenafil and Tadalafil in men with erectile dysfunction and diabetes.
Method: A clinical, crossover and open label study was used.
A group of 95 patients were randomly recruited and answered an adapted questionnaire before and after usage of Sildenafil 100 mg and Tadalafil 20 mg to determine the improvement and compare efficacy and tolerability of each drug.
RESULTS: The one tailed Wilcoxon signed-rank test results for all the questions suggest that there is no statistically significant difference in response between Tadalafil and sildenafil $p > 0.05$. However, for erection maintenance ability after penetration and for the overall response, the results suggest that there are statistically significant differences in response between Tadalafil and sildenafil $p < 0.05$ in favor of Tadalafil.
Conclusion: Both drugs were highly effective and well tolerated in diabetic patients. Patient's score on the erection scale with Tadalafil was superior than sildenafil in all questions. However, statistically significant differences were only detected in maintenance ability after penetration and the overall response. Probably, more significance could be detected if the sample size was larger.

INTRODUCTION

Erectile dysfunction (ED) is a consistent or recurrent inability of a man to attain and/or maintain penile erection that is sufficient for sexual activity (1, 2). The rate of ED amongst diabetic men is much higher than amongst the general population. Diabetic men have symptoms of ED approximately 10 to 15 years earlier than do men in the general population (3). Additionally, diabetics with poor glycemic control, represented by higher glycosylated hemoglobin, are also more likely to be impotent (4). Penile blood flow is controlled by the autonomic erection center, which provides parasympathetic (S_2–S_4) and sympathetic (T_{12}–L_2) input to the pelvic plexus including the cavernous nerves that innervate the cavernosal arteries and trabecular smooth muscle. These nerves are responsible for the delivery of high local concentrations of nitric oxide (NO) to the trabecular smooth muscle, which results in relaxation. NO diffuses across the smooth muscle membrane and activates guanylate cyclase to produce cyclic guanosine monophosphate (cGMP) (5).

The biochemical cascade that ensues results in altered potassium and calcium ion channel permeability ultimately, the decrease in cytosolic calcium concentration causes smooth muscle relaxation and increases regional blood flow. Phosphodiesterase enzymes (PDEs) regulate this pathway by inactivating cGMP, which results in elevated cytosolic calcium concentrations and smooth-muscle contraction. Experimentally, diabetes-induced rats have decreased levels of neuronal and endothelial nitric oxide synthase (NOS) which may lead to impaired NO-mediated smooth muscle relaxation. Elevated glucose levels can lead to overproduction of free radical species and result in smooth muscle dysfunction(6).

Finally, as in most men with ED, a severe psychogenic component may further exacerbate erectile failure. Up to 50% of diabetic men have contributing psychosocial factors that may be improved with therapy (7).

The first-line therapy for most men with erectile-dysfunction is treated with an orally administered phosphodiesterase$_5$ inhibitor ($PIDE_5I$): sildenafil citrate, Tadalafil or vardenafil HCI. These medications are effective, well tolerated and safe in men with ED of diverse causes including diabetes (8, 9). The most frequently reported adverse events of the PDE_5 inhibitors are related to their mild vasodilatory effects and include headache, flushing, dyspepsia, and nasal congestion or rhinitis (10, 11). Sildenafil and, to a lesser extent, vardenafil cross-react slightly with PDE_6, which may explain why some patients (3% or less) using these drugs at therapeutic doses have reported experiencing mild and transient abnormal vision, consisting primarily of color tinged vision but also including increased sensitivity to light or blurred vision (12). Tadalafil, on the other hand, has been shown to cross-react with PDE_{11} at therapeutic concentrations, though this has not demonstrated itself to be a clinical issue (13).

Corresponding author: Salem Hasan Abukres, E. mail: abokrase2007@hotmail.com

Diagnosis of ED is primarily based on patient`s self-report although the diagnosis may be supported by objective testing (or partner reports). However, these measures cannot substitute for the patient's self-report in classifying the disorder or establishing the diagnosis (14). The most important component of diagnosing erectile dysfunction is obtaining a complete medical and sexual history. It is important to distinguish the condition from other sexual dysfunctions, such as premature ejaculation and loss of libido (15). The duration of the problem, time of onset and degree of patient and partner concern should also be elucidated. The circumstances surrounding erectile dysfunction may be helpful in determining whether a situational or non-organic factor is involved. Sudden onset, maintenance of nocturnal erections, presence of psychological problems and concurrent major life events or relationship issues may be associated with non-organic ED (16). Concurrent medical illnesses and any medications the patient may be taking should be reviewed.

The International Index of Erectile Function (IIEF) was developed by Rosen et al(11). It is a validated multidimensional (15-item) questionnaire that has been translated into several languages and cross-validated. The EF domain is a highly sensitive and reliable barometer of treatment efficacy. On the basis of an analysis of 1151 subjects, IIEF EF domain scores of ≥ 26 are correlated with 'no' ED'(12). Abridged versions of the IIEF, including the IIEF-5 (containing only five items) or Sexual Health Inventory for Men, are also available (12, 13).

This study was conducted to compare the effectiveness and tolerability of Sildenafil citrate 100 mg with Tadalafil 20 mg in the treatment of ED in type - 2 diabetic patients.

METHODS

STUDY DESIGN

This is an open-label, randomized, fixed-dose trial with a crossover design using the patients as their own controls. Patients gave verbal informed consent before participating in the study conducted in Tripoli Diabetic Center (center 1) and Tripoli Central Hospital (center 2), Tripoli, Libya.

DRUGS

Sildenafil citrate 100 mg (**Viagra™**) Pfizer Pharmaceutical USA and Tadalafil 20 mg (**Cialis™**) ICOS LLC Pharmaceutical USA.

PATIENTS

A group of 95-otherwise healthy men except suffering from diabetes mellitus type II and having erectile dysfunction (ED), aged over 18 years were recruited in the present study. The primary excluded criteria (before patients became naive for use of PDEI) were: any patient who is administering any drug other than insulin or oral hypoglycemic and /or suffering from major complication of diabetes. Secondary excluding criteria (before patients entered in the study) were: any patient who has sudden onset of the ED concurrent with nocturnal penile erection and / or suffering from concurrent major life events or relationship issues and / or did not have sexual desire and premature ejaculation and / or previously taken any PDE $_5$ inhibitors. This was needed to exclude bias.

The patients who were naive for treatment with phosphodiesterase $_5$ inhibitors were randomly distributed in two groups: group A - 47 patients, and group B - 48 patients. Group A received Sildenafil 100 mg and group B received Tadalafil 20 mg for one month. This was followed by one month washing out period. Then the patients were crossed over, the group A received Tadalafil while the group B received sildenafil. The drugs were purchased from local pharmacies in Tripoli.

THE QUESTIONNAIRE

For the determination of ED severity and to assess the effectiveness of the drugs, a questionnaire adopted from international index of erection function (IIEF) and translated to Arabic language was used see (Table 1). Each answer was given a score ranging from 0 to 5 for the possible 6 options. The scoring was done according to the option the patient had selected from the question. To ensure safety and obtain the best results with PDE $_5$ inhibitors, the patients adequately were instructed to take the drug one hour before the anticipated sexual intercourse, and they were informed that sexual stimulation is necessary; the drug is not an aphrodisiac. The patients were also asked to select only one option for each question.

STATISTICAL ANALYSIS

Each answer option was given a score ranged from 0 for option A to 5 for option F. All scores were tested for normal distribution using Q-Q plots and Kolmogorov-Smirnov test. Effects of the treatments were assessed by Friedman test and Wilcoxon signed-rank test. The Freidman test and Wilcoxon signed-rank tests are designed to avoid the assumption of normality implicit in the repeated-measures analysis of variance and paired t-test. The Friedman test is a non-parametric equivalent of the repeated measures ANOVA. In all the tests described below, p value ≤ 0.05 was considered significant.

In this study, the Freidman test was used to test the hypotheses

H_0 : Tadalafil and Sildenafil have the same effect on the five erection function domain questions.

H_1 :One treatment (either Sildenafil or Tadalafil) tends to yield at least a different effect from the other treatment.

Corresponding author: Salem Hasan Abukres, E. mail: abokrase2007@hotmail.com

Table 1 The questionnaire

Question	Answer options	Score
Q1. What is your degree of erection? This question represents attaining and quality of erection ability	A-No sexual intercourse or no erection at all	0
	B-Very weak erection (small elongation of penis)	1
	C-Weak erection (more elongation of the penis)	2
	D-Half erection (semi erection)	3
	E-Good erection (full but not rigid)	4
	F-Excellent erection (full rigid erection)	5
Q2. When you get an erection did you lost it before penetration? This question represents penetration ability	A -No sexual intercourse or no erection at all	0
	B- Yes in all sexual attempts	1
	C-Yes in most sexual	2
	D-Yes occasionally	3
	E- Yes in little attempts	4
	F-Almost no or no	5
Q3. When you get an erection did you lost it after penetration? This question represents maintenance ability	A-No sexual intercourse or no erection at all	0
	B- Yes in all sexual attempts	1
	C-Yes in most sexual attempts	2
	D-Yes occasionally	3
	E- Yes in little attempts	4
	F-Almost no or no	5
Q4. After you finish the intercourse are you had an orgasm? This question represents orgasm ability	A-No sexual intercourse or no erection at all	0
	B-Almost no or no	1
	C- Yes in few times	2
	D-Yes in most cases	3
	E-Yes in most sexual attempts	4
	F-Yes always or almost always	5
Q5. Are you satisfied? This question represents satisfy ability	A-No sexual intercourse or no erection at all	0
	B-Almost no or no	1
	C- Yes in few times	2
	D-Yes in half cases	3
	E-Yes in most sexual attempts	4
	F-Yes always or almost always	5

RESULTS

A. Comparison of scores before and after treatment with sildenafil and Tadalafil

Compared to the baseline, both drugs significantly increased the main score or each question (*p* values > 0.001, Freidman test, Figure 1). The overall score (summation of all responses to the five questions) was also higher than the baseline for both drugs (p values > 0.001, Figure 2). Non-responders (any patient who has the same score for all answers before and after treatment with PDE_5 I) were 16 patients (16.84%) for both drugs.

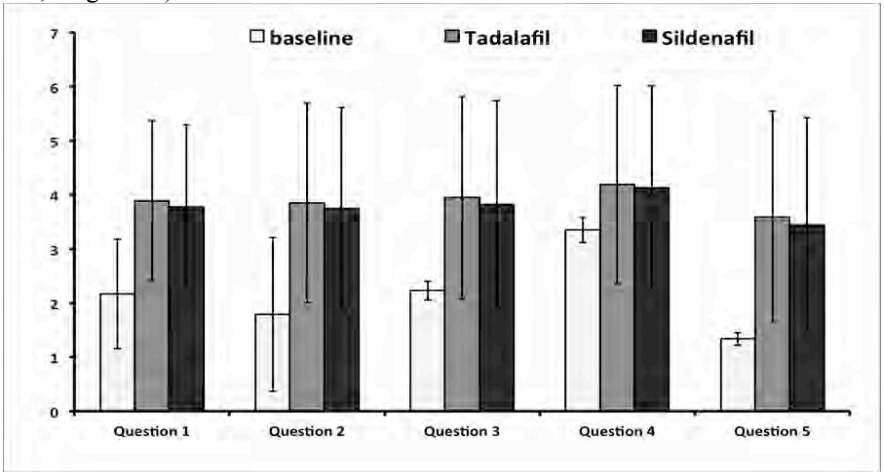

Figure 1. The mean score, standard deviation and standard error of responses to each question for: baseline, Tadalafil and Sildenafil (p> 0.05)

Corresponding author: Salem Hasan Abukres, E. mail: abokrase2007@hotmail.com

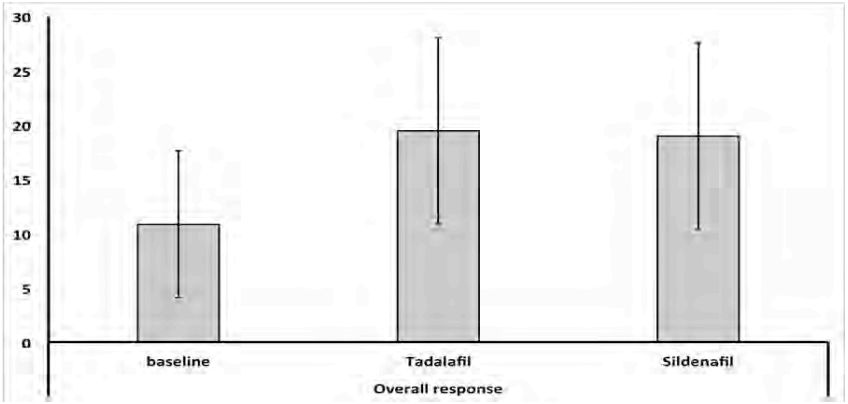

Figure 2. The overall responses for baseline, Tadalafil and Sildenafil

B. Comparison of efficacy of sildenafil and Tadalafil according to the score in 5-questions

In the present study, Wilcoxon signed-rank test was used to compare efficacy of Tadalafil and Sildenafil in treatment of ED in a group of diabetic patients. Results of the present study indicated that there were statistically significant differences between Tadalafil and Sildenafil regarding Q3 (maintenance ability after penetration) and for the overall score (summation of all scores to the five questions) (*p* values > 0.05). See Table 2.

Table 2. Wilcoxon signed-rank test results for Tadalafil and Sildenafil

Question number	p-value (2-Tailed)	p-value (1-Tailed)
Q1	0.188	0.094
Q2	0.216	0.108
Q3	0.075	0.0375*
Q4	0.180	0.090
Q5	0.110	0.055
Overall Response	0.049*	0.0245*

ADVERSE EFFECTS

Generally, both drugs were well tolerated, and no patients had withdrawal due to adverse effects. Both drugs resulted in similar side effects, except for blurred vision which was reported by Sildenafil users only (Table 3). The most important possibility to note in these results is that 11 (11.57%) patients reported that there was a prolonged effect of Tadalafil which ranged from four days to one week which was not reported with Sildenafil. This prolonged effect was without any priapism. An old patient aged 72 years commented about prolong effect of Tadalafil that the "penis is always ready"!

Table 3. Adverse events after treatments

Event	Tadalafil n (%)	Sildenafil n (%)
Headache	13(13.68%)	7(7.36%)
Flushing	6(6.31%)	9(9.47%)
Dyspepsia	12(12.63%)	6(6.31%)
Nasopharyngitis	2(2.10%)	1(1.05%)
Myalgia	9(9.47%)	2(2.10%)
Blurred vision	0(0%)	3(3.15%)

DISCUSSION

Both drugs were significantly effective compared to the baseline for all the five erection function domain questions, and for overall response (p value > 0.05). Comparing to each other, statistically significance differences between Tadalafil and sildenafil were in scores to question three (Q3) and in the overall responses p (0.0375*) and (0.0245*), respectively. Both drugs were well tolerated, and no patient had withdrawal due to adverse effects. The common reported adverse effects were headache, dyspepsia, nasopharyngitis, and myalgia. Blurred vision was reported only with sildenafil. This is inconsistent with previous studies10)11 ,(..

It is important to note that, in the present study, Tadalafil produced prolonged effect compared to Sildenafil which ranged from four days to one week, that was not reported with sildenafil. This prolonged effect was without any priapism. A 72-old patient commented about prolong effect of Tadalafil that "penis is always ready"!.

A validated, internationally established questionnaire (IIEF-5) which is simplified formula of the International index of erection function (IIEF),(16) was adopted in the present study. While the IIEF can be used for all forms (psychological and organic) of ED, the adopted questionnaire concentrates on organic ED because diabetic patients have a high risk this type of ED.(17, 18) The adopted questionnaire is consistent with global definition of erectile dysfunction (1). Therefore, the questions in the present investigation probes getting and maintaining erection until the normal end of sexual intercourse, i.e. ejaculation with an orgasm. This is a clear definition of ED which was not used by another study (19), which has defined ED as a consistent change in quality of erection that adversely affected the subject's satisfaction with sexual intercourse.

Washing - out period in this study was one month to ensure that the action of first drug goes off completely and excludes the psychological effect of the first drug. In contrast, other studies either did not mention,(10) or used too short (7 to 10 days) washing-out period (11).

The frequency of sexual intercourses as a comparer of drugs was not used as it may depend on other factors like individual variation and age of patients and/or his partner rather than drug's efficacy (20). The results were

Corresponding author: Salem Hasan Abukres, E. mail: abokrase2007@hotmail.com

collected after one month of drug first dose so that the patient's answers were the average of sexual intercourses during that period. This is in contradistinction to only one attempt as used by another study (21). The sample (mean age 55.51 years) was recruited randomly from two different medical centers in contrast with a previous study by Eardley et al.(22), which obtained their sample from only one medical center. Therefore, the present' results are more applicable on population than Eardley et al.

In this study, the maximum dose (100 mg Sildenafil, 20 mg Tadalafil) of each drug was used because PDE_5 inhibitors are less effective in diabetic patients with lower doses (1). Thus, to avoid the psychological impact of failure of lower doses, the maximum doses were used. The number of non-responders (patient who has the same score for all answers before and after treatment with PDE_5I) was identical for both drugs. This may be due to the fact that both drugs have same mechanism of action. A study,(1) excluded sildenafil non-responders. The current study excluded all PDE_5 inhibitors users to decrease study bias while von Keitz et al.(23) did not mention if they include or excluded previous sildenafil users. Exclusion of previous users would prevent bias that may be caused by previous experience.

Several studies compared only one drug with placebo or two regimes of same drug. For example, Buvat et al.(23) compared scheduled use versus on-demand regimen of 20 mg of Tadalafil. The above study found that 73% improvement in vaginal penetration ability with Tadalafil compared to 77% in the present investigation. The erectile function domain was improved by 73.33% in the above study as compared to 77.84% (calculated from Table 2) in this study. The major difference between the present and Buvat et al. study is the maintenance ability which was 78.80% in this study and 58% in Buvat et al. study. Another study,(24) which compared Tadalafil with placebo in diabetic patients, found that Tadalafil improved erection function by 66.66% compared with 77.8% in the present study. Difference in the improvement of the patients of the present study with the previous study,(25) may be explained by the inclusion criteria of the present study which included only diabetic patients free from major complication of diabetes without any other diseases except ED.

This study concludes that Sildenafil and Tadalafil were effective and well tolerated in type 2 diabetic patients. The prolonged action of Tadalafil is probably the most vital factor which may lead to that Tadalafil is superior to Sildenafil in all question about sexual function domains. Nevertheless, statistically significances were only detected in question three (maintenance ability) of the adapted questionnaire and in over-all response. This study opens the possibility that more significances could be detected if a larger sample was used.

REFERENCES

1. Consensus N. Development Panel on Impotence. NIH Consensus Conference. Impotence. JAMA. 1993;270:83-90.
2. Rosen RC, Wing R, Schneider S, Gendrano N. Epidemiology of erectile dysfunction: the role of medical comorbidities and lifestyle factors. Urologic Clinics. 2005;32(4):403-17.
3. Bacon CG, Hu FB, Giovannucci E, Glasser DB, Mittleman MA, Rimm EB. Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. Diabetes care. 2002;25(8):1458-63.
4. Cartledge J, Eardley I, Morrison J. Nitric oxide‐mediated corpus cavernosal smooth muscle relaxation is impaired in ageing and diabetes. BJU international. 2001;87(4):402-7.
5. Denninger JW, Marletta MA. Guanylate cyclase and the· NO/cGMP signaling pathway. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1999;1411(2-3):334-50.
6. Usta MF, Kendirci M, Gur S, Foxwell NA, Bivalacqua TJ, Cellek S, et al. The breakdown of preformed advanced glycation end products reverses erectile dysfunction in streptozotocin‐induced diabetic rats: Preventive versus curative treatment. The journal of sexual medicine. 2006;3(2):242-52.
7. Kolodny R, Masters W, Johnson V. Sexual anatomy and physiology. Textbook of Sexual Medicine Little, Brown and Co, Boston, MA. 1979:1-28.
8. Briganti A, Salonia A, Gallina A, Saccà A, Montorsi P, Rigatti P, et al. Drug insight: oral phosphodiesterase type 5 inhibitors for erectile dysfunction. Nature Reviews Urology. 2005;2(5):239.
9. Aversa A, Bruzziches R, Pili M, Spera G. Phosphodiesterase 5 inhibitors in the treatment of erectile dysfunction. Current pharmaceutical design. 2006;12(27):3467-84.
10. Schwarz E, Kapur V, Rodriguez J, Rastogi S, Rosanio S. The effects of chronic phosphodiesterase-5 inhibitor use on different organ systems. International journal of impotence research. 2007;19(2):139.
11. Pomara G, Morelli G, Pomara S, Taddei S, Ghiadoni L, Dinelli N, et al. Cardiovascular parameter changes in patients with erectile dysfunction using PDE‐5 inhibitors: A study with sildenafil and vardenafil. Journal of andrology. 2004;25(4):625-9.
12. Huddleston AJ, Knoderer CA, Morris JL, Ebenroth ES. Sildenafil for the treatment of pulmonary hypertension in pediatric patients. Pediatric cardiology. 2009;30(7):871-82.
13. Bischoff E. Potency, selectivity, and consequences of nonselectivity of PDE inhibition. International journal of impotence research. 2004;16(S1):S11.
14. Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, et al. Summary of the recommendations on sexual dysfunctions in men. The journal of sexual medicine. 2010;7(11):3572-88.
15. Rosen RC, Cappelleri J, Smith M, Lipsky J, Pena B. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. International journal of impotence research. 1999;11(6):319.

16. Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. BMJ: British Medical Journal. 2000;321(7259):499.
17. 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(6):822-30.
18. 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(2):346-51.
19. Cappelleri JC, Siegel RL, Glasser DB, Osterloh IH, Rosen RC. Relationship between patient self-assessment of erectile dysfunction and the sexual health inventory for men. Clinical therapeutics. 2001;23(10):1707-19.
20. Rhoden E, Telöken C, Sogari P, Souto CV. The use of the simplified International Index of Erectile Function (IIEF-5) as a diagnostic tool to study the prevalence of erectile dysfunction. International journal of impotence research. 2002;14(4):245.
21. Lue TF. Erectile dysfunction. New England Journal of Medicine. 2000;342(24):1802-13.
22. Angulo J, Cuevas P, Gabancho S, Allona A, Martín-Morales A, Moncada I, et al. Diabetes impairs endothelium-dependent relaxation of human penile vascular tissues mediated by NO and EDHF. Biochemical and biophysical research communications. 2003;312(4):1202-8.
23. Eardley I, Mirone V, Montorsi F, Ralph D, Kell P, Warner MR, et al. An open‐label, multicentre, randomized, crossover study comparing sildenafil citrate and tadalafil for treating erectile dysfunction in men naive to phosphodiesterase 5 inhibitor therapy. BJU international. 2005;96(9):1323-32.
24. Porst H. The 3 PDE 5 inhibitors sildenafil, tadalafil and vardenafil in patients with diabetes and ED-results of a comparative trial in 107 patients. The Journal of Sexual Medicine. 2005;2:21.
25. von Keitz A, Rajfer J, Segal S, Murphy A, Denne J, Costigan T, et al. A multicenter, randomized, double-blind, crossover study to evaluate patient preference between tadalafil and sildenafil. European urology. 2004;45(4):499-509.

Corresponding author: Salem Hasan Abukres, E. mail: abokrase2007@hotmail.com