Tadalafil Once a Day for Men with Erectile Dysfunction: Is It Superior than On-Demand Administration?

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ABSTRAK

Latar belakang: *Tadalafil adalah sebuah PDE5I yang telah dilisensikan untuk menyembuhkan disfungsi ereksi sejak tahun 2003, efektif dari 30 menit setelah pemberian dan kemanjurannya dipertahankan hingga 36 jam. Baru-baru ini juga diberikan OAD dalam dosis yang lebih rendah untuk memungkinkan kegiatan seksual spontan. Namun, apakah pemberian OAD lebih efektif dibandingkan PRN dalam meningkatkan EF masih belum ditetapkan. Studi ini bertujuan untuk mengetahui apakah pemberian tadalafil sekali sehari lebih baik dalam meningkatkan fungsi ereksi pada pasien disfungsi ereksi (DE) dibandingkan pemberian on-demand/pro re nata (PRN).* ***Metode:*** *penelusuran dilakukan dengan menggunakan Medline, Scopus, Cochrane, dan CINAHL. Risiko bias pada tiap studi dinilai menggunakan Cochrane Risk of Bias Tool.* ***Hasil:*** *kami menemukan 231 studi dari penelusuran literatur, namun hanya empat studi yang sesuai kriteria seleksi. Berdasarkan penilaian kami, studi oleh Kang et al. merupakan yang paling sesuai dengan situasi klinis kami. Studi ini mendapatkan bahwa subyek yang mendapat tadalafil once a day (OAD) mengalami peningkatan yang lebih tinggi dan signifikan untuk skor IIEF-EF (6.5 (SB 4.5) vs 4.9 (SB 4.2), p=0.032), proporsi "ya" terhadap SEP-2 (81.8% vs 64.7%, p=0.025), dan proporsi "ya" terhadap SEP-3 (77.3% vs 60.3%, p=0.034).* ***Kesimpulan:*** *pemberian tadalafil OAD akan memberikan peningkatan fungsi ereksi yang lebih baik dibandingkan dengan pemberian PRN.*

Kata kunci: *tadalafil, sekali sehari, disfungsi ereksi, IIEF.*

ABSTRACT

Background: *Tadalafil is a PDE5I which has been licensed for the treatment of erectile dysfunction (ED) since 2003, is effective from 30 minutes after administration and its efficacy is maintained for up to 36 hours. More recently, it is also given OAD in a lower dose to allow spontaneous sexual activities. However, whether OAD administration is more effective than PRN administration in improving the EF is yet to be established. This study aimed to evaluate whether OAD administration of tadalafil leads to a better improvement of erectile function (EF) in patients with erectile dysfunction (ED) compared to PRN administration.* ***Methods:*** *literature search of electronic database was performed through Medline, Scopus, Cochrane Library, and CINAHL databases. Cochrane Risk of Bias Tool was then employed to assess the risk of bias in each study.* ***Results:*** *initial literature search resulted in 231 hits, but only four studies were included in final selection. Based on our judgements, the study by Kang et al. was the most applicable in our clinical setting. This study showed that subjects who received tadalafil OAD had statistically significant higher increases of mean IIEF-EF (6.5 (SD 4.5) vs 4.9 (SD 4.2), p=0.032), proportion of "yes" responses to SEP-2 (81.8% vs 64.7%, p=0.025), and proportion of "yes" responses to SEP-3 (77.3% vs*

60.3%, p=0.034). ***Conclusion:*** *administration of tadalafil OAD leads to a better improvement of EF compared to PRN administration.*

Keywords: *tadalafil, once-a-day, erectile dysfunction, IIEF.*

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient for satisfactory sexual performance.[1] According to the Massachusetts Male Aging Study (MMAS), one of the first epidemiology studies on ED involving a large number of subjects, the condition affects 52% of men between the ages of 40 and 70 years. Furthermore, by the age of 70, approximately 68% of men reported to have ED, suggesting that ED is age-dependent.[2] Nicolosi et al. reported the prevalence of sexual dysfunction in several Asian countries, including Indonesia. Based on their study, the prevalence of ED among adult Indonesian men was 11% (95% CI = 7-15).[3] Several risk factors have been associated with ED. They include hypertension, diabetes, hyperlipidemia, and smoking.[4] Furthermore, trauma to the pelvic region and radical prostatectomy have also been reported to cause ED.[5,6]

Treatment of ED starts from managing the modifiable risk factors and underlying conditions, which may involve lifestyle modifications. First-line therapy for ED is phosphodiesterase 5 inhibitors (PDE5Is), e.g. sildenafil, tadalafil, and vardenafil. The differences between each PDE5I include the onset of action and duration of effect. To date, there is no guideline on which drug is more recommended for the treatment of ED. Patient's choice and physician's judgement must be considered when prescribing PDE5Is.[1]

Tadalafil, a PDE5I which has been licensed for the treatment of ED since 2003, is effective from 30 minutes after administration and its efficacy is maintained for up to 36 hours. It is administered PRN with doses of 10 mg and 20 mg.[7] More recently, it is also given OAD in a lower dose to allow spontaneous, rather than scheduled, sexual activities. However, whether OAD administration is more effective than PRN administration in improving the EF is yet to be established.

CASE ILLUSTRATION

A 61-year old sexually-active man came to a urologist, complaining of difficulty to achieve erection during sexual intercourse. On the occasions that he had an erection, he could not maintain penetration. Patient has been taking medications for hypertension and hyperlipidemia since 3 years ago. Patient did not have any history of surgery/trauma to the spine/pelvic region. When patient wanted to have sexual intercourse, he usually took tadalafil 20 mg, 30 minutes before the beginning of sexual intercourse. However, he felt it was rather inconvenient because he could not have spontaneous sexual intercourse with his sexual partner without taking tadalafil beforehand. The urologist read some publications stating that OAD, low-dose administration of tadalafil helps patients to have spontaneous sexual intercourse. The urologist wondered whether OAD administration of tadalafil is also more superior in improving EF compared to PRN administration in terms of efficacy and safety.

CLINICAL QUESTION

Does OAD administration of tadalafil lead to a better improvement of EF in patients with ED compared to PRN administration?

METHODS

Search Strategy

Literature search of electronic databases was performed in November 2017. We searched the literatures through Medline, Scopus, Cochrane Library, and CINAHL databases. The following key terms were used as MeSH and free text terms: "tadalafil", "erectile dysfunction", "on demand", "as needed", "pro re nata", "once a day", and "daily" (**Table 1**). Multiple synonyms of each term were also searched. All titles and abstracts retrieved by electronic search were screened for relevance and duplicates by two

reviewers (DTP and PARR). Following abstract screening, all full-text manuscripts of studies which did not undergo prior exclusion were reviewed for eligibility (**Figure 1**).

Eligibility Criteria

Studies which were included in this report fulfilled the following criteria: (1) study design was randomized control trial (RCT), systematic review, or meta-analysis; (2) subjects were at least 18 years of age and diagnosed with ED; (3) study evaluated the efficacy or safety of tadalafil OAD compared to PRN administration for ED.

Studies were excluded if: (1) full text of English article was not available; (2) study did not measure EF using the International Index of Erectile Function-Erectile Function (IIEF-EF) or the Sexual Encounter Profile (SEP)-2 ("Were you able to insert your penis into your partner's vagina?") and SEP-3 ("Did your erection last long enough for you to have successful intercourse?") scoring systems; (3) study was conducted in patients with prostate cancer; and (4) study was conducted in patients with history of surgery in the pelvic region.

Table 1. Keywords and search hits in Pubmed, Scopus, Cochrane Library, and CINAHL databases

Search Engine	Search Terms	Number of Articles
Pubmed	("tadalafil" AND ("erectile dysfunction"[MeSH Terms] OR erectile dysfunction [Text Word]) AND ("on demand" OR "as needed" OR "pro re nata") AND ("once a day" OR "daily"))	69
Scopus	TITLE-ABS-KEY ("tadalafil" AND "erectile dysfunction" AND ("on demand" OR "as needed" OR "pro re nata") AND ("once a day" OR "daily"))	100
Cochrane Library	"tadalafil" AND "erectile dysfunction" AND ("on demand" OR "as needed" OR "pro re nata") AND ("once a day" OR "daily") in Title, Abstract, Keywords	54
CINAHL	"tadalafil" AND "erectile dysfunction" AND ("on demand" OR "as needed" OR "pro re nata") AND ("once a day" OR "daily")	8

* Searches were performed on November 10th, 2017

Critical Appraisal

Critical appraisals of the included studies were performed by DTP and PARR, independently, using the RCT Critical Appraisal Sheet from the Centre for Evidence-Based Medicine. The Cochrane Risk of Bias Tool was then employed to assess the risk of bias in each study using seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other source of bias. Authors' judgments on the risks of bias for each study were divided into three categories: low risk, high risk, or unclear risk of bias (**Figure 2**).

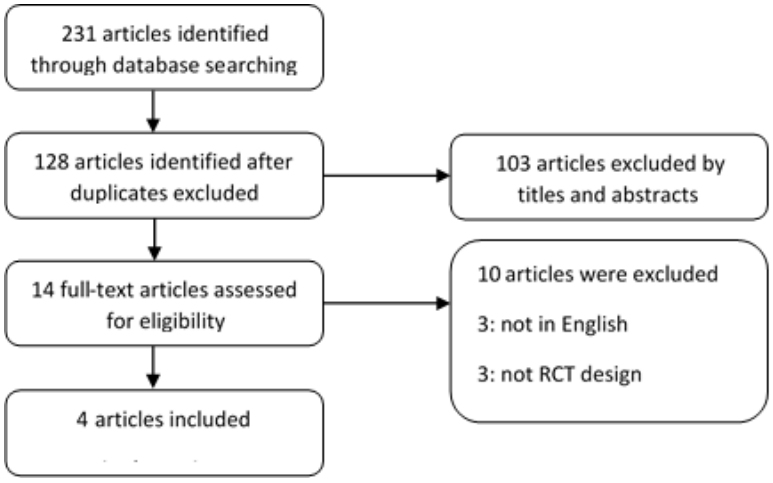

Figure 1. Flow chart of search strategy for study selection.

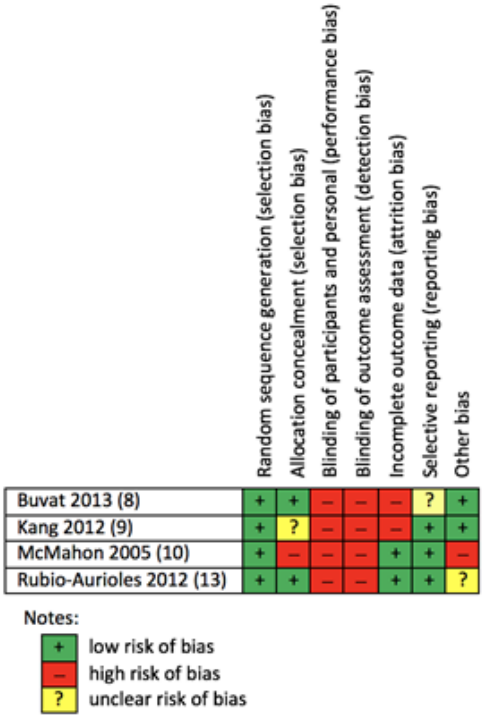

Figure 2. Authors' judgements on each risk of bias item for appraised studies.

RESULTS

Initial literature search using pre-determined terms in four search engines (Pubmed, Scopus, Cochrane Library, and CINAHL) resulted in 231 hits. Duplicates screening excluded 128 articles, while title and abstract screenings excluded another 103 articles. Full-text articles for the 14 titles not-excluded were assessed for eligibility, resulting in further 10 articles being excluded for final review due to: three articles were not in English, three articles did not use RCT design, one article used the same study subjects as one publication included in the critical appraisal, and three articles included subjects who did not meet the inclusion criteria of this study. The following four papers were included for final appraisal and assessment (**Table 2**).

Buvat et al.[8] studied the effect of tadalafil OAD, tadalafil PRN, and sildenafil PRN towards several parameters including the IIEF-EF and SEP. The RCT involved 509 subjects with ED in a 24-week treatment period. Tadalafil OAD was given in a flexible dose adjustment between the 2.5 mg and 5 mg preparations, while tadalafil PRN was given in a flexible dose adjustment between the 10 mg and 20 mg preparations. Although the improvement of EF was not the main outcome, this study included the changes of IIEF-EF and SEP from the baseline following treatment in the analysis. Both the tadalafil OAD and tadalafil PRN groups showed increases in mean IIEF-EF (9.4 (SD 7.0) vs 9.6 (SD 6.1), p >0.05) and proportion of "yes" responses to SEP-3 (47.7% vs 49.9%, p >0.05). The differences, however, were not statistically significant.

In a 12-week RCT parallel study among 168 ED subjects aged 20 years and above with/without underlying diseases, Kang et al.[9] studied the effect of tadalafil OAD 5 mg in 84 subjects and tadalafil PRN 20 mg in 84 subjects on EF as measured by IIEF-5 and SEP scores. Baseline characteristics of both groups were similar. Sixty-six subjects who received tadalafil OAD and 68 subjects who received tadalafil PRN completed the 12-week treatment period. Compared with subjects who received tadalafil PRN, subjects who received tadalafil OAD showed statistically significant higher increases of mean IIEF-EF (6.5 (SD 4.5) vs 4.9 (SD 4.2), p = 0.032), proportion of "yes" responses to SEP-2 (81.8% vs 64.7%, p = 0.025), and proportion of "yes" responses to SEP-3 (77.3% vs 60.3%, p = 0.034).

McMahon et al.[10] conducted an RCT crossover study among 145 patients with ED over a 12-week treatment period comparing tadalafil OAD (10 mg) with tadalafil PRN (20 mg). Compared with baseline, tadalafil OAD and PRN enhanced all efficacy outcomes (IIEF-EF, SEP). Subjects receiving tadalafil OAD experienced a higher increase of mean IIE-EF score compared to subjects receiving tadalafil PRN (11.9 vs 8.3, p = 0.001). Likewise, SEP-2 and SEP-3 scores also experienced gains in the mean scores following treatment with tadalafil, with the OAD regimen having higher increases compared with the PRN regimen (SEP-2 85% vs 73%, p <0.05; SEP-3 80% vs 67%, p <0.05).

The last study which was assessed in this report is the study by Rubio-Aurioles et al.[11] The study involved men at least 18 years of age with history of ED and satisfactory response to current oral PDE5I PRN. Three hundred and seventy-eight subjects were divided into six groups which received, alternatingly, tadalafil

OAD 5 mg, tadalafil PRN 20 mg, and sildenafil PRN 100 mg for 8 weeks. EF was measured by IIEF-EF only. Similar to other literatures included in this report, the study showed that subjects who received tadalafil OAD had a higher mean IIEF-EF increase compared to those who received tadalafil PRN, despite not being statistically significant (8.7 (SD 6.7) vs 9.5 (SD 6.8), p = 0.092).

Based on our judgements, the study by Kang et al.[9] is the most applicable in our clinical setting. The patients' characteristics were similar to our patients and they used the same parameter to assess the EF by using the much simpler, IIEF-5 questionnaire. However, as with most clinical trials evaluating the effect of PDE5Is towards EF, there were high risks of performance and detection biases due to the absences of participant

Table 2. Summary of characteristics and outcomes of included studies

Study	Study design	Populations	Number of patients	Age, years	Follow-up period of treatment	Intervention and dose regimen of tadalafil, mg	Efficacy outcome, %			
								OAD	PRN	p-value
Buvat et al. 2013[8]	RCT parallel	ED patients	509	53.0	24 weeks	OAD; flex 5 (5-2.5) PRN; flex 10 (10-20)	IIEF-EF SEP-3	9.4 (7.0) 47.7	9.6 (6.1) 49.9	0.73 > 0.05
Kang et al. 2012[9]	RCT parallel	ED patients	168	55.6	12 weeks	OAD; fixed 5 PRN; fixed 20	IIEF-5 SEP-2 SEP-3	6.5 (4.5) 81.8 77.3	4.9 (4.2) 64.7 60.3	0.032 0.025* 0.034*
McMahon et al. 2005[10]	RCT crossover	ED patients	145	57.0	12 weeks	OAD; fixed 10 PRN; fixed 20	IIEF-EF SEP-2 SEP-3	11.9 85 80	8.3 73 67	0.001 <0.05 <0.05
Rubio-Aurioles et al. 2012[11]	RCT crossover	ED patients	378	56.2	8 weeks	OAD; flex 5 (5-2.5) PRN; flex 20 (20-10)	IIEF-EF	8.7 (6.7)	9.5 (6.8)	0.092

RCT, randomized controlled trial; OAD, once a day; PRN, on demand; flex, flexible, dose adjustment was allowed to achieve the optimal dose; IIEF-EF, IIEF-EF domain score changes from baseline; IIEF-5, IIEF-5 domain score changes from baseline; SEP-2, proportion changes of "yes" responses to SEP-2 from baseline; SEP-3, proportion changes of "yes" responses to SEP-3 from baseline; p-values were determined by unpaired t-test. *p-values were determined by chi-square tests.

and outcome assessment blinding.

Some of the studies also compared the safety of tadalafil OAD to PRN. Buvat et al.8 reported 10/257 (3.9%) and 7/252 (2.8%) patients from the OAD and PRN groups experienced adverse events, respectively (p = 0.623). However, no detail was listed regarding the adverse events. Kang et al.[9] reported 6/84 (7.1%) patients who received tadalafil OAD and 7/84 (8.3%) patients who received tadalafil PRN experienced adverse events with the difference being not statistically significant. Facial flushing was the most common adverse events (OAD group: n = 4; PRN group: n = 4), followed by headache (OAD group: n = 2; PRN group: n = 2), and dizziness (PRN group: n = 1). Both articles did not report any serious adverse event caused by both tadalafil OAD and PRN during study period.

DISCUSSION

Tadalafil is a selective PDE5I with a half-life of 17.5 h, which is longer than other available PDE5Is. This proves to be an advantage to men taking tadalafil by providing a wide range of possibilities in which to engage in sexual intercourse. The launch of low-dose tadalafil OAD, which can maintain a pharmacodynamic plasma concentration of 55 ng/mL throughout the 24-hour dosing interval[12], enables men taking it to have spontaneous sexual intercourse in contrast to scheduled sexual intercourse when taking the PRN dosage.[13]

The inconvenience caused by scheduled sexual intercourse when taking tadalafil PRN may also have psychological implications for patients. These psychological factors could affect patients' sexual intercourse performance, confidence, and quality of life. Tadalafil's half-life could be an important changing factor regarding this concern. In theory, a much longer effective plasma concentration could be maintained with an OAD administration compared to PRN regimen, thus allowing patients to feel ready for sexual intercourse at any time and enabling them to separate the stigma of drug intake from the act of sexual intercourse.

We studied whether tadalafil OAD administration in patients with ED resulted in better improvement of EF compared to tadalafil PRN. Our extensive search retrieved four RCTs which fulfilled our eligibility criteria for this report. All four studies reported increased IIEF-EF and IIEF-5 scores as well as higher proportion of "yes" responses to SEP-2 and SEP-3 following treatment with PDE5Is with most of them showing higher gains of IIEF-EF and IIEF-5 scores as well as higher proportion increase of "yes" responses to SEP-2 and SEP-3 in patients who received tadalafil OAD compared to tadalafil PRN.

In general, there was no significant difference between tadalafil OAD compared to tadalafil PRN in term of incidence of adverse effects. Regardless of which dosing regimen was used, the adverse effects were relatively rare and well tolerated. However, several studies found that tadalafil OAD had a lower incidence of headache and flushing compared to the tadalafil PRN dosing. One possible explanation is that headache and flushing are more likely to be associated with peak drug plasma concentration, which is much higher in tadalafil PRN compared with tadalafil OAD dosing.[13]

CONCLUSION

Administration of tadalafil OAD for the management of ED provides not only the possibility to have spontaneous sexual intercourse to the users, but also leads to better improvement of EF compared to PRN administration. However, patient's preference and physician's judgment are still the most important considerations when deciding to give PDE5I to patients with ED.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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REFERENCES

1. Hatzimouratidis K, Giuliano F, Moncada I, Muneer A, Salonia A, Verze P. EAU guidelines on male sexual dysfunction: Erectile dysfunction and premature ejaculation. 2017.
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinklay JB. Impotence and its medical and physiological correlates: Results of the massacheusetts male aging study. J Urol. 1994;151:54–61.
3. Nicolosi A, Glasser DB, Kim SC, Marumo K, Laumann EO. Sexual behaviour and dysfunction and help-seeking patterns in adults aged 40-80 years in the urban population of asian countries. BJU Int. 2005;95(4):609–14.
4. Suzuki E, Nishimatsu H, Oba S, Takahashi M, Homma Y. Chronic kidney disease and erectile dysfunction. World J Nephrol. 2014;3(4):220–9.
5. Papadopoulou E, Varouktsi A, Lazaridis A, Boutari C, Doumas M. Erectile dysfunction in chronic kidney disease: From pathophysiology to management. World J Nephrol. 2015;4(3):379–87. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4491929&tool=pmcentrez&rendertype=abstract.
6. Hatzimouratidis K, Eardley I, Giuliano F, et al. Guidelines on male sexual dysfunction: Erectile dysfunction and premature ejaculation. Eur Urol. 2010;57(5):804–14. Available from: http://uroweb.org/wp-content/uploads/14-Male-Sexual-Dysfunction_LR.pdf.
7. Curran MP, Keating GM. Tadalafil. Drugs. 2003;63:2203–12.
8. Buvat J, Büttner H, Hatzimouratidis K, et al. Adherence to initial PDE-5 inhibitor treatment: Randomized open-label study comparing tadalafil once a day, tadalafil on demand, and sildenafil on demand in patients with erectile dysfunction. J Sex Med. 2013;10(6):1592–602.
9. Kang DH, Lee JY, Chung JH, et al. Comparison of efficacy for erectile function and lower urinary tract symptoms of tadalafil 20 mg on-demand and 5 mg once daily in patients with erectile dysfunction. Int J Clin Pract. 2012;66(8):813–20.
10. McMahon C, Kloner RA, Hutter AM, Porst H. Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. J Sex Med. 2005;2(3):415–27.
11. Rubio-Aurioles E, Porst H, Kim ED, et al. A randomized open-label trial with a crossover comparison of sexual self-confidence and other treatment outcomes following tadalafil once a day vs. tadalafil or sildenafil on-demand in men with erectile dysfunction. J Sex Med. 2012;9(5):1418–29.
12. Wrishko R, Sorsaburu S, Wong D, Strawbridge A, McGill J. Safety, efficacy, and pharmacokinetic overview of low-dose daily administration of tadalafil. J Sex Med. 2009;6(7):2039–48.
13. Peng Z, Yang L, Dong Q, Wei Q, Liu L, Yang B. Efficacy and safety of tadalafil once-a-day versus tadalafil on-demand in patients with erectile dysfunction: A systematic review and meta-analyses. Urol Int. 2017;(37):343–52.