ORIGINAL RESEARCH

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Vardenafil in the Treatment of Male Erectile Dysfunction: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: We carried out this systemic review and meta-analysis of relevant randomized controlled trials to determine different dosage regimens of vardenafil in the treatment of male erectile dysfunction (ED).

Methods: Using appropriate keywords, we searched PubMed, the Cochrane library and Embase for relevant literature before March 2020. We evaluated odds ratio (OR), mean difference (MD) and 95% confidence interval (95% CI) to assess the results of each study.

Results: We included 14 studies with a total of 3221 patients. Compared with the placebo, vardenafil significantly increased IIEF-overall satisfaction (WMD: 3.37, 95%CI: 2.02~4.71), IIEF-erectile function (WMD: 7.93, 95%CI: 6.00~9.85), IIEF-sexual desire (WMD: 0.79, 95%CI: 0.24~1.35), IIEF-intercourse satisfaction (WMD: 5.24, 95%CI: 3.35~7.13), IIEF-orgasmic function (WMD: 3.81, 95%CI: 2.26~5.35), SEP-Q2 (WMD: 26.36, 95%CI: 22.95~29.77), and SEP-Q3 (WMD: 35.18, 95%CI: 31.89~38.48).

Conclusions: Vardenafil has demonstrated significant efficacy in the treatment of ED, but the optimal dose and course of vardenafil remain to be established.

Keywords: Erectile dysfunction; Meta-analysis; Urology; Vardenafil

Key Summary Points

- Vardenafil has significant efficacy in the treatment of erectile dysfunction (ED).
- Vardenafil significantly decreased the International Erectile Function Index (IIEF) - erectile function versus sildenafil.
- There was no significant difference in IIEF-erectile function between vardenafil and tadalafil.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13176380.

INTRODUCTION

Erectile dysfunction (ED), which refers to persistent penile erection that cannot be obtained or maintained adequately for sexual intercourse, seriously compromises the mental health and self-image of ED patients; it also jeopardizes marital relations and impairs the quality of life of ED patients and their partners. The risk factors of ED include age, smoking, depression, diabetes and cardiovascular disease, among which age is one of the most significant factors for ED[1-3]. Approximately half of men aged 40 to 70 years have ED. With the aging of the society and increasing life pressure, it is estimated that the number of ED patients worldwide will exceed 320 million by 2025[4, 5].

Penile erection is a hemodynamic process involving the relaxation of the smooth muscle of the cavernous body and the associated arterioles. During sexual stimulation, the terminal neurons in the penis sponge release nitric oxide (NO), which activates guanosinolate cyclase in smooth muscle cells and increases the level of cGMP, finally leading to relaxation of smooth muscle and increase of blood flow in the penis. The actual level of cGMP is regulated jointly by the rate of synthesis by guanosylate cyclase and by the rate of degradation of cGMP by phosphodiesterase (PDEs).

ED treatment has gone through many stages. With the introduction of phosphodiesterase type 5 (PDE5) inhibitors in the 1990s, the main treatment method has gradually changed to oral PDE5 inhibitors[6]. The meta-analysis of all available literature was aimed at obtaining updated evidence to evaluate the efficacy of vardenafil in the treatment of ED and to provide a basis for the selection of clinical treatment.

METHODS

Search Strategy

In order to identify studies on the clinical outcome of vardenafil in the treatment of male ED, we reviewed relevant articles in the Cochrane library, PubMed and Embase from inception until March 2020. We also reviewed the references of all included articles to identify other studies. Search terms included vardenafil, Levitra, Vardenafil, erectile dysfunction, erectile, dysfunction, random, randomized controlled trial, and RCT. These terms were used in combination with “AND” or “OR”. The literature review was performed independently by two investigators, with a third investigator resolving any disputes as needed.

This article followed the principles of PICOS (participants, interventions, comparisons, results and study design), the key search terms included (P) ED patients; (I) patients receiving vardenafil; (C/O) results included; and; International Erectile Function Index (IIEF) - overall satisfaction, IIEF erectile function, IIEF sexual desire, IIEF sexual satisfaction, IIEF orgasmic function, Sexual Encounter Profile (SEP) - Q2 and sep-q3, (S) RTC only. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Study Selection Criteria

Eligible studies should meet the following criteria: (1) RCT; (2) patients had ED; (3) patients were treated with vardenafil; 4) papers were published in English or Chinese.

The exclusion criteria were as follows: (1) duplicate articles or results; (2) clear data errors; (3) case reports, case-control studies, theoretical research, conference reports,

systematic reviews, meta-analyses, or other forms of research or comment not designed in a randomized controlled manner; (4) irrelevant outcomes.

Two investigators independently determined whether studies met the eligibility criteria, and the third investigator was asked resolve any disputes where appropriate.

Data Extraction and Quality Assessment

We extracted two categories of information from each eligible study: basic information and primary study outcomes. Basic information relevant to this meta-analysis included: author names, year of publication, sample size, age, body mass index (BMI), interventions and Jadad score. Primary clinical outcomes included IIEF-overall satisfaction, IIEF-erectile function, IIEF-sexual desire, IIEF-intercourse satisfaction, IIEF-orgasmic function, SEP-Q2, and SEP-Q3. The quality of the study was based on the Jadad score, which was determined based on the extent to which each study met the following criteria: the study included a specific statement about randomization; the method used for randomizing patients was appropriate; the study was conducted in a double-blind manner; the double-blind method was appropriately described; information was provided about any patients who dropped out of the study. Jadad score < 3 indicated low quality of research and therefore had a high risk of bias. Two investigators independently extracted the data, and a third investigator was asked to resolve any disputes to reach a consensus.

Statistical Analysis

STATA v10.0 (TX, USA) was used for all analyses. We evaluated heterogeneity in study results by using chi-squared and I^2 tests. High heterogeneity was considered present if chi-squared P was ≤ 0.05 and I^2 was >50% and the random-effects model was chosen. A chi-squared $P>0.05$ and an $I^2 \leq 50\%$ indicated that heterogeneity was acceptable, and the fixed-effects model was instead used. Continuous variables were expressed as mean ± standard deviations and compared using mean difference (MD). Categorical data was given as number and percentage and compared using relative risk (RR)/odds ratios (ORs). All the indexes were analyzed by MD and 95%CI.

RESULTS

Overview of Included Studies

We identified 563 articles *via* keyword search and excluded 466 articles after title / abstract review. We then fully evaluated the remaining 97 articles and excluded 83 articles that failed to meet the inclusion criteria, including lack of clinical outcomes (n=49), no qualified interventions (n=13), and non-RCT (n=21). Ultimately, 14 studies including 3221 patients [7-20] met the eligibility criteria for this meta-analysis. The study selection process is outlined in Figure 1.

Table 1 summarizes the basic information for each study, including name of each author, year of publication, country, sample, age, BMI, interventions and Jadad score. The mean Jadad score for the included RCTs was 3.54, indicating that all included studies were of high quality. By the design of the included studies, we divided all the indexes in the subgroup analysis: vardenafil vs. placebo, vardenafil vs. sildenafil, vardenafil vs. sertralin, and vardenafil vs. tadalafil.

IIEF

Compared with placebo, vardenafil significantly increased IIEF-overall satisfaction (WMD: 3.37, 95%CI: 2.02~4.71), IIEF-erectile function (WMD: 7.93, 95%CI: 6.00~9.85), IIEF-sexual desire (WMD: 0.79, 95%CI: 0.24~1.35), IIEF-intercourse satisfaction (WMD: 5.24, 95%CI: 3.35~7.13), and IIEF-orgasmic function (WMD: 3.81, 95%CI: 2.26~5.35).

Compared with sildenafil, vardenafil significantly decreased IIEF- erectile function (WMD: -0.85, 95%CI: -1.41~-0.30). There was no significant difference in IIEF-erectile function (WMD: 0.10, 95%CI: -0.10~0.30) between vardenafil and tadalafil. Compared with sertralin, vardenafil significantly increased IIEF-erectile function (WMD: 5.60, 95%CI: 3.67~7.53). The above results are presented in Figure 2-6.

SEP

Compared with placebo, vardenafil significantly increased SEP-Q2 (WMD: 26.36, 95%CI: 22.95~29.77), and SEP-Q3 (WMD: 35.18, 95%CI: 31.89~38.48). The above results are presented in Figure 7-8.

Quality and Bias Assessment

A variety of complementary methods were used to assess the quality and bias risk of the study, including funnel plot, rank test of Begg and Mazumdar, and Egger's test. In these studies, significant symmetry was found in the logarithmic WMD funnel plot of IIEF erectile function, indicating a lower risk of publication bias (Fig. 9). The results of Begg's and Mazumdar's rank test (Z=0.77, p=0.442) and Egger's test (p=0.748) both suggested no significant risk of bias in the study results.

DISCUSSION

ED is the persistent inability to achieve and/or maintain a full erection in order to have a satisfying sex life. According to the causes, ED can be divided into: (1) psychological ED, which is mainly caused by mental stress, anxiety, depression, fear, feelings and experience factors; (2) organic ED, caused by vascular, neurological, and endocrine factors, and drugs (such as 8 - receptor blockers, diuretics, etc.); compound ED due to psychological and organic causes. It is now believed that most ED patients have organic lesions, with 20% of them having diabetes, 26% having hypertension, and 76% having hyperlipidemia. Studies found that about 75% of patients with chronic stable coronary heart disease also had ED. As a common disease in middle-aged and elderly men, ED seriously affects the quality of life of patients. With improved understanding of ED mechanism, it has been realized that penile erection is related to NO and regulated by PDE5. Meanwhile, numerous basic medical studies have proved that ED, in essence, is a kind of impairment of vascular endothelial cell function.

In clinical studies, the scales commonly used to evaluate the therapeutic effect of ED include IIEF, Psychological and Interpersonal Relationship Scale (PAIRS)-Sexual confidence score, SEP, and Erection Hardness Grading Score (EHS), etc. IIEF includes five domains: erectile function domain (0~30), intercourse satisfaction

domain (0~15), orgasmic function domain (0~15), overall satisfaction domain (2~10), and sexual desire domain (2~10). In the SEP, the SEP2 ('Were you able to insert your penis into your partner's vagina?') and SEP3 ('Did your erection last long enough for you to have successful intercourse?') were frequently used to evaluate treatment effectiveness.

As a first-line drug for the treatment of ED, PED-5 inhibitors are widely used in clinical practice. Currently, there are three drugs in clinical practice, sildenafil, vardenafil and tadalafil, which have been proved to be safe and effective. The use of sildenafil, the first generation PDE-5 inhibitor, led to revolutionary advances in the treatment of ED. PDE-5 is the most important PDE in the corpus cavernosum of the penis. Vardenafil inhibits the degradation of cGMP PDE-5 in the body of the penis sponge, and increases the release of endogenous NO locally in the sponge body under the action of sexual stimulation so as to relax the smooth muscle and increase the blood flow in the body of the penis sponge. Thus, vardenafil enhances the natural response to sexual stimulation.

The current analysis has some limitations. The number of included studies is limited. In addition, individual studies varied in exclusion/inclusion criteria, Third, the severity of ED in patients varied among the studies and the dose and course of treatment also varied among the studies. Finally, pooled data were analyzed as individual patient data was not available, precluding more in-depth analyses.

CONCLUSIONS

In our study, we found that compared with the placebo, vardenafil significantly increased IIEF-overall satisfaction, IIEF-erectile function, IIEF-sexual desire, IIEF-intercourse satisfaction, IIEF-orgasmic function, SEP-Q2, and SEP-Q3. Besides, vardenafil significantly decreased the IIEF- erectile function *versus* sildenafil. There was no significant difference in IIEF-erectile function between vardenafil and tadalafil. Vardenafil significantly increased IIEF-erectile function *versus* sertralin. But due to the limited number of included studies, more studies are needed to confirm the efficacy of vardenafil *versus* sildenafil, vardenafil *versus* sertralin, and vardenafil *versus* tadalafil.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions

HW and ZJ have made substantial contributions to conception and design of the study, written the manuscript; BC, ZH and XZ searched literature, extracted data from the collected literature and analyzed the data; HW revised the manuscript; All authors approved the final version of the manuscript.

Disclosures

Hai Wang, Boda Cao, Zhongming Huang, Xin Zhao and Zhigang Ji have nothing to disclose.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res, 2001. **13**(4): p. 192-9.

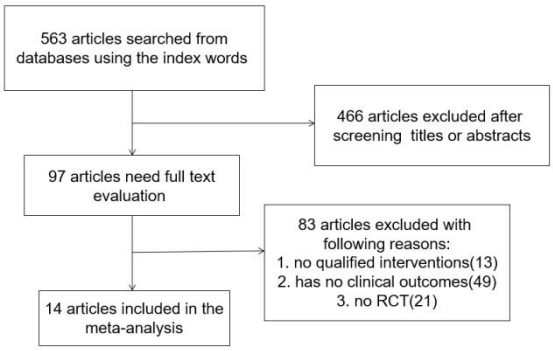

Figure 1. Literature search and selection strategy

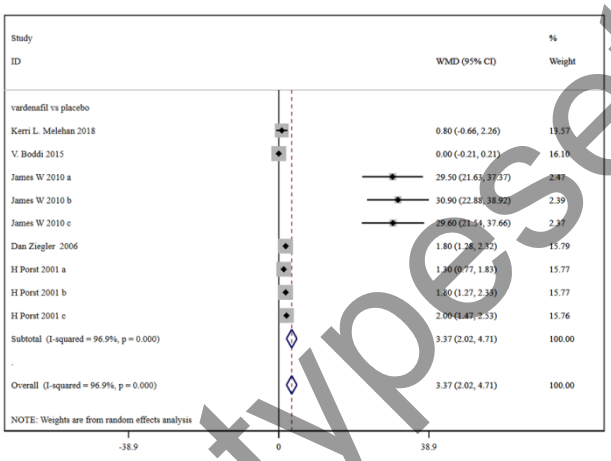

Figure 2. Forest plot for IIEF-overall satisfaction

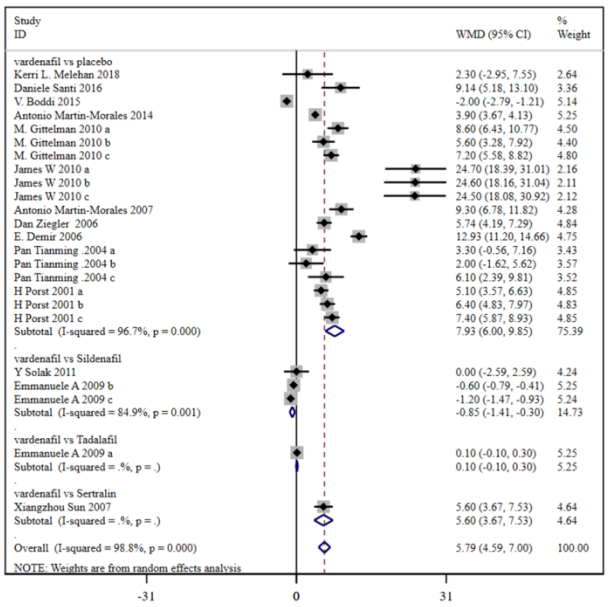

Figure 3. Forest plot for IIEF-erectile function

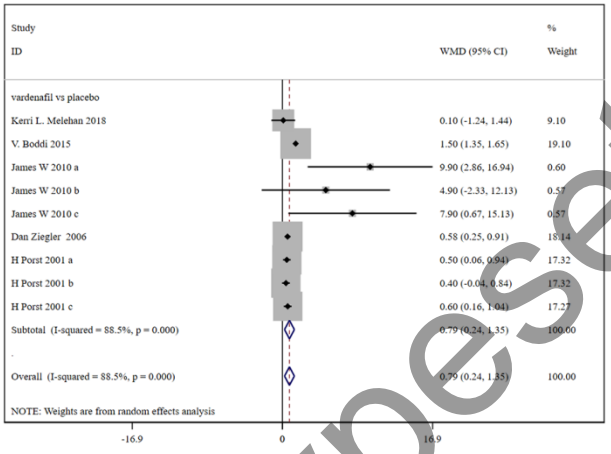

Figure 4. Forest plot for IIEF-sexual desire

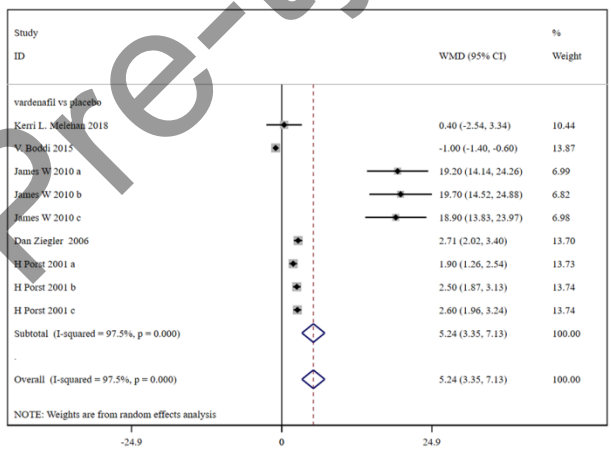

Figure 5. Forest plot for IIEF-intercourse satisfaction

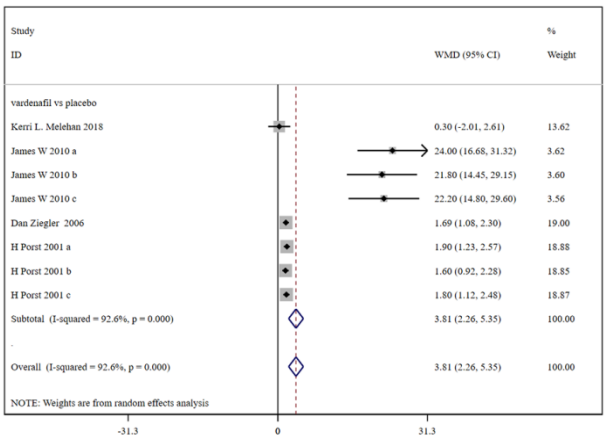

Figure 6. Forest plot for IIEF-orgasmic function

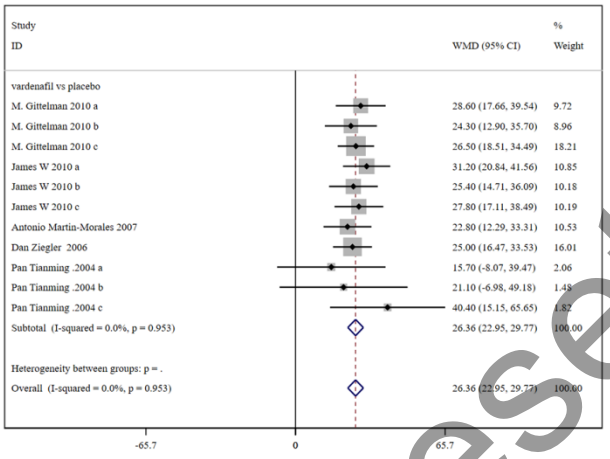

Figure 7. Forest plot for SEP-Q2

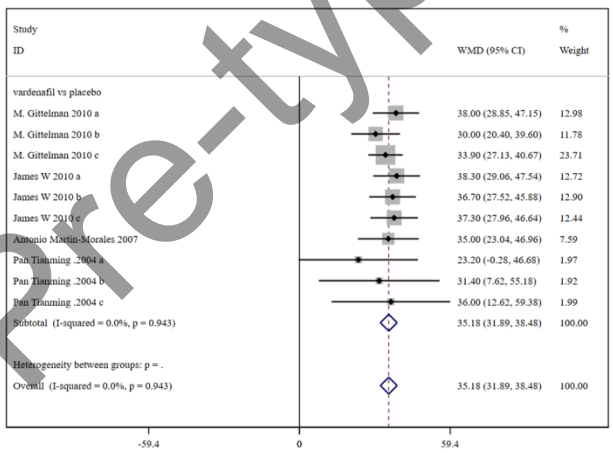

Figure 8. Forest plot for SEP-Q3

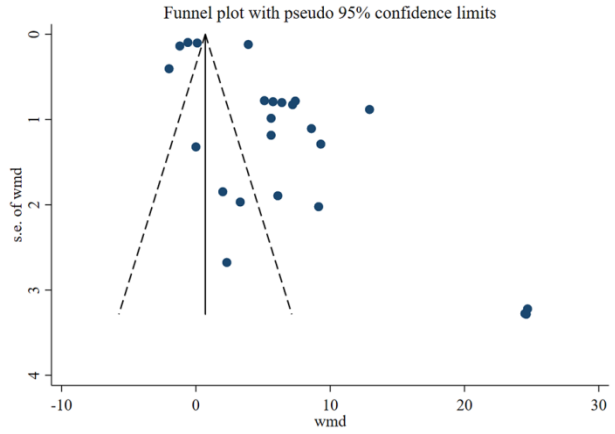

Figure 9. Funnel plot analysis of the included studies

Table 1 The basic characteristics description of included studies

ly	Jadad score	Intervention		No. of patients		Age	
		T	C	T	C	T	C
ehan 2018	4	10 mg daily vardenafil	placebo	20	21	54.8	55.7
nti 2016	4	Vardenafil 10mg twice-daily	placebo	26	28	-	-
i 2015	4	vardenafil	placebo	11	19	44.6	46.5
Morales 2014	4	vardenafil orodispersible tablets (ODT) 10 mg on-demand	placebo	84	88	58.7	56.2
2011	3	vardenafil	sildenafil	32	32	47.2	47.2
an 2010 a	4	10 mg vardenafil ODT	placebo	83	80	52.5	53.5
an 2010 b	4	10 mg vardenafil ODT	placebo	84	80	70.3	70.5
an 2010 c	4	10 mg vardenafil ODT	placebo	167	160	-	-
2010 a	4	vardenafil 10 mg	placebo	94	97	-	-
2010 b	4	vardenafil 10 mg	placebo	93	87	-	-
2010 c	4	vardenafil 10 mg	placebo	93	87	-	-
A 2009 a	4	Vardenafil 20 mg	Tadalafil 20 mg	14	22	58.1	56.3
A 2009 b	4	Vardenafil 20 mg	Sildenafil 50 mg	14	22	58.1	57.1
A 2009 c	4	Vardenafil 20 mg	Sildenafil 100 mg	14	19	58.1	56.7

Sun 2007	3	vardenafil 20mg	Sertralin 50mg	30	30	-	-
Morales 2007	3	flexible-dose vardenafil（The initial dose of vardenafil was 10 mg,which could be titrated up to 20 mg or down to 5 mg at weeks 4 and 8）	placebo	61	60	52.5	52.5
er 2006	3	10 mg vardenafifil (5 mg in patients aged 65 years and older)	placebo	154	149	50.2	50.4
r 2006	3	vardenafil	placebo	39	21	48	50
ng 2004 a	3	vardenafil 5 mg	placebo	22	22	-	-
ng 2004 b	3	vardenafil 10 mg	placebo	22	22	-	-
ng 2004 c	3	vardenafil 20 mg	placebo	22	22	-	-
2001 a	3	vardenafil 5 mg	placebo	146	147	53.3	51.9
2001 b	3	vardenafil 10 mg	placebo	140	147	52.2	51.9
2001 c	3	vardenafil 20 mg	placebo	147	147	51.6	51.9