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Review – Sexual Medicine

Comparative Effectiveness and Safety of Oral Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction: A Systematic Review and Network Meta-analysis

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Abstract

Context: Phosphodiesterase type 5 inhibitors (PDE5-Is) are currently the first-line therapy for erectile dysfunction (ED), but available studies investigating the comparative effects of different PDE5-Is are limited.
Objective: To compare the efficacy and safety of different classes of oral PDE5-Is for ED.
Evidence acquisition: A systematic search was performed in PubMed, Cochrane Library, and Embase to identify randomized controlled trials that compared different PDE5-Is or PDE5-Is with a placebo for ED. The methodological quality of included studies was appraised with the Cochrane Collaboration bias appraisal tool, and the quality of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation system.
Evidence synthesis: A total of 118 trials (31 195 individuals) were included. There was no major difference in the results between the traditional meta-analysis and the network meta-analysis. Network meta-analysis demonstrated that PDE5-Is were superior to placebo to improve erectile function. Compared with tadalafil (relative risk [RR]: 0.61; 95% confidence interval [CI], 0.33–0.90) and vardenafil (RR: 0.63; 95% CI, 0.35–0.92), avanafil was less effective on Global Assessment Questionnaire question 1. Tadalafil was more effective than vardenafil (mean difference [MD]: 1.49; 95% CI, 0.50–2.50) and udenafil (MD: −1.84; 95% CI, −3.31 to −0.33) as measured by the erectile function domain of the International Index of Erectile Function. For all efficacy outcomes, the absolute effects and the rank tests indicated that tadalafil and vardenafil were the most effective agents. After adjusting for dosage, the conclusion remained the same. Safety analysis showed there was no major difference among different agents.
Conclusions: In recommended doses, oral PDE5-Is are more effective than placebo for ED, and tadalafil seems to be the most effective agent, followed by vardenafil. PDE5-Is are generally safe and well tolerated, and there is no major difference on the safety profile.

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1. Introduction

Erectile dysfunction (ED), defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse [1], is one of the most common sexual disorders among men. Past surveys indicate that nearly 50% of men reported some degree of ED [2–4], and about 65% were not satisfied with the hardness of their erection [4]. ED also causes a huge economic burden to society. According to the US National Health and Nutrition Examination Survey, the annual costs of ED treatment in the United States could reach $15 billion if all patients sought medical care [5].

Current therapies for ED include phosphodiesterase type 5 inhibitors (PDE5-Is), hormones, vacuum constriction devices, intraurethral suppositories, intracavernosal injections, and surgery [6,7]. Oral PDE5-Is including sildenafil, tadalafil, and vardenafil are currently the first-line therapy for ED [6,7]. Four PDE5-Is (sildenafil, vardenafil, tadalafil, and avanafil) are approved worldwide, and two agents (udenafil and mirodenafil) are approved only in Korea [8]. Lodenafil, a new PDE5-I, is still undergoing clinical trials.

PDE5-Is block the PDE5 enzyme that degrades cyclic guanosine monophosphate and thus results in the relaxation of smooth muscle in the corpus cavernosum, and finally increased blood flow and erection [9–11]. A large number of studies were conducted after the introduction of PDE5-Is (sildenafil) in 1998. These studies demonstrated that oral PDE5-Is are highly effective and well tolerated for ED patients [9,12]. However, available studies investigating the comparative effects of different PDE5-Is are limited. Given the variety of PDE5-Is available for prescription to ED patients and the limited evidence regarding the comparative efficacy of different PDE5-Is, it is hard for physicians to prescribe the best medicine.

Network meta-analysis, in the context of a systematic review, is a meta-analysis in which multiple treatments are compared using both direct comparisons of interventions within randomized controlled trials and indirect comparisons across trials based on a common comparator [13,14]. In this study, we carried out a systematic review and network meta-analysis to compare the efficacy and safety between different PDE5-Is for the treatment of ED in a broad spectrum of the population.

2. Evidence acquisition

2.1. Data sources and searches

We carried out an electronic search of Cochrane Library (Issue 4, 2012), PubMed (1966 to April 2012), and Embase (1984 to April 2012). The search strategy consisted of three parts (strategies for PDE5-Is, ED, and a specific filter for clinical trials) using the following keywords in combination with both Medical Subject Headings terms and text words: *phosphodiesterase inhibitor, tadalafil, sildenafil, vardenafil, lodenafil, mirodenafil, udenafil, erectile dysfunction, impotence*, and *randomized controlled trial*. There was no limitation on publication status or language. We also searched the metaRegister and World Health Organization International Clinical Trials Registry Platform for ongoing studies. Reference lists of the included studies were checked manually to identify further studies.

2.2. Studies selection

We included randomized controlled trials that compared different oral PDE5-Is or oral PDE5-Is versus placebo for ED. The patients in this study were limited to the broad-spectrum population diagnosed with ED. Studies that examined the use of oral PDE5-Is in special population groups (eg, men with diabetes mellitus or hypertension) were excluded. The primary outcomes for this study were the Global Assessment Questionnaire question 1 (GAQ-1), and change from baseline to study end in the International Index of Erectile Function-Erectile Function domain score (IIEF-EF). The secondary outcomes included (1) change from baseline to study end in Sexual Encounter Profile question 2 (SEP-2), (2) change from baseline to study end in Sexual Encounter Profile question 3 (SEP-3), and (3) adverse events (AEs) that included the number of treatment-related adverse events, serious or severe adverse events, patients who experienced any adverse event (AE), and specific AEs. Trials were eligible if one of these outcome measures was reported. Study eligibility was independently determined by two authors. The authors evaluated the eligibility of remaining studies by examining the titles, abstracts, and full articles progressively. Discrepancies were resolved by discussion.

2.3. Data extraction and quality assessment

Data were extracted independently by two authors using a standard form. Data extracted included study characteristics (eg, title, publication time, and patients number), patient characteristics (eg, age, height, weight, race, ED severity, and ED duration), intervention, control, method (eg, randomization, blinding, and loss to follow-up), and outcomes (eg, estimates, standard error, and p value). Discrepancies were resolved by discussion. The authors of original studies were consulted for missing information where necessary.

Both methodological quality and quality of the evidence were assessed independently by two authors. The methodological quality of included studies was appraised with the Cochrane Collaboration bias appraisal tool [15]. The quality of evidence on GAQ-1, IIEF-EF, SEP-2, and SEP-3 was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [16,17]. The quality of evidence was presented as follows: (1) *high*, indicating further research is very unlikely to change our confidence in the estimated effect; (2) *moderate*, indicating further research is likely to have an important impact on our confidence in the estimated effect and may change the estimate; (3) *low*, indicating further research is very likely to have an important impact on our confidence in the estimated effect and is likely to change the estimate; and (4) *very low*, indicating that we are very uncertain about the estimate [16,17].