TITLE: Phosphodiesterase 5 Inhibitors: A Review of the Clinical Effectiveness and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES:

Erectile dysfunction is the most commonly encountered form of sexual dysfunction in men and can cause significant distress, impaired quality of life, and have a negative effect on overall self-esteem and intimate relationships.[1] Risk factors for erectile dysfunction include older age, cardiovascular disease, smoking, diabetes, pelvic irradiation or surgery (e.g., radical prostatectomy), hypertension, medications (e.g., antidepressants such as selective serotonin reuptake inhibitors), and psychiatric conditions (e.g., anxiety, depression).[1]

There are three oral medications currently on the market in Canada belonging to the phosphodiesterase 5 (PDE-5) inhibitor class: sildenafil, tadalafil, and vardenafil.[2-4] These medications are all approved for use in the treatment of erectile dysfunction.[2-4] Sildenafil, tadalafil and vardenafil, are approved for use to be taken orally on an as needed basis a short period of time prior to intercourse (30 to 60 minutes; referred to as on demand dosing).[2-4] Tadalafil is also approved for once daily administration on a regular basis for the treatment of erectile dysfunction, but at a lower dose (10mg to 20mg for on demand dosing compared to 2.5mg to 5mg for the daily dosing).[4] In addition to its approved indication of the treatment of erectile dysfunction, PDE-5 inhibitors are also used intermittently to treat antidepressant induced sexual dysfunction[5] and following retropubic prostatectomy to reduce the risk of impotence.[6]

Systematic reviews and meta-analyses have demonstrated the efficacy of the three PDE-5 inhibitors compared to placebo in the treatment of erectile dysfunction.[7,8] Information on the comparative clinical and cost-effectiveness of the three PDE-5 inhibitors in treating erectile dysfunction could aid in making formulary decisions and in individual patient management. Further, information on the comparative clinical efficacy of the three PDE-5 inhibitors in specific situations such as following prostatectomy or to treat antidepressant induced sexual dysfunction could also inform such decisions. This report will review information about the comparative clinical effectiveness and cost-effectiveness of PDE-5 inhibitors.

RESEARCH QUESTIONS:

1. What is the comparative clinical effectiveness of the intermittent use of phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction?

2. What is the comparative clinical effectiveness of the intermittent use of phosphodiesterase 5 inhibitors for the treatment of male and female sexual dysfunction due to the pharmacological treatment of major depressive disorder?

3. What is the clinical effectiveness and duration of treatment of daily use of phosphodiesterase 5 inhibitors following post radical retropubic prostatectomy?

4. What is the cost-effectiveness of the daily use of low dose phosphodiesterase 5 inhibitors compared to the usual intermittent dose for patients with erectile dysfunction?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 6, 2010) University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and June 22, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies containing safety data**,** economic studies, and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs and non-randomized studies.

SUMMARY OF FINDINGS:

This rapid response report was initially intended to focus on the adult population aged 18 to 65 years, but there was only one study that restricted enrollment to this age group. As such, the report was not restricted to this age group. One relevant health technology assessment (HTA) report,[9] four systematic reviews or meta-analyses,[6,8,10,11] two randomized controlled trials (RCTs)[12,13] and one non-randomized study containing safety data[14] were identified and summarized in this report. Two other relevant RCTs were identified, but were included in the HTA report, so were not summarized in this rapid response review.[15,16] Two additional studies (one RCT and one non-randomized study) included sildenafil, vardenafil, and tadalafil as treatment alternatives, but did not provide comparative data.[17,18] Studies of the efficacy of PDE-5 inhibitors in the management of antidepressant associated sexual dysfunction were identified, but compared a single PDE-5 inhibitor to placebo and therefore are not included.[19-22] No guidelines or economic studies were identified.

Several studies used the International Index of Erectile Function (IIEF) as an outcome measure. The IIEF is a 15 item questionnaire with five domains: Erectile Function, Orgasmic Function, Sexual Desire, Intercourse Satisfaction and Overall Satisfaction.[23] Domain and total scores

(maximum of 75 points) can be calculated.[23] A one point and two point difference on the individual questions and domain scores, respectively, are considered clinically relevant.[12]

Male Erectile Dysfunction

Health technology assessments

In 2009 the Agency for Healthcare Research and Quality (AHRQ) carried out a technology assessment of the efficacy and harms of pharmacotherapy for the management of erectile dysfunction.[9] The results of this review were also published in Annals of Pharmacotherapy.[7] The assessment addressed a number of research questions, one of which was the comparative efficacy of the PDE-5 inhibitors. English language RCTs involving adults aged 18 years and older with ED (with or without comorbidities) were eligible for inclusion. Further, to be included studies had to involve an assessment of oral or injected medication for male erectile dysfunction compared to placebo or another active treatment. For studies of harm, non-randomized controlled trials and observational studies were also included. A systematic approach was used to search the relevant literature, select studies for inclusion, abstract relevant data, and assess study quality.

Three of the included studies were crossover trials with tadalafil, and sildenafil treatment arms. One included study had tadalafil, sildenafil, and vardenafil treatment arms. The studies were described as being of low quality. In the four studies, differences in efficacy between PDE-5 inhibitors were inconsistent, nonsignificant, or small in magnitude. A larger proportion of patients preferred treatment with tadalafil than with sildenafil or vardenafil. Differences in the incidence of adverse events between PDE-5 inhibitors were not significant, with the percentage of patients experiencing adverse effects with sildenafil ranging from 24.0% to 34.0%, tadalafil ranging from 28.0% to 35.0% and vardenafil being 27.0%. No conclusions specific to the comparative efficacy of the PDE-5 inhibitors were made; however the authors indicated that more studies comparing the efficacy of PDE-5 inhibitors were needed. This review appeared to be rigorous in its conduct, but was limited by the available evidence and its quality. Quality of life endpoints were not reported. Generalizability of the results to the target population of adults aged 18 years to 65 years is not clear.

Systematic Reviews and Meta-Analyses

A 2008 systematic review of PDE-5 inhibitors for erectile dysfunction was carried out to assess methods of identifying and exploring bias in meta-analyses.[8] Indirect comparisons of the efficacy of PDE-5 inhibitors were also reported. Randomized trials of men with erectile dysfunction that compared the efficacy or safety of sildenafil, tadalafil, and vardenafil to placebo or another PDE-5 inhibitor were included. An eight-item assessment of methodological quality was used. One person selected studies for inclusion and abstracted data. Data abstraction was checked by a second person.

Eighty-eight placebo-controlled or comparative studies were included (sildenafil: n=52; tadalafil: n=19; vardenafil: n=16; more than one PDE-5 inhibitor treatment arm: n=1). The authors of the review described the methodological quality of the studies as poor. The average age of study participants was not reported. The three PDE-5 inhibitors were described as highly effective, with no differences between the three drugs being observed on a general efficacy question and

score on the International Index of Erectile Function (IIEF). Outcomes for safety data were not reported. The authors did not make any conclusions about the efficacy of the PDE-5 inhibitors since this was mainly a statistical methods study.

A 2006 meta-analysis evaluated the efficacy of PDE-5 inhibitors in erectile dysfunction.[10] To be included, studies had to use the highest fixed dosages for sildenafil, tadalafil, or vardenafil and be randomized, double-blind, placebo-controlled and parallel-group in design. Further, the group of included patients had to be broad spectrum sample (not just patients with selected medical conditions) and outcomes had to be measured using the IIEF. A systematic approach was used to search the relevant literature, select studies for inclusion, abstract data, and assess study quality. Quality of the studies was determined using the Jadad Score. The Erectile Function Domain Score of the IIEF was the outcome measure used in the analysis which involved an indirect comparison of the three PDE-5 inhibitors.

There were 14 studies included in the meta-analysis (sildenafil: n=3; tadalafil: n=8, and vardenafil: n=3). The average age of study participants ranged from 52 years to 63 years. The quality of the studies was described by the authors as good. Pooled improvements on the IIEF were as follows: sildenafil 9.65 points (95% CI: 8.50 to10.79), tadalafil 8.52 points (95% CI: 7.61 to 9.42), and vardenafil 7.50 points (95% CI: 6.50, 8.50) points, respectively. The difference between sildenafil and vardenafil (2.15 points) was statistically significant (p=0.006) in favour of sildenafil. The authors concluded that sildenafil might be more efficacious than vardenafil, but that caution should be taken in this interpretation and that true head-to-head comparisons were needed. It is not clear if this result would be generalizable to less than maximal dosages of the PDE-5 inhibitors or to other measures of efficacy. No safety data were presented.

A 2005 systematic review and meta-analysis compared the clinical efficacy of PDE-5 inhibitors using an indirect comparisons methodology for meta-analysis.[11] The rationale for this approach was that no direct no head-to-head trials had been published by 2005. RCTs that used any one of the three oral PDE-5 inhibitors (tadalafil, sildenafil, or vardenafil) in men with erectile dysfunction were included. As well, studies had to have home-based settings, a minimum duration of three weeks, at least 10 people per group and relevant outcome data. Studies with a quality score of two or higher on a five point scale (Jadad Scale) were included. A systematic approach was used to search the relevant literature, select studies for inclusion, abstract relevant data, and assess study quality. The indirect comparisons were made when there was a common comparator, the dosages used were therapeutically equivalent, and the outcome measure was the same. For most outcomes, these criteria could not be satisfied.

There were 35 studies of sildenafil, eight studies of tadalafil, and seven studies of vardenafil, all of which compared the PDE-5 inhibitor to placebo. The average age of study participants was reported to be in the mid-50s or older. The actual age ranges for individual studies were not reported. Studies ranged from four weeks to 12 weeks in duration. The pooled rate of successful intercourse was 65% for sildenafil, 62% for tadalafil, and 59% for vardenafil whereas the placebo rates were 23% to 28%. The pooled rate of improved erections was 76% for sildenafil, 75% for tadalafil, and 71% for vardenafil, compared to the placebo rates of 22% to 24%. The withdrawal rate from any cause was 8% for sildenafil, 13% for tadalafil, and 20% for vardenafil. The authors concluded that for common outcomes, the efficacy of the PDE-5 inhibitors was similar. One limitation to the findings of this review was that the majority of studies of tadalafil and vardenafil excluded patients who previously did not respond to treatment with

PDE-5 inhibitors while sildenafil studies did not. The authors stated that this difference in enrolment criteria could potentially make tadalafil and vardenafil appear to be more effective in indirect comparisons.

Randomized Controlled Trials

A 2009 RCT[13] assessed the comparative efficacy of fixed dosages of sildenafil (50 mg or 100 mg), tadalafil (20mg), and vardenafil (20mg) after eight weeks of open-label treatment (Table 1). The study was carried out in eight sexual medicine centers in Italy. Patients were included who were male, over 18 years old with erectile dysfunction for a minimum of six months. As well, patients were included if they had scores of less than 20 on the IIEF and were in stable, heterosexual relationships for six months or longer. There were numerous exclusion criteria:

> "any unstable, inadequately controlled medical or psychiatric condition or substance-abuse disorder; penile anatomical abnormalities that would significantly impair erectile function; primary hypoactive sexual desire; erectile dysfunction after spinal chord injury, radical prostatectomy, and pelvic surgery; retinitis pigmentosa; non-arteritic anterior ischemic optic neuropathy, moderate to severe renal or liver impairment; angina or severe congestive heart failure; stroke; use of nitrates, anticoagulants, androgens, trazodone, antiandrogens, cytochrome CYP450 3A4 inhibitors, or any investigational drug within 30 days of visit 1 (wash-out period); serum total testosterone <12 nmol/L; and known hypersensitivity to any component of the investigational medicinal products."p.2550[13]

For the first eight weeks of the study, 134 patients were randomly assigned to one of the four treatment arms. Following the initial eight weeks of treatment, physicians could select any of the four treatments for an additional three months and then again for another six months, but only the outcomes of first eight weeks of treatment were presented in the report. Relevant outcome measures included the IIEF Q15 (question 15) and IIEF Q1 to Q5 (questions one to five). Physiological parameters were also assessed. All groups improved from baseline to follow-up and there were no statistically significant differences between groups on the efficacy outcomes (Table 2). The authors concluded that there were no differences between PDE-5 inhibitors in terms of subjective perception treatment benefit. Limitations to this study include the use of a fix-dose regimen (rather than titrating to a treatment response), its open-label design, and a 25% drop-out rate. Generalizability of these findings could be affected by the numerous exclusion criteria. As well, while the majority of patients were under the age of 65 years some were not, which could affect the generalizability to the population under age 65 years.

A 2006 a randomized, double-blind, crossover study assessed the comparative safety and efficacy of vardenafil 20 mg (n=530) and sildenafil 100 mg (n=527) in treating erectile dysfunction in patients with diabetes, hypertension, or hyperlipidemia (Table 1).[12] The drugs were administered as fixed dosages. Data were pooled from two studies (one carried out in the United States and one carried out in Mexico and Europe). In these studies patients were randomly assigned to one of the two PDE-5 inhibitors for four weeks, then underwent a one week washout period, followed by four weeks of treatment with the alternate drug. Efficacy of the medication was assessed using the IIEF, Sexual Encounter Profile (SEP) diary questions SEP2 and SEP3, a Global Assessment Question (GAQ), and Treatment Satisfaction Scale (TSS). Adverse event data were also collected. Patients were included if they were males aged 18 years and older with a history of erectile dysfunction for at least six months and also had one of the previously stated comorbidities. There were a number of exclusion criteria as follows:

> "any unstable medical or psychiatric condition or substance-abuse disorder; penile anatomical abnormalities that would significantly impair erectile function; primary hypoactive sexual desire; ED after spinal chord injury; radical prostatectomy; retinitis pigmentosa; positive test for hepatitis B surface antigen or hepatitis C; unstable angina pectoris or severe congestive heart failure; myocardial infarction, stroke, ischemia (except stable angina), or life-threatening arrhythmia within the previous 6 months; atrial tachyarrhythmia with a heart rate of > 100 beats per minute; severe chronic liver disease or liver function abnormalities; clinically significant chronic hematological disease; significant peptic ulcer disease within the previous year; resting hypotension or hypertension; symptomatic postural hypotension within 6 months of Visit 1; uncontrolled diabetes mellitus (hemoglobin A1c > 12%); malignancy within the previous 5 years (other than skin cancer); inadequately treated hypothyroidism or hyperthyroidism; ED induced by antihypertensive and/or antihyperlipidemic medication (applicable to centers in Germany only); use of concomitant medications such as any therapy for ED within 4 weeks prior to Visit 1, nitrates, and anticoagulants; androgens, trazodone, or anti-androgens, inhibitors of cytochrome CYP450 3A4, any investigational drug within 30 days of Visit 1; serum total testosterone > 10% below the lower limit of normal;serum creatinine > 2.0 mg/dL; and known hypersensitivity to any component of the investigational medication."(p.1039)[12]

Efficacy outcomes generally favoured vardenafil over sildenafil but the clinical significance of these differences were not clear (Table 1). In addition to the outcomes reported in Table 1, fourteen of 15 individual items on the IIEF scored higher for vardenafil than sildenafil. Change scores on 12 of 19 questions on the TSS were statistically significantly higher in the vardenafil groups than in the sildenafil group. Treatment-related adverse drug reactions did not differ between groups. Headache was the most common adverse reaction, occurring in 10% of patients treated with vardenafil and 11% treated with sildenafil. The authors concluded that vardenafil was not inferior to sildenafil in terms of overall preference and was nominally superior in terms of efficacy. Generalizability of this study could be limited by the exclusion criteria. Further, the average age of participants was 57.9 years with a standard deviation of 9.8, suggesting that a considerable proportion would be over the age of 65 years. Limitations to this study include the lack of dose titration and the lack of longer-term data.

Table 1: RCTs of comparative effectiveness of PDE-5 inhibitors in erectile dysfunction not included in a meta-analysis or systematic review

Study Authors, Year of Publication	Sample	Interventions	Duration of treatment	Outcome
Jannini et al., 2009[13]	Tadalafil 20 mg 56.3 years (95% CI 49.7–64.2) n=35 Sildenafil 50 mg 57.1 years (95% CI 50.1–63.7) n= 34 Sildenafil 100 mg 56.7 years (95% CI 50.2–65.1) n= 32	Tadalafil 20 mg Sildenafil 50 mg Sildenafil 100 mg Vardenafil 20 mg	8 weeks	Statistically significant improvement in IIEF score over baseline in all groups; no statistical differences between groups Change scores: Tadalafil 20 mg IIEF Q15: 0.90 (95% CI: 0.6–1.9) IIEF Q1 to Q5: 2.18 (95% CI: 1.9–4.6) Sildenafil 50 mg

Study Authors, Year of Publication	Sample	Interventions	Duration of treatment	Outcome
	Vardenafil 20 mg 58.1 years (95% CI 51.2–65.2) n= 33			IIEF Q15: 1.09 (95% CI: 0.10–1.21) IIEF Q1 to Q5: 2.86 (95% CI: 2.3–5.6) Sildenafil 100 mg IIEF Q15: 1.16 (95% CI: 0.44–1.04) IIEF Q1 to Q5: 3.52 (95% CI: 2.1–4.4) Vardenafil 20 mg IIEF Q15: 1.28 (95% CI: 0.51–1.89) IIEF Q1 to Q5: 2.28 (95% CI: 2.3–4.7)
Rubio-Aurioles et al., 2006[12]	Mean (SD) Age: 57.9 years (9.8)	Sildenafil 100 mg n=527 Vardenafil 20 mg n=530	4 weeks of each drug	Change from baseline in total IIEF score: Vardenafil 20 mg: 10.00 Sildenafil 100 mg: 9.40 p = 0.01 Change from baseline in IIEF Intercourse satisfaction domain score Vardenafil 20 mg: 4.41 Sildenafil 100 mg: 4.17 p = 0.01 Change from baseline in IIEF overall satisfaction score Vardenafil 20 mg: 2.80 Sildenafil 100 mg: 2.65 p = 0.04 SEP2 “Were you able to insert your penis into your partner’s vagina?” Vardenafil 20 mg: 83.90% Sildenafil 100 mg: 82.28% p = 0.04 SEP3 “Did your erection last long enough for you to have successful intercourse?” Vardenafil 20 mg: 74.44% Sildenafil 100 mg: 71.55% p = 0.0038

Study Authors, Year of Publication	Sample	Interventions	Duration of treatment	Outcome
				GAQ "Has the treatment you have been taking over the past 4 weeks improved your erections? Vardenafil 20 mg: 58.2% Sildenafil 100 mg: 41.8% p=not reported

IIEF: International Index of Erectile Function

Nonrandomized Studies

A 2009 nonrandomized study was carried out in order to determine whether tadalafil (the PDE-5 inhibitor with the longest half-life) had more prolonged or severe adverse effects compared to PDE-5 inhibitors with shorter half-lives (sildenafil and vardenafil) in 409 men with erectile dysfunction.[14] Patients who had not been previously treated with a PDE-5 inhibitor were recruited from a specialist andrology clinic and were permitted to choose one of the three PDE-5 inhibitors after a counseling session. Maximal doses of the PDE-5 inhibitors were routinely used in the clinic, but the specific or average dosages were not described in the report. Bother from adverse effects was assessed using a 0 (no bother) to 100 (worst bother imaginable) visual analog scale (VAS) after three months of treatment.

The average age of study participants was 56.9 years. The most common treatment was with tadalafil (52.3%), followed by sildenafil (31.3%) and vardenafil (16.4%) Differences between drugs in the overall prevalence of adverse effects were not statistically significant; however, the duration of adverse effects tended to be longer in patients treated with tadalafil. The average duration of any adverse effect was 14.9 hours with tadalafil, 7.7 hours for vardenafil, and 3.9 hours for sildenafil. Only the difference in the duration of headache reached statistical significance. Approximately 3% of those taking sildenafil experienced adverse effects with a duration exceeding 12 hours, compared to 30% of those taking tadalafil (OR = 6.1, 95% CI: 1.3 to 28.2) and 19% of those taking vardenafil (OR = 2.5; 95% CI: 0.4 to 16.8). Statistically significant differences in the prevalence of flushing and vision were found and were highest with sildenafil. Mean VAS scores did not differ between the three PDE-5 inhibitors (31.1 mm for sildenafil, 36.6 mm for tadalafil, and 40.8 mm for vardenafil). The authors concluded that the risk of prolonged adverse effects was higher with tadalafil; however, the level of bother associated with these adverse effects did not differ between the PDE-5 inhibitors. The non-randomized assignment of treatments is one limitation of this study.

Daily Use Following Prostatectomy

Systematic Reviews and Meta-Analyses

A 2009 systematic review evaluated the safety and efficacy of PDE-5 inhibitors for the treatment and prevention of ED following radical prostatectomy.[6] Randomized, placebo controlled studies that had been published as full-text articles between the time period of January 1997 and June

2008 were included in the review. The selected studies were summarized as a narrative review. A meta-analysis of the data was not performed.

Four studies were identified and included that assessed the efficacy of a PDE-5 inhibitor following radical prostatectomy for the prevention of erectile dysfunction. Of these studies, two used daily or nightly administration, one used on-demand dosing, and one used both. The three studies with treatment arms that had daily or nightly administration are summarized in Table 2. From these results, the authors concluded that the use of PDE-5 inhibitors following radical prostatectomy is appealing, but more RCTs are need to determine the appropriate time to initiate treatment, the dosage regimen, the optimal duration of treatment, and which PDE-5 inhibitor to use.

Table 2: Studies included in the systematic review of daily administered PDE-5 inhibitors for the prevention of erectile dysfunction following radical prostatectomy[6]

Study Authors, Year of Publication	Sample	Intervention and Comparator	Duration of treatment	Outcome
Padma-Nathan et al., 2008[24]	78 men Age not reported	Sildenafil 50mg or 100mg each night vs placebo	36 weeks beginning four weeks after surgery	Normalization of spontaneous erections: 4% placebo versus 27% sildenafil (p=0.0156)
McCullough et al., 2008[25]	54 men (subset of Nathan et al.[24]) Age range: 38 to 67 years	Sildenafil 50mg or 100mg each night vs placebo	48 weeks beginning post-surgery	Percent responders: placebo – 5% sildenafil 50mg – 24% sildenafil 100mg – 33%
Montorsi et al., 2008[26]	628 men Age 18 to 64 years	On demand vardenafil 5mg to 20mg vs. nightly vardenafil 5mg to 10mg or placebo	9-month double-blind treatment period, a two month single-blind washout period, and an optional two month open-label period with on demand vardenafil. Initiation of treatment within 14 days of surgery	No differences between treatments on the International Index of Erectile Function or sexual completion rates were higher in both vardenafil arms compared to placebo after 9 months of treatment. Percent with IIEF scores ≥ 22: Placebo: 24.8% Vardenafil nightly: 32.0% Vardenafil on demand: 48.2% Positive response for SEP3: Placebo: 25.0% Vardenafil nightly: 34.5% Vardenafil on demand: 45.9%

IIEF: International Index of Erectile Function SEP3: Sexual Encounter Profile Question 3

Limitations

There were no studies of the cost-effectiveness of the daily use of low dose PDE-5 inhibitors compared to on demand dosing in patients with erectile dysfunction identified by the literature search. Further, no studies that compared the clinical effectiveness of the intermittent use of PDE-5 inhibitors for the treatment of sexual dysfunction related to antidepressant use were identified.

The identified and included studies generally did not restrict the age of study participants to 18 years to 65 years old, which may limit the generalizability of the results to a population restricted to this age group. Further, many of the studies used fixed dose regimens rather than titrating to a response to therapy. It is not clear if similar results would be observed if the PDE-5 inhibitors were titrated to obtain an adequate response to treatment. The efficacy of the once daily dosing regimen of tadalafil was not assessed relative to other PDE-5 inhibitors in the included studies. The several of the included systematic reviews were based upon indirect comparisons of PDE-5 inhibitors using placebo-controlled RCTs rather than true head-to-head comparisons. It should be noted, however, that the results of the indirect comparisons were similar to head-to-head RCTs.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The majority of the information identified addressed the question about comparative clinical effectiveness of the PDE=5 inhibitors for the treatment of erectile dysfunction. Two meta-analyses demonstrated no significant differences in efficacy of the three PDE-5 inhibitors in the treatment of erectile dysfunction, while another demonstrated that sildenafil might be more efficacious than vardenafil. All three meta-analyses were based upon the statistical method of indirect comparison, not direct head-to-head comparisons. Further, the meta-analysis that found sildenafil to be superior to vardenafil had relatively restrictive inclusion criteria and only looked at maximal fixed dosages of each drug. Two additional RCTs also had conflicting results, one favouring vardenafil over sildenafil and the other demonstrating no difference. The clinical importance of differences in efficacy measures was not stated in the RCT or meta-analysis that demonstrated differences between PDE-5 inhibitors. One observational study suggested that adverse effects might be prolonged with tadalafil, but this did not appear more bothersome to the patients. Overall, the included reports suggest that there are minimal differences between PDE-5 inhibitors in the treatment of erectile dysfunction in men over the age of 18 years.

One systematic review was identified about the use of daily PDE-5 inhibitors following radical prostatectomy. Treatment with daily administered sildenafil or vardenafil for 36 to 48 weeks following radical prostatectomy was effective for prevention of erectile dysfunction. More evidence is needed to determine the optimal timing of treatment, dosage, and duration.

No information was found about the comparative efficacy of PDE-5 inhibitors for the treatment of antidepressant associated sexual dysfunction. In addition, cost-effectiveness evidence of daily low-dose treatment with PDE-5 inhibitors relative to on demand dosing was not found and therefore conclusions cannot be made.

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