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Phosphodiesterase 5 Inhibitors for the Treatment of Erectile Dysfunction: A Trade-off Network Meta-analysis

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Abstract

Context: Erectile dysfunction (ED) is a major health care problem worldwide and phosphodiesterase 5 inhibitors (PDE5Is) are the pharmacological treatment of choice. However, the optimal PDE5I for ED treatment is not known.
Objective: To investigate trade-offs between efficacy and adverse events for various PDE5Is in treating ED.
Evidence acquisition: A review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. Medline, Scopus, reference lists of relevant articles, and systematic reviews were searched. Eligible studies were randomized controlled trials comparing at least one PDE5I for treating ED with placebo or another PDE5I.
Evidence synthesis: We included 82 trials (47 626 patients) for efficacy analysis and 72 trials (20 325 patients) for adverse event analysis. In the trade-off analysis of starting dosages, sildenafil 50 mg had the greatest efficacy but also had the highest rate of overall adverse events. Tadalafil 10 mg had intermediate efficacy but had the lowest overall rate of all adverse events. Vardenafil 10 mg and avanafil 100 mg had similar overall adverse events than sildenafil 50 mg but a markedly lower global efficacy. Udenafil 100 mg had similar global efficacy to that of tadalafil 10 mg but its overall adverse event rates were higher.
Conclusions: This is the first trade-off analysis of the different PDE5Is currently available. For individuals who prioritize high efficacy, sildenafil 50 mg appears to be the treatment of choice. Men wishing to optimize tolerability should take tadalafil 10 mg or switch to udenafil 100 mg in the case of insufficient efficacy.
Patient summary: For patients with erectile dysfunction who wish to prioritize high efficacy, sildenafil 50 mg appears to be the treatment of choice. Men who wish to optimize tolerability should take tadalafil 10 mg or switch to udenafil 100 mg in the case of insufficient efficacy.

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1. Introduction

Men with erectile dysfunction (ED) suffer from a persistent inability to obtain or maintain an erection to allow satisfactory sexual intercourse [1]. ED affects the lives of millions of men worldwide at all ages, but increases in prevalence to 50% among men aged 40–70 yr [2] and may substantially influence quality of life [3].

Phosphodiesterase 5 inhibitors (PDE5Is) are the first-line medication for ED. Seven PDE5Is (avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil, and vardenafil) with different dosages and formulations are currently used and all have well-established efficacy in randomized trials [4–6]. However, despite the use of up-to-date systematic review methods, conventional meta-analyses have fallen short in quantifying and comparing efficacy and adverse events across different drugs, dosages, and formulations. Since different efficacy measures were applied that were inconsistently reported, these summaries did not use all the information available. This is a disadvantage when requiring trade-offs in a decision-analytic context. We propose a method to include all available efficacy measures and use a recently published approach [7] that allows complete assessment of efficacy and side effects across different drugs and direct benchmarking of treatments [7,8].

Here we present this method, a combination of two network meta-analyses and a trade-off approach, in the context of ED and summarize the efficacy and adverse events of currently available PDE5Is.

2. Methods

We performed systematic reviews according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [9]. A review protocol was elaborated that is available on request from the authors.

2.1. Search strategy and selection criteria

We searched (Pre-)Medline (PubMed interface) from inception and Scopus. Electronic searches were limited to clinical trials, reviews, and meta-analyses (date of last search January 22, 2013). We imposed no restrictions on language or year of publication. We searched for additional relevant studies by examining the reference lists of the papers and reviews selected. The search strategies are presented in Supplementary File 1.

We included randomized controlled studies comparing at least one PDE5I with placebo or with another PDE5I in the treatment of ED. We excluded crossover trials, dose titration studies, daily dosing studies, open label studies, and studies that were only available as abstracts. All currently used PDE5Is were considered. In the case of multiple publications on the same patients, the most complete report was chosen.

2.2. Outcome measures and data extraction

Data were extracted in duplicate (L.C. and S.E.L.S.) and a third reviewer (T.M.K.) resolved any disagreements. The authors of included studies were contacted and asked for additional information if required. Dichotomous data were abstracted into two-by-two tables. For continuous data, summary estimates per group (mean, changes in means) with measures of variability (standard deviation [SD], 95% confidence interval [CI]) as available were extracted.

We focused on the following four efficacy outcomes: the change from baseline to study end in the Erectile Function domain score of the International Index of Erectile Function (IIEF-EF) >26 [10–12]; Global Assessment Questionnaire question 1 (GAQ-1); and Sexual Encounter Profile (SEP) [13–15] question 2 (SEP-2) and question 3 (SEP-3). For the side-effects assessment, we considered any side effect or adverse event as reported in the studies. For these outcomes, we summarized all available formulations and dosages. A geometric plot of the comparison network for the studies included is shown in Supplementary Figure 1.

2.3. Statistical analysis

Details of the methods have been published elsewhere [7,8,16].

2.3.1. Meta-analysis of efficacy parameters

If a study did not report on one of the four efficacy endpoints, the result was imputed using a multiple impute procedure (five imputation data sets) using the available outcomes in that specific study to create complete sets for all outcomes. For each study arm we calculated the (overall) outcome by taking the average of the four outcomes. For that new data set of outcomes, we fitted a linear regression model with drug and dosage as covariates using a similar concept as Hasselblad [17] and Berlin et al [18] weighted with the total number of patients in each treatment arm as a substitute for the inverse of the variance. Randomization within each trial was preserved using an indicator covariate for each study. This covariate adjusted for potential differences in patient prognostic profiles and other differences between trials.

2.3.2. Meta-analysis of adverse events

For each treatment arm, the number of patients with a side effect was divided by the total number of patients in that treatment arm. For each participant, we simulated the outcome by sampling from a normal distribution with mean and standard deviation of the outcome in a specific treatment arm as described in the study report. Owing to chance, the mean and standard deviation parameters could differ from the original values. We corrected these differences using a linear transformation. We generated such a data set for all the treatment arms. This approach led to the same likelihood functions as those from the original data. To that new data set, a linear regression model was fitted. Drug and dosage, creating a unique code for each treatment, were entered as covariates. An indicator variable for each study was entered into the model to preserve randomization within each trial. This variable adjusted for all possible differences (patients and design) between studies. It could be argued that the occurrence of an outcome is a Poisson process and the number of side effects in a treatment arm follows a Poisson distribution. Therefore, the analysis was repeated, sampling the total number of side effects from a Poisson distribution.

2.3.3. Trade-off meta-analysis

To provide a trade-off between efficacy and adverse events for each of the treatments assessed, we plotted the overall efficacy parameter against any adverse event from the network meta-analyses. Recommended starting dosages (defined according to manufacturer recommendations and European Association of Urology guidelines [1]) for PDE5Is were highlighted.

Analyses were performed with Stata SE 11.2 (Stata Corp, College Station, TX, USA) and the SPSS 18 (IBM, Chicago, IL, USA) statistics software package.

3. Results

We included 82 trials with a total of 47 626 patients for the efficacy analysis and 72 trials with a total of 20 325 patients

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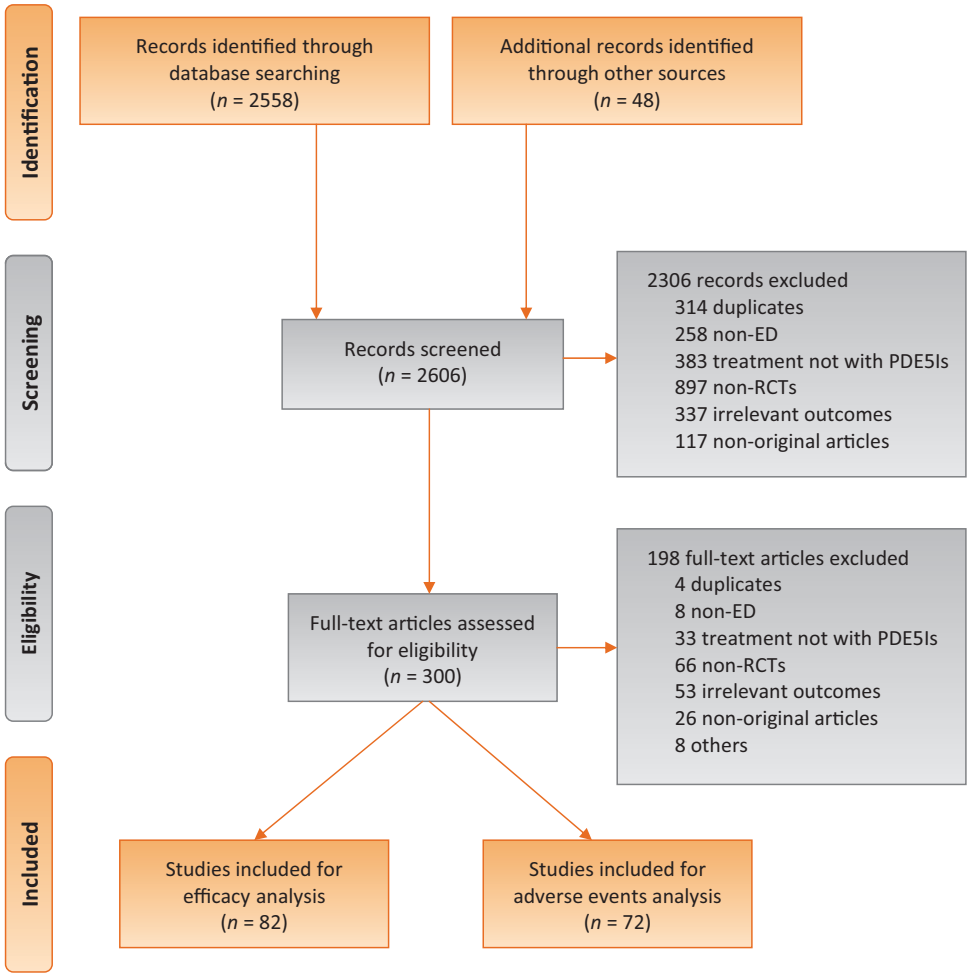

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. ED = erectile dysfunction; PDE5I = phosphodiesterase 5 inhibitor; RCT = randomized controlled trial.

for the adverse events analysis (Supplementary File 2). The study selection procedure is described in Figure 1 and study descriptions for efficacy outcomes and for adverse events are listed in Supplementary Tables 1 and 2. The studies included assessed various dosages of avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil, and vardenafil. In total, 20 different treatments were assessed. The dosages used in most of the trials included were within the recommended dose ranges.

3.1. *Overall efficacy analysis*

A forest plot for overall efficacy is shown in Figure 2. On average, all treatments were significantly more efficient than placebo. In order of relative efficacy against placebo, with starting dosages in bold, these were: **sildenafil 50 mg,** 0.47 (95% CI 0.34–0.59); sildenafil 100 mg, 0.46 (0.35–0.56); tadalafil 25 mg, 0.44 (0.10–0.78); udenafil 200 mg, 0.44 (0.30–0.57); mirodenafil 100 mg, 0.42 (0.28–0.56), sildenafil 25 mg, 0.41 (0.26–0.56); vardenafil 20 mg, 0.39 (0.35–0.44); tadalafil 20 mg, 0.38 (0.32–0.44); **vardenafil 10 mg**, 0.35 (0.32–0.38); **lodenafil 80 mg**, 0.35 (0.17–0.53); **udenafil 100 mg**, 0.33 (0.20–0.47); **tadalafil 10 mg**, 0.33 (0.26–0.40); tadalafil 5 mg, 0.31 (0.19–0.44); tadalafil 2 mg, 0.30 (0.01–0.58); **avanafil 100 mg**, 0.29 (0.15–0.44); avanafil 200 mg, 0.29 (0.18–0.40); **mirodenafil 50 mg**, 0.26 (0.05–0.47); sildenafil 10 mg, 0.26 (0.01–0.50); vardenafil 5 mg, 0.25 (0.17–0.33); and avanafil 50 mg, 0.21 (0.02–0.39).

3.2. *Adverse event/side effect analysis*

A forest plot of 16 treatments for which data on any adverse event were available from the original reports is shown in Figure 3. In order of increasing frequency, with starting dosages in bold, these were: avanafil 50 mg, 8.55% (95% CI 6.74–10.36%); vardenafil 5 mg, 8.68% (7.45–9.91%); **tadalafil 10 mg**, 10.23% (8.49–11.97%); tadalafil 5 mg, 11.39% (9.08–13.71%); **udenafil 100 mg**, 11.42% (9.68–13.15%); sildenafil 25 mg, 12.14% (10.76–13.52%); **mirodenafil 50 mg**, 16.12% (13.40–18.84%); avanafil 200 mg, 16.44% (15.10–17.78%); **avanafil 100 mg**, 18.14% (16.79–19.48%); **vardenafil 10 mg**, 18.15% (17.71–18.58%); **sildenafil 50 mg**, 18.42% (17.98–18.87%); mirodenafil 100 mg, 18.61% (16.74–20.48%); tadalafil 20 mg, 21.01% (19.61–22.41%); sildenafil 100 mg, 21.88% (21.02–22.74%); udenafil 200 mg, 23.57% (21.65–25.48%);

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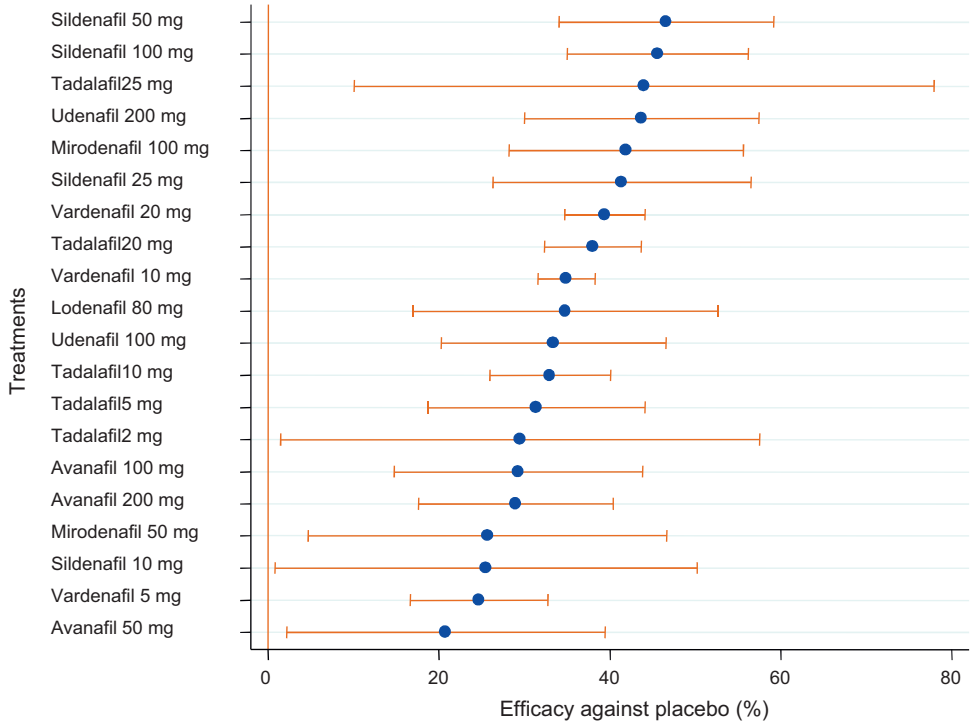

Fig. 2 – Forest plot of overall efficacy (from 82 trials, 47 626 patients) for phosphodiesterase 5 inhibitors at different dosages. Data are shown as mean and 95% confidence interval.

and vardenafil 20 mg, 25.11% (24.40–25.82%). Results from the Poisson sampling were only marginally different.

Data for three salient subgroups (patients with ED due to diabetes, ED due to prostatectomy, and ED due to psychogenic disorder) were too sparse to assess overall efficacy and any adverse events. The data for these subgroups are presented in Supplementary Tables 3 and 4.

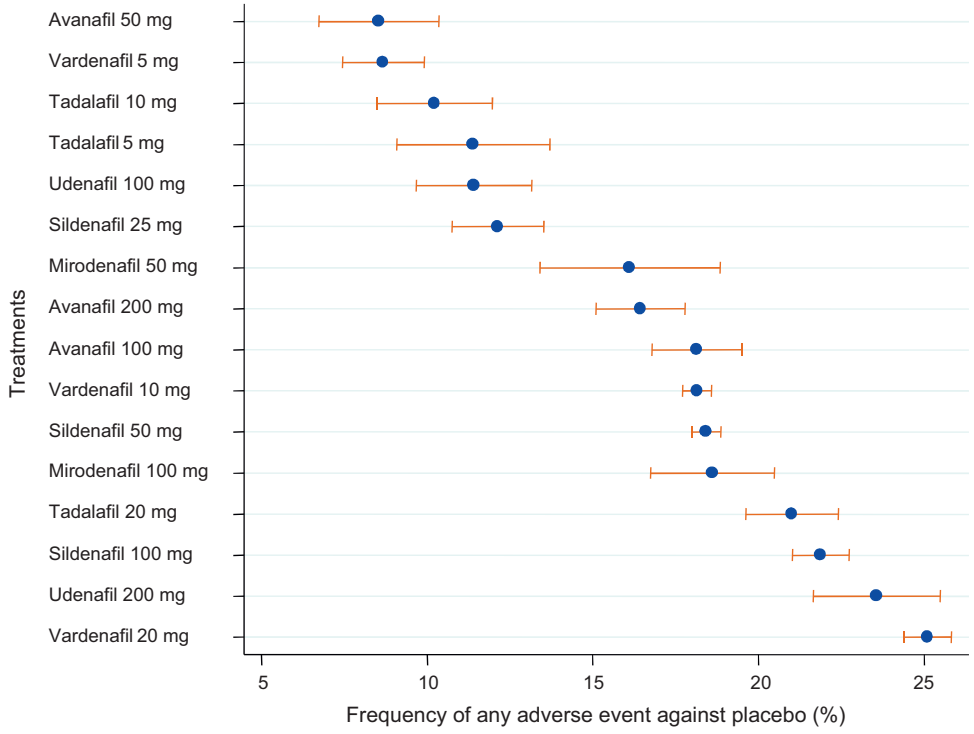

Fig. 3 – Forest plot of any adverse event (from 72 trials, 20 325 patients) for phosphodiesterase 5 inhibitors at different dosages. Data are shown as mean and 95% confidence interval.

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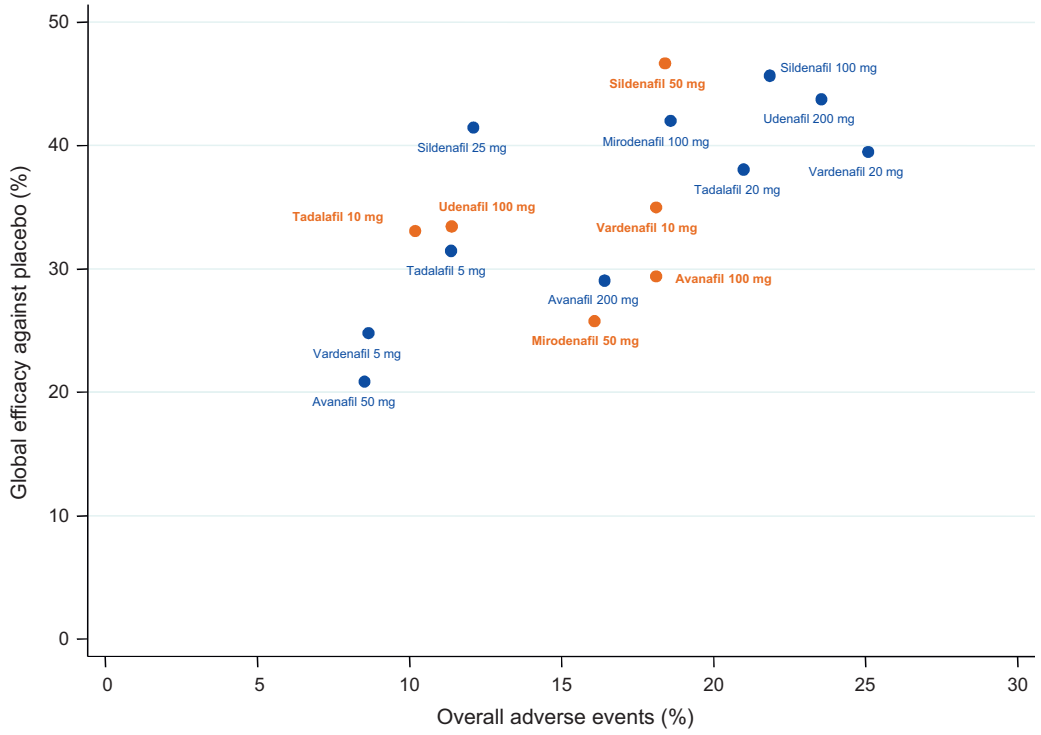

Fig. 4 – Trade-off chart for phosphodiesterase 5 inhibitors at different dosages. Treatments in red are starting dosages.

3.3. *Trade-off analysis*

In the trade-off analysis of starting dosages, sildenafil 50 mg had the greatest efficacy but also the highest rate of overall adverse events. Tadalafil 10 mg had intermediate efficacy and the lowest overall rate of all adverse events. Vardenafil 10 mg and avanafil 100 mg had similar overall adverse events to sildenafil 50 mg but markedly lower global efficacy. Udenafil 100 mg had similar global efficacy to tadalafil 10 mg but a slightly higher rate of overall adverse events. The complete trade-off chart is presented in Figure 4.

4. Discussion

4.1. *Main findings*

This is the first study providing a trade-off analysis between the different PDE5Is currently on the market. For men prioritizing high efficacy, sildenafil 50 mg appears to be the treatment of choice. Men wishing to optimize tolerability should take tadalafil 10 mg or switch to udenafil 100 mg in the case of insufficient efficacy.

4.2. *Results in the context of the literature*

PDE5Is have revolutionized the treatment of ED. They are very common medications and the World Wide Web contributes significantly to their widespread use. In terms of overall efficacy and adverse events, our data confirm the results of previous reports that PDE5Is are more effective than placebo in treating ED and are generally safe and well tolerated [4–6]. Interestingly, our efficacy analysis revealed equivalence of sildenafil 50 mg and sildenafil 100 mg, and of avanafil 100 mg and avanafil 200 mg. This finding is somewhat unexpected and we speculate that it results from differences in the distribution of prognostic profiles within the different treatment strata assessed. Since we did not have access to the individual patient data for all trials, it was not possible to account for these differences in the analysis. Adjustments for patient characteristics at the study level did not alter this finding (data not shown).

Although there are several differences in specific characteristics between the PDE5Is, such as time to onset of action, duration of effect, interaction with fatty meals, and adverse events, no randomized controlled trial has directly compared all currently available PDE5Is. The most commonly reported adverse events include headache, flushing, dyspepsia, and nasal congestion [1,5]. Findings regarding the choice of or preference for different PDE5Is are inconsistent. Tsertsvadze et al [4] found similar efficacy and safety profiles, whereas Yuan et al [5] suggested that tadalafil is the most effective agent, followed by vardenafil. Although both efficacy and safety are essential in the treatment of ED from both a physician and especially a patient perspective, no study has considered both aspects together. Therefore, the present report, which provides a trade-off analysis, fills an important gap and supplies a highly relevant tool for decision-making in daily clinical practice for straightforward patient-tailored treatment of ED.

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4.3. Strength and limitations

The methods applied in this paper allow steps beyond conventional reviews. The approach incorporates all available information from clinical trials while fully maintaining randomization. In contrast to the previous network meta-analysis by Yuan et al [5], our study not only provides a trade-off analysis but also considers different PDE5I dosages. Moreover, we minimized selection bias since we did not select studies on the basis of reported outcomes. Unfortunately, very few studies reported all relevant patient outcomes. We assumed that the outcomes are correlated and that missing data are at random. Therefore, we supposed that missing outcomes could be generated or predicted by the value of the available data and applied multiple imputations while considering the uncertainty of imputed data. Thus, a direct comparison of various treatments and a rank ordering are readily available. Finally, the combination of efficacy and adverse events provides an evidence base for formal decision-analytic models. The major limitation of the study lies in the reporting quality of some trials. For example, despite contacting corresponding authors, precision estimates (SDs and CIs) were still lacking for many papers. For the efficacy analysis, we pooled four outcomes since efficacy endpoints varied between studies, but all are clinically relevant. Thus, combining all information is valuable for patients and we assumed that if all four outcomes were present in a study, taking their average as an overall outcome is valid. We excluded papers with a crossover design, because they did not report within-subject correlations. Depending on the within-subject correlation, the variance of the within-subject comparison of the adverse event score will be lower than the between-subject comparison. As the weights are inversely proportional to the variance, this characteristic would mean that the weights of the crossover studies should be increased. For the adverse events analysis, the within-study variance of the adverse event scores was not available, so a regular meta-regression analysis investigating heterogeneity was not possible. In fact, given that our data represent averaged adverse event profiles for the PDE5Is considered, it is unclear how predictive the mean values are for an individual patient. We were not able to assess effect modification (ie, subgroup-specific effects). We thus assumed heterogeneity and allowed the outcome parameter to have an overall variance comprising both between-study and within-study variance. In addition, side effects experienced by patients may vary widely. Thus, it would be ideal to consider the patient perspective regarding the burden of adverse events. However, this is usually not reported and there are no generally accepted methods for a posteriori grading of adverse events. On the basis of expert consensus, we therefore considered adverse events equally important. Taking into account the high number of patients included and the fact that the same strategy was applied for all PDE5Is, this approach seems reasonable, especially in view of the lack of validated other options.

Almost all studies published are fixed-dose, on-demand use trials, and we excluded the few studies that did not clearly specify the dose regarding adverse events. This limitation is important, since the dose of a drug is often titrated in clinical practice, and flexible dose studies tend to report fewer adverse events. None of the trials reported whether or how many patients had two or more adverse events. Therefore, we had to assume that the occurrence of an adverse event was independent of the presence of another adverse event. In addition, we cannot exclude the possibility that the policy to assess efficacy and side effects, as well as the completeness of reporting, differed between trials and treatments. The impact of this variability on the results is impossible to determine, but underreporting of adverse events, particularly in earlier trials, is possible. Finally, some treatments summarized in this report are not available in all countries. For example, udenafil is not available in Europe (including Switzerland) or the USA.

4.4. Implications for practice and research

From the trade-off chart, clinicians can gain a quick overview of treatment efficacy for each drug against the corresponding likelihood of adverse events. On the basis of this chart, they may propose exchange of drug with unsatisfactory treatment or a less desired treatment profile. We believe that our method provides a useful and complete overview of the evidence. Besides its value for clinical practice, researchers and/or agencies commissioned to provide comprehensive summaries and decision-analytic models might find the presentation of evidence of use. From a decision-making point of view, there are new opportunities that could be explored, such as adding the patient perspective regarding the minimum beneficial effect expected and the burden of adverse events used as benchmark criteria for optimal treatment regimens. In addition, when attributing treatment costs, our approach could result in a straightforward economic analysis. Our simple trade-off concept could be expanded by including study size or methodological aspects. Our findings should be updated once new evidence on the efficacy and adverse events of less examined drugs becomes available.

5. Conclusions

The data presented here suggest that the various therapeutic options available for treating ED require careful discussion with the patient about his expectations of treatment effects. Physicians should explore whether patients with ED desire immediate stronger efficacy at the cost of a higher risk of side effects, or tolerability of the drug at the cost of lower efficacy.

Author contributions: Thomas M. Kessler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kessler, Bachmann.
Acquisition of data: Chen, Staubli, Schneider, Ivic, Bachmann, Kessler.
Analysis and interpretation of data: Kessels, Bachmann, Kessler.
Drafting of the manuscript: Chen, Staubli, Bachmann, Kessler.

Critical revision of the manuscript for important intellectual content: Schneider, Kessels, Ivic.
Statistical analysis: Kessels, Bachmann.
Obtaining funding: Kessler.
Administrative, technical, or material support: Bachmann, Kessler.
Supervision: Kessler.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.03.031.

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