Effect of phosphodiesterase-type 5 inhibitors on erectile function: an overview of systematic reviews and meta-analyses

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ABSTRACT

Introduction Phosphodiesterase-type 5 inhibitors (PDE5i) are the recommended first-line treatment for erectile dysfunction. Previous systematic reviews and meta-analyses suggest that they are a safe and effective option in many patient groups. Similarly, PDE5i may be effective as part of combination therapy in non-responders to PDE5i. We will generate an overview of systematic reviews, meta-analyses and network meta-analyses aiming to summarise the available knowledge regarding the efficacy and safety of PDE5i in the general population and in multiple subgroups of patients.

Methods and analysis This overview was designed in accordance with the PRIO-harms and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and its protocol was registered at PROSPERO. We will systematically search PubMed, Web of Science, Cochrane Library and Scopus databases from inception to November 2020 without any language restrictions. We will include systematic reviews or meta-analyses: (1) comparing the efficacy and safety of any dose of PDE5i with each other, with placebo or with other effective treatments for the management of erectile function; (2) exploring the use of any PDE5i alone or in combination with other treatment modalities in the general male population or in specific subgroups and (3) conducted with systematic procedures. Our overview will employ the AMSTAR 2 tool to evaluate the quality of the included studies and the Grading of Recommendations Assessment, Development and Evaluation approach to assess the strength of evidence for all outcomes. We will construct forest plots of risk estimates with the corresponding CI for all outcomes.

Ethics and dissemination In this overview, we will undertake an extensive literature search in an attempt to evaluate the potential benefits and risks of treatment with one PDE5i versus another or versus placebo and provide recommendations for clinicians and policy-makers. No ethical approval is required.

PROSPERO registration number CRD42020216754.

INTRODUCTION

Sildenafil was initially developed for the treatment of angina pectoris but its effect on erectile function has brought on a revolution in the management of erectile dysfunction (ED). Thereafter, other phosphodiesterase-type 5 inhibitors (PDE5i) have demonstrated their efficacy and safety for the treatment of ED. Seven PDE5i (avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil and vardenafl) at different dosages and formulations are currently available and four of them (avanafil, sildenafil, tadalafil and vardenafl) are considered the first-line option for ED. Accumulating evidence suggests that PDE5i may also be safe and effective in many patient groups such as in individuals with diabetes, hypertension, benign prostatic hyperplasia, prostatectomy-induced ED or end-stage renal disease. Similarly, previous systematic reviews and meta-analyses indicate that PDE5i may be used in combination with other effective treatment modalities such as intracavernosal injections or low-intensity extracorporeal shockwave therapy in non-responders to PDE5i.
Clinicians and policy-makers require a comprehensive overview of the available evidence in order to determine the potential benefits and harms of PDE5i. Within this framework, overviews of systematic reviews and meta-analyses are a relatively new approach that provides a holistic approach of a given topic and aids evidence-based clinical decision making. They aim to summarise and evaluate the strength of scientific evidence as presented in multiple systematic reviews, meta-analyses or network meta-analyses. These studies are becoming increasingly more common in many healthcare domains and in sexual medicine as they provide higher level of recommendations and highlight the gaps in the literature.

Aim
In this context, we will generate an overview of systematic reviews, meta-analyses and network meta-analyses aiming to summarise the available knowledge regarding the efficacy and safety of PDE5i in the general population and in multiple subgroups of patients.

METHODS AND ANALYSIS
This overview of systematic reviews was designed in accordance with the Preferred Reporting Items for Overviews of systematic reviews PRIO-harms guidelines. Our protocol was drafted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols (online data supplemental file).

Search strategy
Two independent reviewers will conduct a systematic literature search of PubMed, Web of Science, Cochrane Library and Scopus databases from inception to November 2020 without any language restrictions. The search terms will include: (systematic review OR meta-analysis) AND (phosphodiesterase-5 OR sildenafil OR tadalafil OR avanafil OR vardenafil OR mirodenafil OR udenafil OR lodenafil) AND (erectile OR erection OR orgasm OR impotence OR IIEF) as well as relevant synonyms, truncated words and MeSH terms. The search strategy developed for PubMed is depicted in online data supplemental file 2. To identify additional articles meeting our inclusion criteria, we will handsearch the reference lists of all eligible studies and sources of grey literature, such as conference abstracts published in major urology and sexual medicine journals. If we identify a study in a language not spoken from the study authors, it will be translated either via a native speaker or a machine translator. We will reupdate all searches before final analyses.

Selection criteria
We will comprise systematic reviews with or without meta-analyses in patients with ED that: (1) provide outcomes derived from randomised controlled trials; (2) compare the efficacy and safety of any dose of PDE5i with another PDE5i, with placebo or with other effective treatments; (3) explore the use of any approved PDE5i (avanafil, sildenafil, tadalafil, vardenafil) alone or in combination with other treatment modalities both in the general male population as well as in specific subgroups and (4) were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA statement. On the contrary, we will exclude: (1) systematic reviews or meta-analyses on patients under 18 years of age; (2) systematic reviews or meta-analyses assessing the efficacy and safety of PDE5i for indications not relevant to erectile function and (3) narrative reviews, editorials and letters to the editor.

Outcomes
The primary outcome of our overview will be the improvement of erectile function in the general population. This will be defined as the mean change in the erectile function after PDE5i administration measured with the International Index of Erectile Function (IIEF). Secondary outcomes will include (1) improvement of erectile function based on the IIEF in specific subpopulations such as patients with diabetes, hypertension, end-stage renal disease, adiposity, lower urinary tract symptoms, hypogonadism, radical prostatectomy-induced ED as part of a penile rehabilitation strategy or as an adjunct treatment, depression, psychiatric or neurological disorders, monotherapy-resistant ED as well as elderly and young individuals or other subgroups of patients; (2) severe adverse events after PDE5i intake both in the general population as well as in specific patient subgroups and (3) drop-out rates after treatment with PDE5i. All outcomes will be presented as defined in each included systematic review or meta-analysis.

Study selection and data collection
Two authors will independently search the predetermined electronic databases and the sources of grey literature. After removing duplicate records, the two authors will evaluate the relevance of all retrieved records to the prespecified inclusion criteria, based on title and abstract. Subsequently, the potentially eligible systematic reviews and meta-analyses will be assessed in the full-text form for final inclusion to our overview. All reasons for exclusion will be documented. Any disagreements will be resolved by consensus.

Data extraction will be performed independently by two authors based on a predefined Microsoft Excel spreadsheet. We will tabulate information regarding systematic review or meta-analysis characteristics, intervention details and outcomes. To ensure coherence between the authors, a pilot test will be performed before data extraction.

Quality assessment and strength of evidence
Our overview will employ the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 tool to evaluate the quality of the included systematic reviews or meta-analyses. The strength of evidence for all outcomes will be based on the Grading of Recommendations

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Assessment, Development and Evaluation (GRADE) approach.\textsuperscript{18} If GRADE was applied in an included systematic review, meta-analysis or network meta-analysis, it will be reported as determined from the authors. On the contrary, if GRADE was not performed, we will assess the strength of evidence based on the reported results from this systematic review or meta-analysis. In particular, two reviewers will evaluate risk of bias, inconsistency, indirectness, imprecision and publication bias among trials included in each systematic review or meta-analysis. Any disagreements will be resolved by consensus.

Data synthesis
A descriptive analysis will be performed and the extent of overlapping among systematic reviews and meta-analyses will be estimated applying the corrected covered area and will be presented using novel graphical approaches.\textsuperscript{19} When a systematic review and a meta-analysis addressing the same outcome will be identified, data from the meta-analysis will be reported, provided that the meta-analysis includes more primary studies. Similarly, when a systematic review or a meta-analysis and a network meta-analysis addressing the same outcome will be identified, data from the network meta-analysis will be reported, provided that the network meta-analysis includes more primary studies. Among studies with the same design (systematic reviews or meta-analyses or network meta-analyses) assessing similar outcomes, only data from the most recent study will be considered. However, if these meta-analyses were published at a similar period (within 24 months), data from the most methodologically rigorous study will be provided (based on AMSTAR 2).\textsuperscript{20} Furthermore, in studies reporting outcomes for erectile function change after PDE5i intake both with validated and non-validated or dichotomous (yes/no) questionnaires, data concerning the validated questionnaire will only be retrieved.

We will construct forest plots of risk estimates with the corresponding CI for all outcomes. In particular, meta-analytical effects for common themes as reported in each study (such as risk ratio, OR or mean difference) will be pooled to provide a descriptive estimate.\textsuperscript{21} Additionally, we will evaluate heterogeneity with the I\textsuperscript{2} and estimate publication bias with the Egger’s test for each outcome.\textsuperscript{22} Meta-analyses performed with a fixed effects model will be reanalysed using the DerSimonian and Laird random effects model. Outcome data will be extracted as reported in each meta-analysis without reviewing the relevant primary studies.\textsuperscript{24} All analyses will be performed using Microsoft Excel (V.16.42) and R statistical software (V.3.6.3).

Patients and public involvement
This overview of systematic reviews was conceptualised and developed due to the unmet need of male patients and their partners to receive an effective and safe treatment for ED. Even though our study will not involve patients at any step of its implementation, the results of the overall project will be sent to the communication department of Aristotle University of Thessaloniki for a press release. Moreover, because of the growing interest in this topic, the results of the study will not only be published in scientific journals, but also in more general or multidisciplinary journals to reach a broader audience. Of importance, this study will pinpoint the current gaps in the literature and serve as a valuable guide for the design and implementation of further research on the field, improving healthcare facilities and aiding clinicians to properly consult and treat patients with ED receiving PDE5i.

ETHICS AND DISSEMINATION
Patients and public were not involved for this study protocol and no primary data were collected from individuals. Therefore, no ethics committee approval was required for the present study. In this overview of systematic reviews and meta-analyses, we will undertake an extensive and systematic literature search in an attempt to evaluate the potential benefits and risks of treatment with one PDE5i vs another or placebo. Accordingly, we will assess the effects of PDE5i as part of combination therapy. We will provide relevant recommendations that may serve as a basis for clinicians and policy-makers. Our data will be disseminated through a publication in a prestigious, peer-reviewed journal as well as through conference presentations.

Contributors NP, IM, A-BH, AO and DH contributed to the conception or design of the work. NP, IM, A-BH, MT, PT and DK contributed to the acquisition, analysis or interpretation of data for the work. NP and IM drafted the manuscript. A-BH, MT, PT, DK, AO and DH critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1. Goldstein I, Lef T, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998;338:1397–404.

2. Chen L, Staubli SEL, Schneider MP, et al. Phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction: a trade-off network meta-analysis. Eur Urol 2015;68:674–80.

3. Salonia A, Bettochi C, Carvalho J. EAU guidelines on sexual and reproductive health 2020. In: European association of urology guidelines. 2020 edn. Arnhem, The Netherlands: European Association of Urology Guidelines Office, 2020. https://uroweb.org/guideline/sexual-and-reproductive-health/

4. Yuan J, Zhang R, Yang Z, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol 2015;63:902–12.

5. Liao X, Qiu S, Bao Y, et al. Comparative efficacy and safety of phosphodiesterase type 5 inhibitors for erectile dysfunction in diabetic men: a Bayesian network meta-analysis. World J Urol 2019;37:1061–74.

6. Mykoriatis I, Pyrgidis N, Sokolakis I, et al. Assessment of combination therapies vs monotherapy for erectile dysfunction: a systematic review and meta-analysis. JAMA Netw Open 2021;4:e2036337.

7. Lavis JN. How can we support the use of systematic reviews in policymaking? PLoS Med 2009;6:e1000141.

8. Tsilidis KK, Kasimis JC, Lopez DS, et al. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2014;350:g7607.

9. Ciocanel O, Prower K, Eriksen A. Interventions to treat erectile dysfunction and premature ejaculation: an overview of systematic reviews. Sex Med 2019;7:251–69.

10. Greenberg DR, Richardson MT, Tijerina JD, et al. The quality of systematic reviews and meta-analyses in erectile dysfunction treatment and management published in the sexual medicine literature. J Sex Med 2019;16:394–401.

11. Allen MS, Walter EE. Erectile dysfunction: an umbrella review of meta-analyses of Risk-Factors, treatment, and prevalence outcomes. J Sex Med 2019;16:531–41.

12. Bougioukas KI, Liakos A, Tsapas A, et al. Preferred reporting items for overviews of systematic reviews including harms checklist: a pilot tool to be used for balanced reporting of benefits and harms. J Clin Epidemiol 2018;93:9–24.

13. Bougioukas KI, Bouras E, Apostolidou-Kiouti F, et al. Reporting guidelines on how to write a complete and transparent Abstract for overviews of systematic reviews of health care interventions. J Clin Epidemiol 2019;106:70–9.

14. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:g7647.

15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

16. Higgins JPT, Thomas J, Chandler J, eds. Cochrane handbook for systematic reviews of interventions. 2nd edn. Chichester (UK): John Wiley & Sons, 2019.

17. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.

18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

19. Bougioukas KI, Vounzoulakis E, Mantziou CD, et al. Methods for depicting overlap in overviews of systematic reviews: an introduction to static tabular and graphical displays. J Clin Epidemiol 2021;132:34–45.

20. Cooper H, Koenka AC. The overview of reviews: unique challenges and opportunities when research syntheses are the principal elements of new integrative scholarship. Am Psychol 2012;67:446–62.

21. Poole R, Kennedy OJ, Roderick P, et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ 2017;359:j5024.

22. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

23. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

24. Aromataris E, Fernandez R, Godfrey CM, et al. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc 2015;13:132–40.
### PRISMA-P Checklist

| Section/topic | # | Checklist item                                                                                                                                                                                                 |
|---------------|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ADMINISTRATIVE INFORMATION |   |                                                                                                                                                                                                                     |
| Title         |   |                                                                                                                                                                                                                     |
| Identification | 1a | Identify the report as a protocol of a systematic review                                                                                                                                                             |
| Update        | 1b | If the protocol is for an update of a previous systematic review, identify as such                                                                                                                                 |
| Registration  | 2  | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract                                                                                                          |
| Authors       |   |                                                                                                                                                                                                                     |
| Contact       | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author                                                                             |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review                                                                                                                                   |
| Amendments    | 4  | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments |
| Support       |   |                                                                                                                                                                                                                     |
| Sources       | 5a | Indicate sources of financial or other support for the review                                                                                                                                                    |
| Sponsor       | 5b | Provide name for the review funder and/or sponsor                                                                                                                                                                 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol                                                                                                               |
| INTRODUCTION  |   |                                                                                                                                                                                                                     |
| Rationale     | 6  | Describe the rationale for the review in the context of what is already known                                                                                                                                      |
| Objectives    | 7  | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)                                                             |
| METHODS       |   |                                                                                                                                                                                                                     |
| Eligibility criteria | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review |
| Information sources | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage       |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated                                                                 |

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| Section/topic | #  | Checklist item                                                                 | Information reported | Page |
|---------------|----|---------------------------------------------------------------------------------|----------------------|------|
| **STUDY RECORDS** |    |                                                                                  |                      |      |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | ✓                    | 6-7  |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | ✓                    | 6-7  |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | ✓                    | 6-7  |
| Data items | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | ✓                    | 6-7  |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | ✓                    | 5-7  |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | ✓                    | 6-7  |
| **DATA** |    |                                                                                  |                      |      |
| Synthesis | 15a | Describe criteria under which study data will be quantitatively synthesized | ✓                    | 6-7  |
| 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$, Kendall’s tau) | ✓                    | 6-7  |
| 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | ✓                    | 6-7  |
| 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | ✓                    | 6-7  |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ✓                    | 6-7  |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ✓                    | 6-7  |
Data Supplement 2: PubMed search strategy

| ID | Search |
|----|--------|
| #1 | Sildenafil [All Fields] |
| #2 | Avanafil [All Fields] |
| #3 | Tadalafil [All Fields] |
| #4 | Vardenafil [All Fields] |
| #5 | Mirodenafil [All Fields] |
| #6 | Lodenafl [All Fields] |
| #7 | Udenafil [All Fields] |
| #8 | Phosphodiesterase-5 [All Fields] |
| #9 | Phosphodiesterase 5 [All Fields] |
| #10 | Phosphodiesterase Five [All Fields] |
| #11 | Sildenafil Citrate [MeSH Terms] |
| #12 | Phosphodiesterase 5 Inhibitors [MeSH Terms] |
| #13 | OR #1-12 |
| #14 | Sexual [All Fields] |
| #15 | Orgasm [All Fields] |
| #16 | Erectile [All Fields] |
| #17 | Erection [All Fields] |
| #18 | Impotence [All Fields] |
| #19 | IIEF [All Fields] |
| #20 | Orgasm [MeSH Terms] |
| #21 | Erectile Dysfunction [MeSH Terms] |
| #22 | Penile Erection [MeSH Terms] |
| #23 | OR #14-22 |
| #24 | Meta-Analysis [All Fields] |
| #25 | Metanalysis [All Fields] |
| #26 | Meta Analysis [All Fields] |
| #27 | Meta-analysis [Publication Type] |
| #28 | Systematic Review [All Fields] |
| #29 | Systematic Review [Publication Type] |
| #30 | OR #24-29 |
| #31 | #13 AND #23 AND #30 |

The search strategy was developed for PubMed and modified accordingly for the other databases.