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# BMJ Open

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

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Complete List of Authors:	<p>Pyrgidis, Nikolaos; Aristotle University of Thessaloniki, First Department of Urology, G. Gennimatas Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.</p> <p>Mykoniatis, Ioannis; Aristotle University of Thessaloniki, First Department of Urology, G. Gennimatas Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.</p> <p>Haidich, Anna-Bettina ; Aristotle University of Thessaloniki, Department of Hygiene, Social-Preventive Medicine &amp; Medical Statistics</p> <p>Tirta, Maria; Aristotle University of Thessaloniki, First Department of Urology, G. Gennimatas Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.</p> <p>Talimtzi, Persefoni; Aristotle University of Thessaloniki, Department of Hygiene, Social-Preventive Medicine &amp; Medical Statistics</p> <p>Kalyvianakis, Dimitrios; Aristotle University of Thessaloniki, First Department of Urology, G. Gennimatas Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.</p> <p>Ouranidis, Andreas; Aristotle University of Thessaloniki, Thessaloniki 54124, Greece Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece.</p> <p>Hatzichristou, Dimitrios; Aristotle University of Thessaloniki, First Department of Urology, G. Gennimatas Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.</p>
Keywords:	Erectile dysfunction < UROLOGY, Sexual dysfunction < UROLOGY, EPIDEMIOLOGY

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## TITLE PAGE

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

**Type of submission:** Protocol of an overview of systematic reviews

**Authors (First Name, Last Name)**

Nikolaos Pyrgidis<sup>1,2</sup>, Ioannis Mykoniatis<sup>1,2</sup>, Anna-Bettina Haidich<sup>3</sup>, Maria Tirta<sup>1</sup>, Persefoni Talimtzi<sup>3</sup>, Kalyvianakis Dimitrios<sup>1,2</sup>, Andreas Ouranidis<sup>4</sup>, Dimitrios Hatzichristou<sup>1</sup>

**Authors' affiliations:**

1. Institute for the Study of Urological Diseases, Thessaloniki, Greece
2. First Department of Urology, G. Gennimatas Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.
3. Department of Hygiene, Social-Preventive Medicine & Medical Statistics, Medical School, Aristotle University of Thessaloniki, University Campus, 54124 Thessaloniki, Greece.
4. Department of Pharmaceutical Technology, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece.

**Corresponding author:** Nikolaos Pyrgidis.

Address: Alois 16, Pilaia, Thessaloniki, Greece

Telephone number: 0030 6982 14 2006

Email: [nikospyrgidis@gmail.com](mailto:nikospyrgidis@gmail.com)

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3 **27 ABSTRACT**  
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7 **29 Introduction:** Phosphodiesterase-type 5 inhibitors (PDE5i) are the recommended first-line  
8  
9 30 treatment for erectile dysfunction (ED). Previous systematic reviews and meta-analyses  
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11 31 suggest that they are a safe and effective option in many patient groups. Similarly, PDE5i may  
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13 32 be effective as part of combination therapy in non-responders to PDE5i. We will generate an  
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15 33 overview of systematic reviews, meta-analyses and network meta-analyses aiming to  
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17 34 summarize the available knowledge regarding the efficacy and safety of PDE5i in the general  
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19 35 population and in multiple subgroups of patients.

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21 36 **Methods and analysis:** This overview was designed in accordance with the PRIO-harms and  
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23 37 PRISMA-P guidelines and its protocol was registered at PROSPERO. We will systematically  
24  
25 38 search PubMed, Web of Science, Cochrane Library and Scopus databases from inception to  
26  
27 39 November 2020 without any language restrictions. We will include systematic reviews or meta-  
28  
29 40 analyses: (i) comparing the efficacy and safety of any dose of PDE5i with each other, with  
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31 41 placebo or with other effective treatments for the management of erectile function; (ii)  
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33 42 exploring the use of any PDE5i alone or in combination with other treatment modalities in the  
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35 43 general male population or in specific subgroups; (iii) conducted with systematic procedures.  
36  
37 44 Our overview will employ the AMSTAR 2 tool to evaluate the quality of the included studies  
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39 45 and the GRADE approach to assess the strength of evidence for all outcomes. We will construct  
40  
41 46 forest plots of risk estimates with the corresponding confidence interval for all outcomes.

42  
43 47 **Ethics and dissemination:** In this overview, we will undertake an extensive literature search  
44  
45 48 in an attempt to evaluate the potential benefits and risks of treatment with one PDE5i versus  
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47 49 another or versus placebo and provide recommendations for clinicians and policymakers. No  
48  
49 50 ethical approval is required.  
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53 52 **Keywords:** Phosphodiesterase-type 5 inhibitors, overview of systematic reviews, erectile  
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55 53 dysfunction, overview of meta-analyses  
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3 54 **ARTICLE SUMMARY**  
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6 56 **Strengths and limitations of this study**  
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10 58 • We will provide the first overview exploring the use of PDE5i for the treatment of ED.

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12 59 • We will assess, in a holistic approach, the safety and efficacy of PDE5i.

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14 60 • We will evaluate the quality and the strength of evidence deriving from systematic  
15 61 reviews, meta-analyses and network meta-analyses in an attempt to affect clinical and  
16 62 policy decisions.

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19 63  
20 64 • Due to the excess of available primary studies, we will not search for recently published  
21 65 RCTs or non-RCTs.

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23  
24 66 • We will not extract data from the primary studies but rely on the information provided  
25 67 by the relevant systematic reviews and meta-analyses.  
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## 68 INTRODUCTION

69 Sildenafil was initially developed for the treatment of angina pectoris but its effect on erectile  
70 function has brought upon a revolution in the management of erectile dysfunction (ED) [1].  
71 Thereafter, other phosphodiesterase-type 5 inhibitors (PDE5i) have demonstrated their efficacy  
72 and safety for the treatment of ED [2]. Seven PDE5i (avanafil, lodenafil, mirodenafil,  
73 sildenafil, tadalafil, udenafil, and vardenafil) at different dosages and formulations are  
74 currently available and four of them (avanafil, sildenafil, tadalafil and vardenafil) are  
75 considered the first-line option for ED [3]. Accumulating evidence suggests that PDE5i may  
76 also be safe and effective in many patient groups such as in individuals with diabetes,  
77 hypertension, benign prostatic hyperplasia, prostatectomy-induced ED or end-stage renal  
78 disease [4,5]. Similarly, previous systematic reviews and meta-analyses indicate that PDE5i  
79 may be used in combination with other effective treatment modalities such as intracavernosal  
80 injections or low-intensity extracorporeal shockwave therapy in non-responders to PDE5i [6].

81  
82 Clinicians and policymakers require a comprehensive overview of the available evidence in  
83 order to determine the potential benefits and harms of PDE5i. Within this framework,  
84 overviews of systematic reviews and meta-analyses are a relatively new approach that provides  
85 a holistic approach of a given topic and aids evidence-based clinical decision-making [7]. They  
86 aim to summarize and evaluate the strength of scientific evidence as presented in multiple  
87 systematic reviews, meta-analyses or network meta-analyses [8]. These studies are becoming  
88 increasingly more common not only in many healthcare domains but also in sexual medicine  
89 as they provide higher level of recommendations and highlight the gaps in the literature [9–  
90 11].

### 92 Aim

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

## 96 **METHODS AND ANALYSIS**

97 This overview of systematic reviews was designed in accordance with the PRIO-harms  
98 guidelines [12,13]. Our protocol was drafted based on the Preferred Reporting Items for  
99 Systematic review and Meta-Analysis Protocols (PRISMA-P) and was registered at  
100 PROSPERO database (Data Supplement 1) [14].

101

### 102 **Search strategy**

103 Two independent reviewers will conduct a systematic literature search of PubMed, Web of  
104 Science, Cochrane Library and Scopus databases from inception to November 2020 without  
105 any language restrictions. The search terms will include: (systematic review OR meta-analysis)  
106 AND (phosphodiesterase-5 OR sildenafil OR tadalafil OR avanafil OR vardenafil OR  
107 mirodenafil OR udenafil OR lodenafil) AND (erectile OR erection OR orgasm OR impotence  
108 OR IIEF) as well as relevant synonyms, truncated words and MeSH terms. The search strategy  
109 developed for PubMed is depicted in Data Supplement 2. To identify additional articles  
110 meeting our inclusion criteria, we will hand-search the reference lists of all eligible studies and  
111 sources of grey literature, such as conference abstracts published in major urology and sexual  
112 medicine journals. If we identify a study in a language not spoken from the study authors, it  
113 will be translated either via a native speaker or a machine translator. We will reupdate all  
114 searches before final analyses [15].

115

### 116 **Selection criteria**

117 We will comprise systematic reviews with or without meta-analyses in patients with erectile  
118 dysfunction that: (i) provide outcomes deriving from randomized controlled studies (RCTs) or  
119 non-RCTs; (ii) compare the efficacy and safety of any dose of PDE5i with another PDE5i, with  
120 placebo or with other effective treatments; (iii) explore the use of any PDE5i (sildenafil,  
121 tadalafil, vardenafil, avanafil, mirodenafil, udenafil, lodenafil) alone or in combination with  
122 other treatment modalities both in the general male population as well as in specific subgroups;  
123 (iv) were conducted in accordance with the Cochrane Handbook for Systematic Reviews of  
124 Interventions or the PRISMA statement. On the contrary, we will exclude: (i) systematic  
125 reviews or meta-analyses on patients under 18 years of age; (ii) systematic reviews or meta-  
126 analyses assessing the efficacy and safety of PDE5i for indications not relevant to erectile  
127 function; (iii) narrative reviews, editorials and letters to the editor.

128

### 129 **Outcomes**



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2  
3 130 The primary outcome of our overview is the improvement of erectile function in the general  
4  
5 131 population. Secondary outcomes include (i) improvement of erectile function in specific  
6  
7 132 subpopulations such as patients with diabetes, hypertension, end-stage renal disease, adiposity,  
8  
9 133 lower urinary tract symptoms, hypogonadism, prostatectomy-induced erectile dysfunction,  
10  
11 134 depression, psychiatric or neurologic disorders, monotherapy-resistant erectile dysfunction as  
12  
13 135 well as elderly and young individuals or other subgroups of patients; (ii) adverse events after  
14  
15 136 PDE5i intake both in the general population as well as in specific patient subgroups; (iii)  
16  
17 137 dropout rates after treatment with PDE5i. All outcomes will be presented as defined in each  
18  
19 138 included systematic review or meta-analysis.

139

### 140 **Study selection and data collection**

141 Two authors will independently search the predetermined electronic databases and the sources  
142  
143 of grey literature. After removing duplicate records, the two authors will evaluate the relevance  
144  
145 of all retrieved records to the prespecified inclusion criteria, based on title and abstract.  
146  
147 Subsequently, the potentially eligible systematic reviews and meta-analyses will be assessed  
148  
149 in the full-text form for final inclusion to our overview. All reasons for exclusion will be  
150  
151 documented. Any disagreements will be resolved by consensus.

152

153 Data extraction will be performed independently by two authors based on a predefined  
154  
155 Microsoft Excel spreadsheet. We will tabulate information regarding systematic review or  
156  
157 meta-analysis characteristics, intervention details and outcomes. To ensure coherence between  
158  
159 the authors, a pilot test will be performed before data extraction [16].

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### 161 **Quality assessment and strength of evidence**

162 Our overview will employ the AMSTAR 2 tool to evaluate the quality of the included  
163  
164 systematic reviews or meta-analyses [17]. The strength of evidence for all outcomes will be  
165  
166 based on the Grading of Recommendations Assessment, Development and Evaluation  
167  
168 (GRADE) approach [18]. If GRADE was applied in an included systematic review or meta-  
169  
170 analysis, it will be reported as determined from the authors. On the contrary, if GRADE was  
171  
172 not performed, we will assess the strength of evidence based on the reported results from this  
173  
174 systematic review or meta-analysis. In particular, two reviewers will evaluate risk of bias,  
175  
176 inconsistency, indirectness, imprecision and publication bias among trials included in each  
177  
178 systematic review or meta-analysis. Any disagreements will be resolved by consensus.

179

## 164 **Data synthesis**

165 A descriptive analysis will be performed and the extent of overlapping among systematic  
166 reviews and meta-analyses will be estimated applying the corrected covered area (CCA) and  
167 will be presented using novel graphical approaches [19]. When a systematic review and a meta-  
168 analysis addressing the same outcome will be identified, data from the meta-analysis will be  
169 reported. Similarly, when a systematic review or a meta-analysis and a network meta-analysis  
170 addressing the same outcome will be identified, data from the network meta-analysis will be  
171 reported. Among meta-analyses assessing the same outcome, only data from the most recent  
172 study will be considered. However, if these meta-analyses were published at a similar period  
173 (within 24 months), data from the most methodologically rigorous study will be provided  
174 (based on AMSTAR 2) [20]. Furthermore, in studies reporting outcomes for erectile function  
175 change after PDE5i intake both with validated and non-validated or dichotomous (yes/no)  
176 questionnaires, data concerning the validated questionnaire will only be retrieved.

177  
178 We will construct forest plots of risk estimates with the corresponding confidence interval for  
179 all outcomes. In particular, meta-analytic effects for common themes as reported in each study  
180 (such as risk ratio, odds ratio or mean difference) will be pooled to provide a descriptive  
181 estimate [21]. Additionally, we will evaluate heterogeneity with the  $I^2$  and estimate publication  
182 bias with the Egger's test for each outcome [22,23]. Meta-analyses performed with a fixed  
183 effects model, will be reanalyzed using the DerSimonian and Laird random effects model.  
184 Outcome data will be extracted as reported in each meta-analysis without reviewing the  
185 relevant primary studies [24]. All analyses will be performed using Microsoft Excel (Version  
186 16.42) and R statistical software (version 3.6.3).

## 188 **ETHICS AND DISSEMINATION**

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

197

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3 198 **Contributors:** All authors participated in the drafting, writing, and editing of the manuscript.  
4  
5 199 All gave final approval and agree to be accountable for all aspects of work ensuring integrity  
6  
7 200 and accuracy.  
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9 201

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17 206 **Competing interests:** None declared  
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20 208 **Patient consent for publication:** Not required.  
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## PRISMA-P Checklist

Section/topic	#	Checklist item	Information reported		Page
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
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	Not applicable		
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	✓		
<b>Authors</b>					
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	✓		
<b>Amendments</b>	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	Not applicable		
<b>Support</b>					
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	✓		
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	✓		
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓		
<b>METHODS</b>					
<b>Eligibility criteria</b>	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	✓		
<b>Information sources</b>	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	✓		
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓		
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓		
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)	✓		

Section/topic	#	Checklist item	Information reported		Page
			Yes	No	
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	✓		
<b>Data items</b>	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	✓		
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓		
<b>Risk of bias in individual studies</b>	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	✓		
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	✓		
	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)	✓		
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓		
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓		
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	✓		
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	✓		



## 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	Lodenafil [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	IEEF [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.

# BMJ Open

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

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Urology
Secondary Subject Heading:	Epidemiology
Keywords:	Erectile dysfunction < UROLOGY, Sexual dysfunction < UROLOGY, EPIDEMIOLOGY

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## TITLE PAGE

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

**Type of submission:** Protocol of an overview of systematic reviews

**Authors (First Name, Last Name)**

Nikolaos Pyrgidis<sup>1,2</sup>, Ioannis Mykoniatis<sup>1,2</sup>, Anna-Bettina Haidich<sup>3</sup>, Maria Tirta<sup>1</sup>, Persefoni Talimtzi<sup>3</sup>, Kalyvianakis Dimitrios<sup>1,2</sup>, Andreas Ouranidis<sup>4</sup>, Dimitrios Hatzichristou<sup>1</sup>

**Authors' affiliations:**

1. Institute for the Study of Urological Diseases, Thessaloniki, Greece
2. Urology Department, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece
3. Department of Hygiene, Social-Preventive Medicine & Medical Statistics, Medical School, Aristotle University of Thessaloniki, University Campus, 54124 Thessaloniki, Greece.
4. Department of Pharmaceutical Technology, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece.

**Corresponding author:** Nikolaos Pyrgidis.

Address: Alois 16, Pilaia, Thessaloniki, Greece

Telephone number: 0030 6982 14 2006

Email: [nikospyrgidis@gmail.com](mailto:nikospyrgidis@gmail.com)

## 27 ABSTRACT

28  
29 **Introduction:** Phosphodiesterase-type 5 inhibitors (PDE5i) are the recommended first-line  
30 treatment for erectile dysfunction (ED). Previous systematic reviews and meta-analyses  
31 suggest that they are a safe and effective option in many patient groups. Similarly, PDE5i may  
32 be effective as part of combination therapy in non-responders to PDE5i. We will generate an  
33 overview of systematic reviews, meta-analyses and network meta-analyses aiming to  
34 summarize the available knowledge regarding the efficacy and safety of PDE5i in the general  
35 population and in multiple subgroups of patients.

36 **Methods and analysis:** This overview was designed in accordance with the PRIO-harms and  
37 PRISMA-P guidelines and its protocol was registered at PROSPERO. We will systematically  
38 search PubMed, Web of Science, Cochrane Library and Scopus databases from inception to  
39 November 2020 without any language restrictions. We will include systematic reviews or meta-  
40 analyses: (i) comparing the efficacy and safety of any dose of PDE5i with each other, with  
41 placebo or with other effective treatments for the management of erectile function; (ii)  
42 exploring the use of any PDE5i alone or in combination with other treatment modalities in the  
43 general male population or in specific subgroups; (iii) conducted with systematic procedures.  
44 Our overview will employ the AMSTAR 2 tool to evaluate the quality of the included studies  
45 and the GRADE approach to assess the strength of evidence for all outcomes. We will construct  
46 forest plots of risk estimates with the corresponding confidence interval for all outcomes.

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

51  
52 **PROSPERO registration number:** CRD42020216754

53  
54 **Keywords:** Phosphodiesterase-type 5 inhibitors, overview of systematic reviews, erectile  
55 dysfunction, overview of meta-analyses

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3 56 **ARTICLE SUMMARY**  
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5 57

6 58 **Strengths and limitations of this study**  
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10 60 • We will provide the first overview exploring the use of PDE5i for the treatment of ED.  
11  
12 61 • We will assess, in a holistic approach, the safety and efficacy of PDE5i.  
13  
14 62 • We will evaluate the quality and the strength of evidence deriving from systematic  
15 63 reviews, meta-analyses and network meta-analyses in an attempt to affect clinical and  
16 64 policy decisions.  
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18  
19 65  
20 66 • Due to the excess of available primary studies, we will not search for recently published  
21 67 RCTs.  
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23  
24 68 • We will not extract data from the primary studies but rely on the information provided  
25 69 by the relevant systematic reviews and meta-analyses.  
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## 70 INTRODUCTION

71 Sildenafil was initially developed for the treatment of angina pectoris but its effect on erectile  
72 function has brought upon a revolution in the management of erectile dysfunction (ED) [1].  
73 Thereafter, other phosphodiesterase-type 5 inhibitors (PDE5i) have demonstrated their efficacy  
74 and safety for the treatment of ED [2]. Seven PDE5i (avanafil, lodenafil, mirodenafil,  
75 sildenafil, tadalafil, udenafil, and vardenafil) at different dosages and formulations are  
76 currently available and four of them (avanafil, sildenafil, tadalafil and vardenafil) are  
77 considered the first-line option for ED [3]. Accumulating evidence suggests that PDE5i may  
78 also be safe and effective in many patient groups such as in individuals with diabetes,  
79 hypertension, benign prostatic hyperplasia, prostatectomy-induced ED or end-stage renal  
80 disease [4,5]. Similarly, previous systematic reviews and meta-analyses indicate that PDE5i  
81 may be used in combination with other effective treatment modalities such as intracavernosal  
82 injections or low-intensity extracorporeal shockwave therapy in non-responders to PDE5i [6].

83  
84 Clinicians and policymakers require a comprehensive overview of the available evidence in  
85 order to determine the potential benefits and harms of PDE5i. Within this framework,  
86 overviews of systematic reviews and meta-analyses are a relatively new approach that provides  
87 a holistic approach of a given topic and aids evidence-based clinical decision-making [7]. They  
88 aim to summarize and evaluate the strength of scientific evidence as presented in multiple  
89 systematic reviews, meta-analyses or network meta-analyses [8]. These studies are becoming  
90 increasingly more common not only in many healthcare domains but also in sexual medicine  
91 as they provide higher level of recommendations and highlight the gaps in the literature [9–  
92 11].

### 94 Aim

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

## 98 **METHODS AND ANALYSIS**

99 This overview of systematic reviews was designed in accordance with the PRIO-harms  
100 guidelines [12,13]. Our protocol was drafted based on the Preferred Reporting Items for  
101 Systematic review and Meta-Analysis Protocols (PRISMA-P) and was registered at  
102 PROSPERO database with the following ID number: CRD42020216754 (Data Supplement 1)  
103 [14].

### 105 **Search strategy**

106 Two independent reviewers will conduct a systematic literature search of PubMed, Web of  
107 Science, Cochrane Library and Scopus databases from inception to November 2020 without  
108 any language restrictions. The search terms will include: (systematic review OR meta-analysis)  
109 AND (phosphodiesterase-5 OR sildenafil OR tadalafil OR avanafil OR vardenafil OR  
110 mirodenafil OR udenafil OR lodenafil) AND (erectile OR erection OR orgasm OR impotence  
111 OR IIEF) as well as relevant synonyms, truncated words and MeSH terms. The search strategy  
112 developed for PubMed is depicted in Data Supplement 2. To identify additional articles  
113 meeting our inclusion criteria, we will hand-search the reference lists of all eligible studies and  
114 sources of grey literature, such as conference abstracts published in major urology and sexual  
115 medicine journals. If we identify a study in a language not spoken from the study authors, it  
116 will be translated either via a native speaker or a machine translator. We will reupdate all  
117 searches before final analyses [15].

### 119 **Selection criteria**

120 We will comprise systematic reviews with or without meta-analyses in patients with ED that:  
121 (i) provide outcomes deriving from randomized controlled studies (RCTs); (ii) compare the  
122 efficacy and safety of any dose of PDE5i with another PDE5i, with placebo or with other  
123 effective treatments; (iii) explore the use of any approved PDE5i (avanafil, sildenafil, tadalafil,  
124 vardenafil) alone or in combination with other treatment modalities both in the general male  
125 population as well as in specific subgroups; (iv) were conducted in accordance with the  
126 Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA statement. On  
127 the contrary, we will exclude: (i) systematic reviews or meta-analyses on patients under 18  
128 years of age; (ii) systematic reviews or meta-analyses assessing the efficacy and safety of  
129 PDE5i for indications not relevant to erectile function; (iii) narrative reviews, editorials and  
130 letters to the editor.

131



## 132 **Outcomes**

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

145

## 146 **Study selection and data collection**

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

153

154 Data extraction will be performed independently by two authors based on a predefined  
155 Microsoft Excel spreadsheet. We will tabulate information regarding systematic review or  
156 meta-analysis characteristics, intervention details and outcomes. To ensure coherence between  
157 the authors, a pilot test will be performed before data extraction [16].

158

## 159 **Quality assessment and strength of evidence**

160 Our overview will employ the AMSTAR 2 tool to evaluate the quality of the included  
161 systematic reviews or meta-analyses [17]. The strength of evidence for all outcomes will be  
162 based on the Grading of Recommendations Assessment, Development and Evaluation  
163 (GRADE) approach [18]. If GRADE was applied in an included systematic review, meta-  
164 analysis or network meta-analysis, it will be reported as determined from the authors. On the  
165 contrary, if GRADE was not performed, we will assess the strength of evidence-based on the

1  
2  
3 166 reported results from this systematic review or meta-analysis. In particular, two reviewers will  
4  
5 167 evaluate risk of bias, inconsistency, indirectness, imprecision and publication bias among trials  
6  
7 168 included in each systematic review or meta-analysis. Any disagreements will be resolved by  
8  
9 169 consensus.

10 170

## 11 171 **Data synthesis**

12 172 A descriptive analysis will be performed and the extent of overlapping among systematic  
13 173 reviews and meta-analyses will be estimated applying the corrected covered area (CCA) and  
14 174 will be presented using novel graphical approaches [19]. When a systematic review and a meta-  
15 175 analysis addressing the same outcome will be identified, data from the meta-analysis will be  
16 176 reported, provided that the meta-analysis includes more primary studies. Similarly, when a  
17 177 systematic review or a meta-analysis and a network meta-analysis addressing the same  
18 178 outcome will be identified, data from the network meta-analysis will be reported, provided that  
19 179 the network meta-analysis includes more primary studies. Among studies with the same design  
20 180 (systematic reviews or meta-analyses or network meta-analyses) assessing similar outcomes,  
21 181 only data from the most recent study will be considered. However, if these meta-analyses were  
22 182 published at a similar period (within 24 months), data from the most methodologically rigorous  
23 183 study will be provided (based on AMSTAR 2) [20]. Furthermore, in studies reporting outcomes  
24 184 for erectile function change after PDE5i intake both with validated and non-validated or  
25 185 dichotomous (yes/no) questionnaires, data concerning the validated questionnaire will only be  
26 186 retrieved.

27 187

28 188 We will construct forest plots of risk estimates with the corresponding confidence interval for  
29 189 all outcomes. In particular, meta-analytic effects for common themes as reported in each study  
30 190 (such as risk ratio, odds ratio or mean difference) will be pooled to provide a descriptive  
31 191 estimate [21]. Additionally, we will evaluate heterogeneity with the  $I^2$  and estimate publication  
32 192 bias with the Egger's test for each outcome [22,23]. Meta-analyses performed with a fixed  
33 193 effects model, will be reanalyzed using the DerSimonian and Laird random effects model.  
34 194 Outcome data will be extracted as reported in each meta-analysis without reviewing the  
35 195 relevant primary studies [24]. All analyses will be performed using Microsoft Excel (Version  
36 196 16.42) and R statistical software (version 3.6.3).

37 197

## 38 198 **PATIENTS AND PUBLIC INVOLVEMENT**

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2  
3 199 This overview of systematic reviews was conceptualized and developed due to the unmet need  
4  
5 200 of male patients and their partners to receive an effective and safe treatment for ED. Even  
6  
7 201 though our study will not involve patients at any step of its implementation, the results of the  
8  
9 202 overall project will be sent to the communication department of Aristotle University of  
10  
11 203 Thessaloniki for a press release. Moreover, because of the growing interest in this topic, the  
12  
13 204 results of the study will not only be published in scientific journals, but also in more general or  
14  
15 205 multidisciplinary journals to reach a broader audience. Of importance, this study will pinpoint  
16  
17 206 the current gaps in the literature and serve as a valuable guide for the design and  
18  
19 207 implementation of further research on the field, improving healthcare facilities and aiding  
20  
21 208 clinicians to properly consult and treat patients with ED receiving PDE5i.  
22

209

## 210 **ETHICS AND DISSEMINATION**

211 Patients and public were not involved for this study protocol and no primary data were collected  
22  
23 212 from individuals. Therefore, no ethics committee approval was required for the present study.  
24  
25 213 In this overview of systematic reviews and meta-analyses, we will undertake an extensive and  
26  
27 214 systematic literature search in an attempt to evaluate the potential benefits and risks of  
28  
29 215 treatment with one PDE5i versus another or placebo. Accordingly, we will assess the effects  
30  
31 216 of PDE5i as part of combination therapy. We will provide relevant recommendations that may  
32  
33 217 serve as a basis for clinicians and policymakers. Our data will be disseminated through a  
34  
35 218 publication in a prestigious, peer-reviewed journal as well as through conference presentations.  
36  
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219

220 **Contributors:** NP, IM, AH, AO and DH contributed to the conception or design of the work.  
21  
22 221 NP, IM, AH, MT, PT and KD contributed to the acquisition, analysis, or interpretation of data  
22  
23 222 for the work. NP and IM drafted the manuscript. AH, MT, PT, KD, AO and DH critically  
24  
25 223 revised the manuscript. All gave final approval and agree to be accountable for all aspects of  
26  
27 224 work ensuring integrity and accuracy.  
28  
29 225

225

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30 228 call RESEARCH – CREATE – INNOVATE (project code: T1EDK-00540).  
31  
32 229

229

230 **Competing interests:** None declared

231

232 **Patient consent for publication:** Not required.

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## PRISMA-P Checklist

Section/topic	#	Checklist item	Information reported		Page
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	✓		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable		
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	✓		2
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓		1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓		8
<b>Amendments</b>	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	Not applicable		
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	✓		8
Sponsor	5b	Provide name for the review funder and/or sponsor	✓		8
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓		8
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	✓		4
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓		4
<b>METHODS</b>					
<b>Eligibility criteria</b>	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	✓		5
<b>Information sources</b>	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	✓		5
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓		5, Data Supplement

Section/topic	#	Checklist item	Information reported		Page
			Yes	No	
<b>STUDY RECORDS</b>					
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
<b>DATA</b>					
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	Lodenafil [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.