

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of phosphodiesterase-type 5 inhibitors on erectile function: an overview of systematic reviews and meta-analyses
AUTHORS	Pyrgidis, Nikolaos; Mykoniatis, Ioannis; Haidich, Anna-Bettina; Tirta, Maria; Talimtzis, Persefoni; Kalyvianakis, Dimitrios; Ouranidis, Andreas; Hatzichristou, Dimitrios

VERSION 1 – REVIEW

REVIEWER	Kirby, Mike University of Hertfordshire, The Centre for Research in Primary and Community Care
REVIEW RETURNED	22-Jan-2021

GENERAL COMMENTS	This looks to be a relevant and important topic. I would like the authors to consider whether their strategy will pick up penile rehabilitation strategies. This is otherwise known as erection restoration programme, otherwise looked fine.
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REVIEWER	Hackett, Geoffrey Aston University
REVIEW RETURNED	24-Mar-2021

GENERAL COMMENTS	I was surprised to find that this was a paper about a proposed meta-analysis of PDE5 inhibitors when many have been done before. They also need to look at studies beyond 12 months of daily Tadalafil as this treats the pathological process of endothelial dysfunction as well as BPH whereas on-demand treats a symptom (ED). I do not think that a paper discussing methodology of yet another proposed meta-analysis is worthy of publication.
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REVIEWER	El-Shaer, Waleed Banha University Hospital
REVIEW RETURNED	06-May-2021

GENERAL COMMENTS	this is will be a nice meta-analysis to point out effectiveness of PDE5i and its side effects some few comments their are some typos. the authors stated that " we will not search for recently published RCTs" . why?? the authors stated that " the primary outcome of our overview is the improvement of erectile function in the general population" how can you define improvement of ED (minimal clinically significant difference)
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

This looks to be a relevant and important topic. I would like the authors to consider whether their strategy will pick up penile rehabilitation strategies. This is otherwise known as erection restoration programme, otherwise looked fine.

>>> We thank Reviewer 1 for the comment. Indeed, the optimal penile rehabilitation strategy after surgical operations such as radical prostatectomy remains a matter of debate. Even though, we will restrict our analyses to patients receiving PDE5i due to ED, we will assess the safety and efficacy of PDE5i in patients with radical prostatectomy-induced ED as it is stated in the first outcome of the corresponding part of “Methods and Analysis”. In particular, we will pick up any systematic reviews, meta-analyses or network meta-analyses addressing the effect of any PDE5i versus another PDE5i or placebo or other treatments in patients after radical prostatectomy. For this purpose, we will explore the use of any PDE5i both in the first months after the operation, as part of a rehabilitation program, as well as in the long-term as part of an adjunct treatment. Therefore, our manuscript was modified accordingly to capture the proposal of Reviewer 1.

Reviewer #2

I was surprised to find that this was a paper about a proposed meta-analysis of PDE5 inhibitors when many have been done before. They also need to look at studies beyond 12 months of daily Tadalafil as this treats the pathological process of endothelial dysfunction as well as BPH whereas on-demand treats a symptom (ED). I do not think that a paper discussing methodology of yet another proposed meta-analysis is worthy of publication.

>>> We thank Reviewer 2 and understand his concerns. It is true that multiple systematic reviews and meta-analyses about PDE5i exist. Due to the increasing interest in PDE5i, available systematic reviews and meta-analyses have explored the effect of PDE5i on multiple outcomes. Hence, each systematic review and meta-analysis addresses a specific outcome. On the contrary, physicians and policymakers require, in most cases, a holistic approach of a given topic to facilitate their evidence-based clinical decision-making. In this scope, overviews of systematic reviews and meta-analyses or umbrella reviews are a promising, new approach that assimilates the vast amount of available research and contextualizes the magnitude of a specific topic. These studies are growing in popularity, as they provide high level of recommendations and indicate potential gaps in the literature, by compiling the results of different systematic reviews, meta-analyses and network meta-analyses. Within this framework, we will perform an overview of systematic reviews aiming to summarize the current evidence regarding the efficacy and safety of PDE5i for the management of ED, since, to our knowledge, no similar study exists.

Reviewer #3

this will be a nice meta-analysis to point out effectiveness of PDE5i and its side effects. some few comments . there are some typos. the authors stated that " we will not search for recently published RCTs" . why??

>>> We thank Reviewer 3 for the question. Overviews of systematic reviews and meta-analyses or umbrella reviews aim to summarize and evaluate the strength of scientific evidence as presented in multiple systematic reviews, meta-analyses or network meta-analyses by combining their outcomes. For our study, due to the plethora of primary studies included in each systematic review, meta-analysis or network meta-analysis regarding ED, all relevant measures will be presented as reported in each study without reviewing the corresponding primary studies. On the contrary, in rare cases where overviews of systematic reviews address a confined topic (and not the effect of PDE5i on ED, where, to date, more than 300 RCTs on the matter exist), the authors search for recently published

RCTs, report their findings and them to the corresponding analyses. Therefore, the fact that we will not search for recently published RCTs and restrict our analyses to systematic reviews, meta-analyses or network meta-analyses was listed as an additional limitation of our study.

the authors stated that " the primary outcome of our overview is the improvement of erectile function in the general population" how can you define improvement of ED (minimal clinically significant difference)

>>> We thank Reviewer 3 for the proposal. We will not define improvement of ED based on the minimal clinically important difference, since it was introduced more than 10 years after the launch of sildenafil. On the contrary, we will evaluate the improvement of erectile function, which will be defined as the mean change in the erectile function after PDE5i administration measured with the International Index of Erectile Function (IIEF). Therefore, the corresponding change was added to our manuscript.