National Institute for Health and Care Excellence

Draft for Consultation

Lower urinary tract symptoms in men

Clinical Guideline Update 97.1

Methods, evidence and recommendations

February 2015

Draft for Consultation

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic-specific members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic-specific members.

Where 'standing Committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic-specific members' is referred to this means the recruited group of members with topic-specific expertise.

All of the standing members and the topic-specific members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on the management of lower urinary tract symptoms in men (NICE clinical guideline CG97) was reviewed in July 2014 as part of NICE's routine surveillance progamme to decide whether it required updating. The surveillance report identified new evidence relating to one area of the guidance:

- The use of phosphodiesterase 5 inhibitors (PDE5Is) for the treatment of lower urinary tract symptoms (LUTS) in men

The review question that the Committee considered was:

- What is the clinical and cost-effectiveness of phosphodiesterase 5 inhibitors alone in the treatment of LUTS?

The original guideline can be found here: http://www.nice.org.uk/guidance/CG97

The full surveillance report can be found here: http://www.nice.org.uk/guidance/cg97/documents/cg97-lower-urinary-tract-symptoms-surveillance-review-decision2

1.2 Strength of recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this addendum denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.3 Information for consultation

You are invited to comment on the new and updated recommendations in this update. These are marked as:

- **[new 2015]** if the evidence has been reviewed and the recommendation has been added or updated

The original NICE guideline and supporting documents are available here.

1.4 Recommendations

1. **Do not offer phosphodiesterase-5-inhibitors (PDE5Is) to treat lower urinary tract symptoms in men, except as part of a randomised controlled trial. [new 2015]**

1.5 Patient-centred care

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. People should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.6 Methods

This update was developed based on the process and methods described in the guidelines manual 2012. Where there are deviations from the process and methods, these are clearly stated in the interim process and methods guide for updates pilot programme 2013.Evidence review and recommendations

1.7 Introduction

Lower urinary tract symptoms in men (LUTS) include problems with storage, voiding and post-micturition symptoms that affect the lower urinary tract. Storage symptoms can include frequency, nocturia and urgency. LUTS are common in men in the UK; bothersome LUTS are estimated to affect about 3% of the male population aged 45- 49 years. The prevalence and severity of LUTS increases with age, making LUTS a major burden for the ageing male population.

Management of LUTS can include conservative, pharmacological and surgical approaches. Amongst the pharmacological approaches, alpha blockers, anticholinergics, 5-alpha reductase inhibitors and other combinations may be used depending on the type and severity of LUTS symptoms. Phosphodiesterase 5 inhibitors (PDE5Is) can also be used in the pharmacological treatment of LUTS, and tadalafil is now licensed for this indication.

1.8 Review question

What is the clinical and cost-effectiveness of phosphodiesterase 5 inhibitors alone in the treatment of LUTS?

1.9 Clinical evidence review

The aim of the review was to assess the effectiveness of Phosphodiesterase 5 inhibitors (PDE5Is) in the management of lower urinary tract symptoms (LUTS) in men compared to placebo, other pharmacological, surgical and conservative management.

A systematic search was conducted (see appendix D) which identified 543 articles. The titles and abstracts were screened and 64 articles were identified as potentially relevant. Full text versions of the articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). 21 articles were included in this review (6 were included in the original guideline CG97 and 15 new articles were identified). The review flow chart for this review is in appendix E.

1.9.1 Methods

- The population included men with LUTS, with or without erectile dysfunction (ED), as LUTS can be associated with ED. ED only populations were excluded as the efficacy of PDE5Is on the symptoms of LUTS is the focus of this review. The original guideline CG97 had a subgroup for men of African family origin; this subgroup was included in this update. To capture information from the trials relevant to the population, it was agreed that the relevant baseline characteristics of age, polypharmacy and comorbidities would be extracted where available, to help inform decision making.
- The PDE5Is listed in the BNF, and evaluated in this evidence review include sildenafil, tadalafil and vardenafil. An experimental PDE5I (not listed in the BNF) was also identified and evaluated in this evidence review; this is UK-369,003, or Gisadenafil (FDA website) and was used in two studies (Tamimi, 2010 & Giuliano, 2010). At the current time (November 2014), tadalafil is the only PDE5I licensed for use in benign prostatic hyperplasia (BPH)/LUTS
- The comparators identified from the searches and included in this review are placebo, alpha blockers and antimuscarinics. With regards to the comparison to alpha blockers, two studies (Kim, 2011 & Yokoyama 2013) used suboptimal doses of Tamsulosin (0.2mg/ day), whereas the BNF recommends a dose of 0.4 mg/day.
- The topic specific members (TSMs) were asked to prioritise the patient important outcomes for LUTS using a ranking method [from 1 (most important) to 9 (least important)]. The rankings from each TSM were then compared and the final ranking of outcomes was based on the most common ranking decision. There was general consensus that symptom scores, such as IPSS, was the most important outcome, followed by quality of life, voiding frequency and maximal urinary flow rate (Qmax) and nocturia. It was agreed that the relevant adverse events had been captured in the outcomes.
- GRADE methodology was used to assess the quality of evidence as follows:

Risk of bias:

- As only RCTs were included, criteria suggested by the GRADE methodology (http://www.gradeworkinggroup.org/) were used for assessing risk of bias.

Indirectness:

- Details from the PICOs in the review protocol(s) (see appendix C) were used to assess the directness of the included studies.

Inconsistency:

- Where appropriate and with sufficient data, meta-analyses were conducted for the above outcomes in Review Manager 5.
- Where meta-analysis was conducted, if significant heterogeneity was detected and no specific clinical heterogeneity could be identified after the sensitivity analysis, the quality of evidence would be downgraded 1 level due to inconsistency with random-effect model.

Imprecision:

A routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimal important difference (MIDs). No information was identified in the COMET database. Information about specific MIDs used to assess imprecision was identified in the original guideline CG97. The same MIDs used in CG97 have been used in this update to assess the imprecision for all outcomes. The MIDs used in CG97 and in this update are:

  - IPSS- 3 point change, identified from CG97
  - IPSS QoL – 0.5 point change, identified from CG97
  - Qmax – 2mL/min change, identified from CG97
  - For all other continuous outcomes, the standard MID of 0.5 standard deviation change was used, as per GRADE working group recommendations.
  - No information was identified for the relevant dichotomous outcomes. Therefore, for all dichotomous outcomes in this systematic review, the thresholds suggested by the GRADE Working Group were adopted (RRR or RRI of 25%: 0.75 or 1.25).
- The MIDs were assessed for each outcome as the differences between groups at follow up, using either change or final scores.

Statistical analysis

- The studies included in this review reported both final scores and change scores. The final scores and change scores were combined in the analyses, this is because the difference in mean final values will on average be the same as the difference in mean change scores.
- Analysis for PDE5Is versus placebo and PDE5Is vs alpha blockers was undertaken using Generic inverse variance method; this is because the majority of study outcomes were analysed using Analysis of Covariance (ANCOVA). Not all studies used the same covariates in their ANCOVA models, and to account for this variation a random effects analysis was used.
- Analysis for PDE5Is versus antimuscarinics was undertaken using inverse variance (continuous outcomes) and reported as mean difference (with 95%CIs). This is because the one study included reporting outcomes for this comparison did not analyse data using ANCOVA and reported mean (SD).
- Several studies could not be included in the meta-analysis due to the way that they reported their data (The full evidence tables for these studies are available in Appendix G), these are:
  - Liguori (2009): This study was included in CG97 and NCGC reported mean (SD) values; The publication reports means, but does not state whether these are mean (SD) or mean (SE). Therefore this publication was not included in the final analysis in the update.
  - Tuncel (2010): This publication only reported mean (without SD, SE or 95%CIs) and % change for IPSS. Mean (SD) was reported for Qmax and QoL and this study has been included in these analyses. Adverse event data from this publication has been included in this review.

- Kumar (2014): This study did not report whether figures are mean or median, SE, SD or CIs. Only adverse event data from this publication has been included in this review.
- Singh (2014): This publication reports mean, but does not state whether the figures are mean (SD) or mean (SE). Only adverse event data from this publication has been included in this review.
- Tamimi (2010): This study reported their data from a Normal Dynamic Linear Model (NDLM) with Bayes analysis and simulations using a posterior probability of ≥2.0. Because of the statistics used in the study, it was inappropriate to use a frequentist formula to calculate the SE and SD values. Only adverse event data from this publication has been included in this review

- A sensitivity analysis was undertaken with the inclusion of data from Liguori (2009) and Singh (2014), assuming that they reported mean (SD). This sensitivity analysis did not change the conclusions about the direction of the evidence. These two studies are not included in the final data and analysis presented in this document. The three other studies (Tuncel, 2010; Kumar, 2014 and Tamimi, 2010) were not included in the sensitivity analysis because they did not report data in a way that could be included in the sensitivity anaysis.

- Population: In 7 studies, all participants had LUTS and ED [Abolyosr (2013), Egerdie (2012), Kaplan (2007), Liguori (2009), Maselli (2011), McVary (2007c), Tuncel (2010)]. 13 studies had a mixed population of LUTS with or without ED which ranged from 28% to 71.7%, however Giuliano (2010), Singh (2014), Stief (2008), Takeda (2014) and Tamimi (2010) did not report numbers or % of participants with ED. Yokoyama (2012) did not report whether they included men with ED. There was a lack of detail on polypharmacy use in population involved in the study. With regards to age of the population involved, the mean age in the majority of studies was 60-62 years, with over half of all study participants (where reported) being ≤65 years.

- Intervention: 13 studies had tadalafil as the intervention; the majority of studies used a dose of 5mg/ day, but doses ranges from 2.5 to 20 mg/ day. 4 studies had sildenafil as the intervention; two studies used a dose of 25mg/day, one study each used a dose of 50mg/ day and 100mg/day respectively. One study used vardenafil at 10mg/day, and two studies used an experimental formulation of PDE5I named UK-369,003 in multiple doses ranging from 10-100mg/ day as modified release or 40mg instant release formulation.

- Comparisons: The comparisons to PDE5Is which matched the review protocol and were included in the clinical review were placebo, alpha blockers and antimuscarinics. With regards to the comparison to alpha blockers, two studies (Kim, 2011 & Yokoyama 2013) used suboptimal doses of Tamsulosin (0.2mg/ day).

- Outcomes: Follow up for all studies was the end of treatment period. The longest follow up point has been used to assess the efficacy and safety, this is 12 weeks in all studies with the exception of Pingerra (2014) and Tuncel (2010), which had 8 weeks treatment and follow up and Abolysr (2013), which had 16 weeks treatment and follow up.

  There are two outcomes that refer to International Prostate Symptom Score (IPSS). One is a patient reported symptom score composed of 7 questions regarding voiding, frequency, storage symptoms and nocturia, with a score that ranges from 0 to 35.

  The second is the IPSS Quality of life (QoL) outcome which is a single question *"If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?"* Participants responded to this question on a scale of 0 to 6.

  For both the IPSS symptom score and quality of life measure a higher score indicates poorer symptom score or quality of life. It was idenitifed that PDE5Is can be associated with the rare adverse events of sudden deafness and eye problems (non-arteric anterior ischemic neuropathy [NAION]), and it was agreed that this information would be extracted

and discussed where it was reported in the included studies. However, no information regarding these adverse events was identified amongst the included studies.

For a summary of included studies please see table 1 (for the full evidence tables and full GRADE profiles please see appendices G and H).

Table 1: Included studies summary

Reference	Participants	Intervention and comparators	Outcomes reported
PDE5 vs Placebo or other drugs			
Tadalafil			
Dmochowski (2010)	N=200, men aged >40 years with BPH-LUTS, with or without bladder obstruction (58.6-59.4% had ED)	Tadalafil 20mg/ day vs placebo for 12 weeks	-IPSS[(b)] -Qmax
Egerdie (2012)	N=606, Men aged >45 years with >3 month history of ED and >6 month history of BPH-LUTS	Tadalafil 2.5 or 5mg/ day vs placebo for 12 weeks	-IPSS[(b)] - BII[(b)] -Qmax
Kim (2011)	N=151 men aged >45 years with BPH LUTS for >6 months (49-70.6% had ED)	Tadalafil 5mg vs tamsulosin 0.2mg vs placebo for 12 weeks	-IPSS[(b)] -BII[(b)] -Qmax -Adverse events
Kumar (2014)	N=125 men, aged >50 years, with IPSS score >8 (28-45% had ED)	Tadalafil 10mg vs alfuzosin 10mg for 3 months	-IPSS[(b)] -Qmax - IPSS QoL
Ligouri (2009) [included in CG97, 2007]	N=66, men with ED and LUTS	Tadalafil 20mg alternate days vs alfuzosin 10mg/ day for 12 weeks	-IPSS[(b)] -IPSS QoL -Qmax -Nocturia
Maselli (2011)	N=56, men aged >50 years who previously underwent prostate surgery for LUTS/BPH, presented with persistence of storage symptoms and ED	Tadalafil 5mg/ day vs solifenacin 5mg/ day for 12 weeks	-IPSS[(b)] -IPSS QoL -Qmax -Voiding frequency -Nocturia -Adverse events
McVary (2007b) [included in CG97, 2007]	N=281 men aged >45 years with LUTS secondary to BPH for >6 months (59- 71.7% with ED)	Tadalafil (escalated dose from 5mg – 20mg) vs placebo for 12 weeks	-IPSS[(b)] -IPSS QoL -BII[(b)] -Qmax -Adverse events
Oelke (2012)	N=172 men, aged ≥45 years who had had LUTS for >6 months at screening (69-70.8% had ED)	Tadalafil 5mg once daily vs Tamsulosin 0.4mg vs placebo for 12 weeks	- IPSS[(b)] - Nocturia -BII[(b)] -IPSS QoL -Qmax - Adverse events
Pinggera (2014	N=97 men aged >45 years with moderate-severe BPH- LUTS	Tadalafil 5mg/ day vs placebo for 8 weeks	-Adverse events

Reference	Participants	Intervention and comparators	Outcomes reported
	(61.7-66% had ED)		
Porst (2011)	N=325 men aged >45 years with BPH LUTS for >6 months. ED in treatment group 69.6%, in placebo group 68.3%	Tadalafil 5mg/ day vs placebo for 12 weeks	-IPSS[(b)] -BII[(b)] -Qmax -Adverse events
Roehrborn (2008) [included in CG97, 2007]	N=1058 men, aged >45 years, with BPH LUTS. ED in treatment groups ranged from 64.9- 69.44% and 67.3% in placebo group	Tadalafil 2.5mg vs tadalafil 5mg vs tadalafil 10mg vs tadalafil 20mg vs placebo for 12 weeks	-IPSS[(b)] -IPSS QoL -BII[(b)] -Adverse events
Singh (2014)	N=133 men, aged >45 years with LUTS due to BPH. no ED prevalence states in paper, but IIEF scores at baseline range from 10.08 - 11.77	Tadalafil 10mg vs tamsulosin 0.4mg/ day for 12 weeks	-IPSS[(b)] -IPSS QoL -Qmax -Adverse events
Takeda (2014)	N=610 men aged >45 years, Japanese and Korean men with LUTS. No details on % of study population with ED	Tadalafil 5mg vs placebo for 12 weeks	-change in IPSS[(b)] -IPSS QoL -Qmax -Adverse events
Yokoyama (2012)	N=612 men with LUTS suggestive of BPH. Not stated whether participants has ED, no baseline data to indicate.	Tadalafil 2.5mg vs tadalafil 5.0mg vs tamsulosin 0.2mg vs placebo for 12 weeks	-IPSS[(b)] -IPSS QoL -BII[(b)] -Qmax -Adverse events
Sildenafil			
Abolyosr (2013)	N= 150 men, aged >45 years with LUTS due to BPH +ED	Sildenafil 50mg vs doxazosin 2 mg for 4 months	-IPSS[(b)]
Kaplan (2007) [included in CG97, 2007]	N=62 men aged >50 years with previously untreated LUTS. All participants had LUTS and ED	Sildenafil 25mg/ day vs alfuzosin 10mg/ day for 12 weeks	-IPSS[(b)] -Qmax -Voiding frequency -Nocturia -Adverse events
McVary (2007c) [included in CG97, 2007]	N=370 men aged >45 years with ED and LUTS associated with BPH	Sildenafil 100mg/ day vs placebo for 12 weeks	-Adverse events
Tuncel (2010)	N=60, men with BPH-LUTS and ED	Sildenafil 25mg, 4 x weekly vs tamsulosin 0.4mg/ day	-IPSS[(b)] -Qmax
Vardenafil			
Steif (2008) [included in CG97, 2007]	N= 222, men aged >45 years with BPH/LUTS, numbers with ED not stated, but IIEF score	Vardenafil 10mg/ day vs placebo for 8 weeks	-IPSS[(b)] -Urolife QoL -Qmax -Adverse events

Reference	Participants	Intervention and comparators	Outcomes reported
	of 15.9 in both groups at baseline.		
UK- 369,003 modified release (MR) and instant release (IR)			
Giuliano (2010)	N=310, men aged >18 years with overactive bladder. +/- ED, numbers with ED not reported.	UK-369,003 10, 25, 50, 100mg/ day modified release vs placebo for 12 weeks	-IPSS[(b)] -IPSS QoL -Voiding frequency -Nocturia -Adverse events
Tamimi (2010)	N=418, men aged >40 years with BPH, with or without ED. Numbers with ED not reported.	UK-369,003 10mg vs 25mg vs 50mg vs 100mg modified release vs 40mg instant release vs tamsulosin 0.4mg prolonged release vs placebo for 12 weeks	-IPSS[(b)] -Qmax -Adverse events

(a) Note that several studies have combination trial arms, but the details of these interventions are not included here as we are excluding combination of tadalafil + other treatment from this review.

(b) IPSS and BII are symptom score outcomes

Table 2: Summary of comparisons

Type of PDE5I	PDE5Is vs placebo	PDE5Is vs alpha blockers	PDE5Is vs antimuscarinics
Tadalafil			
	Dmochowski (2010) Egerdie (2012) Kim (2011) Kumar (2014) McVary (2007b) Oelke (2012) Pingerra (2012) Porst (2011) Roehrborn (2008) Takeda (2008) Yokoyama (2012)	Kim (2011) Kumar (2014) Liguori (2009) Oelke (2012) Singh (2014) Yokoyama (2012)	Maselli (2010)
Sildenafil			
	McVary (2007c)	Abolyosr (2013) Kaplan (2007) Tuncel (2010)	
Vardenafil			
	Stief (2008)		
UK-369,003			
	Giuliano (2010) Tamimi (2010)	Tamimi (2010)	

Note: Some studies are multi-arms trials.

1.10 Health economics

The Committee was required to make decisions based on the best available evidence of both clinical and cost effectiveness. An additional search was undertaken using the same clinical search terms with an economic evaluations filter to identify studies assessing the cost-effectiveness or cost-utility of phosphodiesterase 5 inhibitors for the treatment of LUTS (see appendix J). The same criteria were used as for the clinical review. The search retrieved 286 articles. The titles and abstracts were screened for possible inclusion, and no articles were selected for further examination of the full-text version.

A review flowchart is provided in appendix K.

As no relevant published studies were found, and a new analysis was not conducted, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The qualitative approach to economic impacts was appropriate in this circumstance as there was evidence showing that the treatment effect does not reach a clinically important difference. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication.

Table 3 provides the unit costs of PDE5Is, alpha-blockers and 5-alpha-reductase inhibitors. The doses for alpha-blockers, 5-alpha-reductase inhibitors and tadalafil 5 mg were obtained from the British National Formulary. All other doses of PDE5Is are not licensed and based on options available in the Drug Tariff. Therefore, although most of these doses were used in included studies in the clinical systematic review, all annual costs for PDE5Is apart from tadalafil 5 mg should be considered hypothetical and not necessarily what would apply for the treatment of LUTS. All prices were obtained from the Drug Tariff.

Table 3: Prices of medicines for LUTS

	Medicine	Doses per day	Cost per pack	Doses per pack	Cost per dose	Annual cost
Phosphodiesterase type-5 inhibitor*	Tadalafil 5 mg	1	54.99	28	1.96	716.83
	Tadalafil 10 mg	1	26.99	4	6.75	2462.84
	Tadalafil 20 mg	1	26.99	4	6.75	2462.84
	Sildenafil 25 mg	1	1.12	4	0.28	102.20
	Sildenafil 50 mg	1	1.16	4	0.29	105.85
	Sildenafil 100 mg	1	1.25	4	0.31	114.06
	Vardenafil 5 mg	1	7.56	4	1.89	689.85
	Vardenafil 10 mg	1	14.08	4	3.52	1284.80
	Vardenafil 20 mg	1	23.48	4	5.87	2142.55
	UK-369,003	unknown	unknown	unknown	unknown	unknown
Alpha-blocker	Alfuzosin 2.5 mg	3	3.88	60	0.06	70.81
	Doxazosin 2 mg	1	0.92	28	0.03	11.99
	Doxazosin 4 mg	1	1.10	28	0.04	14.34
	Doxazosin 4 mg modified release	1	5.00	28	0.18	65.18
	Tamsulosin 400 micrograms	1	4.63	30	0.15	56.33
	Terazosin 5 mg	1	2.76	28	0.10	35.98
	Terazosin 10 mg	1	8.05	28	0.29	104.94
5alpha-	Dutasteride 500	1	16.80	30	0.56	204.40

	Medicine	Doses per day	Cost per pack	Doses per pack	Cost per dose	Annual cost
reductase inhibitor	micrograms					
	Finasteride 5 mg	1	1.73	28	0.06	22.55

1.11 Evidence statements

1.11.1 Clinical evidence statement

1.11.1.1 PDE5I vs placebo

Overall

There is very low quality evidence from 11 trials and about 4200 men suggesting that there was no clinically important difference between PDE5Is and placebo in the critical outcomes of IPSS (symptom score) and IPSS quality of life. For the important outcome of maximal urinary flow rate (Qmax), there was moderate quality evidence from 12 studies and about 3750 men which showed no clinically important difference in the effects of PDE5Is compared to placebo. For voiding frequency (1 study, very low quality) and nocturia (4 trials, low quality), there was no difference between PDE5Is and placebo . Very low quality evidence from 5 trials and approximately 1200 men was inconclusive with regards to whether the symptom score BII improved with PDE5I use because there were no clinically relevant MIDs on which to judge whether PDE5Is were clinically effective. (more detail on the evidence is included in the sections for tadalafil and other PDE5Is below).

For harms, there was insufficient data to estimate the effect of treatment on dizziness and postural hypotension; however there was a clinically important increase in headaches (risk ratio 2.29 95%CI 1.63 to 3.21) and flushing (risk ratio 4.00 95%CI 1.47 to 10.89) with PDE5I treatment (low quality evidence from 13 studies and approximately 4960 people and 4 studies and about 1550 people respectively). There was very low quality evidence from 14 studies and approximately 3800 people that indicated there may be more withdrawals due to adverse events in the PDE5I group, however there is uncertainty around the estimate.

Tadalafil

There is very low quality evidence that suggests there may be no clinically important difference between tadalafil and placebo in the critical outcome of IPSS (symptom score) (9 studies and approximately 3900 people, very low quality evidence) and there is no clinically important difference between tadalafil and placebo in IPSS quality of life outcome (10 studies and about 3700 men low quality evidence). There was very low quality evidence from up to 10 trials and up to about 3,900 men comparing tadalafil with placebo on the outcome of BII, however it is unclear whether the change was clinically meaningful due to the absence of clinically relevant MIDs for this outcome (the standard MID was not considered appropriate to judge clinical effectiveness for this outcome).. For maximal urinary flow (Qmax) there was very low quality evidence from 4 studies and 860 men which suggested that there may be no clinically important difference between tadalafil and placebo. For harms, there was generally insufficient data to estimate the effect, with the exception of headaches; where low quality evidence from 10 trials in nearly 4,100 men showed a doubling of headaches in people taking tadalafil (risk ratio 2.00 95%CI 1.32 to 3.04).

Other PDE5Is (Sildenafil, Vardenafil, UK-369,003)

Very low quality evidence from 1 study and 360 people suggested that sildenafil may be more effective than placebo in improving IPSS (symptom score); there is very low quality evidence from 1 study and 209 people suggesting that there may be no difference between UK-369,003 and placebo in improving IPSS (symptom score).

There is very low quality evidence from 1 trial with 360 people suggesting that sildenafil may be more effective than placebo in improving IPSS quality of life. One study reported quality of life using the Urolife scale; for this outcome one study with moderate quality evidence showed that vardenafil is more effective than placebo.

One study with 128 people suggests that UK-369,003 may be more effective than placebo in improving maximal urinary flow rate (Qmax) and one study with 360 people suggests that there is no clinically important difference between sildenafil and placebo in improving Qmax.

There is no difference in improvement of voiding frequency in people taking UK-369,003 compared to placebo (1 study, 247 people, very low quality,).

For harms, very low quality evidence from 2 trials, one with sildenafil (n= 369 participants) and one with vardenafil (n= 221 participants) showed a clinically important increase in headaches (sildenafil, risk ratio 3.33 95%CI 1.38 to 8.07; vardenafil, risk ratio 7.32 95%CI 1.70 to 31.47). Evidence also suggested that there may be an increase in flushing with sildenafil (1 study, 369 participants, very low quality evidence) and there may be an increase in withdrawals due to adverse events with both vardenafil (1 study, 221 participants, very low quality evidence) and sildenafil (2 studies, 369 participants, very low quality evidence).

1.11.1.2 PDE5I vs alpha blockers

Overall

There is low and very low quality evidence which shows there is no clinically important no difference between PDE5Is and alpha blockers in improving IPSS symptom scores (9 studies, approximately 1200 people), IPSS quality of life (7 studies, approximately 780 people), maximal urinary flow rate (Qmax) (8 studies, about 820 people) and nocturia (4 studies, 479 people). There is a small but clinically unimportant improvement in voiding frequency (favouring alpha blockers when compared to tadalafil), this is based on very low quality evidence from 1 study with 41 people. It could not be assessed whether any change in BII symptom score (one study [tadalafil], 100 people, very low quality), was clinically important due to the absence of clinically relevant MIDs for this outcome. For harms, the data was inconclusive and the effects of the PDE5Is on flushing, dizziness, headaches and withdrawals could not be estimated (very low quality evidence from up to 7 studies and approximately 1400 people).

Tadalafil

There is no difference in the effects of PDE5Is compared to alpha blockers for the outcomes of IPSS symptom score (5 studies, 739 people, low quality evidence), IPSS quality of life (6 studies, 741 people, very low quality evidence), maximal urinary flow rate (Qmax) (6 studies, 738 people, very low quality evidence) and nocturia (3 studies, 438 people, very low quality evidence). It could not be assessed whether any change in BII symptom score (1 study, 100 people, very low quality evidence) was clinically important due to the absence of clinically relevant MIDs for this outcome. For harms, the data was inconclusive and the effects of tadalafil on flushing, dizziness, headaches and withdrawals could not be estimated (very low quality evidence from up to 6 trials with 1000 people).

Other PDE5Is (Sildenafil & UK-369,003)

There is very low quality evidence from 1 trial with 40 men which suggested that there is no difference between sildenafil and alpha blockers in the critical outcome of IPSS symptom score and IPSS quality of life.. For the outcome of voiding frequency, the evidence suggested that there may be a benefit for alpha blockers (1 study, n=41, very low quality evidence).For UK-369,003, the outcomes for IPSS and maximal urinary flow rate are not estimable due to the way the study reported the outcomes. For harms, there was insufficient data to estimate the effects of sildenafil and UK-369,003 on flushing, dizziness and withdrawals (data from 1 to 6 studies with a range of 100 to 1000 people, very low quality evidence).

1.11.1.3 PDE5I vs antimuscarinics

Tadalafil

There is very low quality evidence from one study with 56 men comparing tadalafil to solifenacin which shows that there is no clinically important difference in the effects of tadalafil on the critical outcomes of IPSS symptom score and IPSS quality of life and the important outcomes of voiding frequency and nocturia. For maximal urinary flow (Qmax), there is a clinically important improvement with antimuscarinic use (MD -5.00 95%CI -6.08 to -3.92). For harms, only the incidence of headache was reported and there was insufficient data to estimate the effect (very low quality).

1.11.2 Health economic evidence statements

No economic evaluations were identified that compared PDE5Is with placebo or other medications for LUTS. PDE5Is are unlikely to be cost effective as they do not provide a clinically important improvement in effectiveness, and cost more, compared with currently recommended alpha-blockers and 5-alpha-reductase inhibitors.

1.12 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	Topic Specific Members' (TSMs) prioritisation of outcomes identified that symptom scores (particularly IPSS) and quality of life measures (particularly IPSS quality of life) were the critical outcomes for this review; this was because these subjective markers are patient reported outcomes and better reflect any change in symptoms that men with LUTS may experience with treatments. The TSMs agreed that while objective measures such as maximal urinary flow rate (Qmax) are useful clinically, they do not accurately reflect any change in symptoms that the patient with LUTS may experience (i.e. an improvement in Qmax does not correlate with improved LUTS symptoms from a patient's perspective). It was agreed that the adverse events outcomes (postural hypotension, dizziness, flushing, headaches and withdrawals due to adverse events) were all important outcomes with equal ranking, as the adverse events associated with any treatment need to be balanced against the benefits of the treatment. The symptom score IPSS and the IPSS quality of life measures were the critical outcomes because these outcomes reflect the bothersome-ness of the symptoms; bothersome LUTS can have a major impact on a man's quality of life, and any change in LUTS are best reflected by a change in the symptom score (IPSS) and the

	IPSS quality of life score. The Standing Committee members questioned the TSMs on the use of the benign prostatic hyperplasia impact index (BII) symptom score. The Committee considered that the BII symptom score outcome was less relevant in decision making because there are no published MIDs for meaningful interpretation using the BII. Also, the Committee felt that using the default change of 0.5 was not appropriate and did not assist their interpretation of the BII outcome. Hence, the Committee agreed that they could not interpret the clinical benefit or harm using the BII outcome. Additionally, it was discussed that the BII symptom score is not well used, and that IPSS is far more widely used in clinical practice. The Committee also discussed the Urolife quality of life outcome, and whether it is validated in a population with LUTS; this is not reported in literature and the TSMs were not familiar with the assessment tool, therefore the Committee decided that this outcome was not important in decision making. There were fewer outcomes prioritised in this update of this guideline (2015) compared to the original CG97 (2010). This was because 7-9 outcomes is the recommended number (in line with GRADE working group recommendations). Notably, in this update the outcome international index of erectile function (IIEF) score was not included as the focus and purpose of the review was the effect of PDE5Is on LUTS alone, not on erectile dysfunction (ED) symptoms. In this update, specific adverse events were also identified that were meaningful to patients and important to decision making, rather than using the approach used in CG97 of including all adverse events reported by a study. The outcome of postural hypotension was added into this guideline update as the TSMs felt that this was an important adverse event to consider if prescribing PDE5Is, because if this occurs it can lead to falls and have a major impact on downstream care and costs. All comparisons reported the critical outcomes of IPSS symptom score and IPSS QoL, these 2 outcomes were pivotal in the Committee's decision making.
Quality of evidence	In this update, evidence was identified for PDE5Is vs placebo, alpha blockers and antimuscarinics. No studies were identified comparing PDE5Is to 5-alpha reductase inhibitors (5ARIs). The main risk of bias associated with the evidence were: • The majority of studies did not adequately report allocation concealment, randomisation or blinding. • Many studies were sponsored by pharmaceutical companies. Five studies could not be included because of the way that the data were presented in the publications; two of these studies were included in a sensitivity analysis to ascertain whether including the data would make a difference to the results (making an assumption the data was mean [SD]); the inclusion of this data made no difference to the results and was not included in the final analysis. The three other studies (Tuncel, 2010; Kumar, 2014 and Tamimi, 2010) were not included in the sensitivity analysis for the critical

outcomes because they did not report data in a way that could be included in the meta-anaysis (no SD, SE or CI reported). The adverse event data from these studies was included in the review.

Population- was composed mostly of men with both LUTS and ED (7 studies, all participants had ED and LUTS, and 13 studies had LUTS with or without ED with % of ED ranging from 28 -71.7%). There was a lack of information in the included studies on the number of participants who had comorbidities or polypharmacy; this is important because LUTS is more prevalent in an older population and therefore complex health needs have t be taken into account when making decisions about the most appropriate treatment.

Interventions- the licensed PDE5I tadalafil accounted for the majority of evidence; with 11/16 studies vs placebo; 6/10 studies vs alpha blocker, and the one study vs antimuscarinics. There was variation in the dose given; 6 of the 14 studies using tadalafil used the BNF recommended dose for BPH- LUTS of 5mg day and the remainder ranged from 2.5mg/ day to 20mg/day

The Committee discussed the evidence for each comparison, this is briefly summarised below:

PDE5Is vs placebo

All outcomes for this comparison were low or very low quality evidence, except one outcome (Urolife quality of life [QoL]) which was moderate quality, however the TSMs indicated that this quality of life score was not validated for use in men with LUTS.

There was no clinically important difference for tadalafil for IPSS, IPSS QoL, maximal urinary voiding volume (Qmax), nocturia and postural hypotension, although there was a statistical benefit for tadalafil for IPSS and IPSS QoL outcomes. There was statistical improvement in BII with tadalafil, but for the reasons noted above, the Committee considered it was not possible to determine if the amount of change was clinically meaningful. There were no results for voiding frequency. For harms, tadalafil was associated with a clinically important increase in incidence of headache.

There may be clinical improvement in IPSS symptom score and IPSS QoL with sildenafil compared to placebo. There was no difference in improvement of Qmax with sildenafil compared to placebo. Voiding frequency was not reported in studies assessing sildenafil. Sildenafil may be associated with a clinically important increase in the adverse events of flushing, headache and withdrawals due to adverse events.

There was no clinically important difference between PDE5Is overall and placebo for IPSS symptom score, IPSS QoL or Qmax. The change in BII with PDE5Is could not be assessed due to a lack of MIDs. With regards to harms, there were increased instances of flushing and headaches in the people taking PDE5Is and there may be increased instances of withdrawals in people taking PDE5Is.

	PDE5Is vs alpha blockers All evidence for this comparison was low or very low quality. Sildenafil shows that there is no clinically important improvement in IPSS QoL. Alpha blockers show an improvement in voiding frequency when compared to tadalafil. For all other outcomes (IPSS symptom score, BII, Qmax, nocturia) there was no difference between tadalafil, sildenafil or UK-369,003 and alpha blockers. There was no difference between any PDE5I and alpha blocker with regards to the adverse events of headache, flushing, dizziness and withdrawals due to adverse events. Postural hypotension was not reported for this comparison. **PDE5Is vs antimuscarinics** There was one study included in this comparison with low and very low quality evidence. There was no difference between tadalafil and solifenacin for IPSS symptom score, IPSS QoL, voiding frequency and nocturia. Qmax had a clinically important improvement with solifenacin compared to tadalafil. There was no difference in the incidence of headaches between the tadalafil and antimuscarinic groups. In summary, there was no clear evidence of an effect for PDE5Is compared to placebo, and no difference between PDE5Is and alpha blockers in a population of men with LUTS and ED.
Trade-off between benefits and harms	There were statistical improvements in the critical outcomes of IPSS symptom score and IPSS QoL with tadalafil, sildenafil and overall compared to placebo, and there may be clinically important improvements in IPSS symptom score and IPSS QoL with sildenafil only. For PDE5Is compared to alpha blockers, sildenafil showed clinical improvement in the critical outcome of IPSS QoL but there was no difference between PDE5Is and alpha blockers for the other critical outcome of IPSS symptom score. There was no difference in headache, flushing and dizziness between PDE5Is and alpha blockers. The Committee considered that for the population included in the evidence base, which was largely men with LUTS and ED, there was a small benefit with PDE5Is compared to placebo, and that PDE5Is were no different in their effectiveness to usual care (alpha blockers). The Committee discussed that the benefits of treatment with PDE5Is for this population may outweigh the reversible adverse events of headache and flushing. However, the Committee were concerned that any improvements in the subjective patient outcomes of IPSS symptom score, IPSS QoL and BII may be confounded by improvement in ED, rather than LUTS specific improvement alone; therefore leading to uncertainty in the benefits of PDE5Is in managing LUTS alone in men with LUTS. The Committee considered that the evidence could not be extrapolated to men with LUTS who did not have ED as this population was not represented by the evidence presented. The standing Committee questioned the TSMs on whether it was

	appropriate for tadalafil to be given to men with LUTS and ED; the TSMs responded and discussed with the Committee the potential need to minimise polypharmacy in patients with complex health needs; if a man with LUTS and ED requires pharmacological management, and if PDE5Is have equal effect to an alpha blocker, it may be more appropriate to prescribe one drug (a PDE5I) rather than two (alpha blocker and ED drug). The TSMs stated that approximately 40% of the population with LUTS present with LUTS and ED. The Committee discussed that the evidence presented for PDE5Is vs alpha blockers was not sufficiently powered or analysed as a non-inferiority (or equivalence) trial and therefore cannot be interpreted as showing that PDE5Is are as effective as alpha blockers. It was noted that the evidence for PDE5Is was mostly of very low quality which reduced the confidence in the evidence representing the true effects of the intervention in a LUTS and ED population. The Committee discussed the balance between side effects of the treatment and benefits; it was noted that the adverse effects of treatment highlighted in the evidence (headaches and flushing) were unpleasant, but not life threatening, and were reversible. The Committee discussed that the potential side effects should be discussed with the patient prior to commencing any therapy and it should be individual patient choice as to whether they felt that the benefits of the treatment outweighed the harms for them. The Committee considered that PDE5Is offered small benefits for men with LUTS and ED, but the evidence was low and very low quality. The Committee believed that there was no evidence of benefit of PDE5Is in men with LUTS alone. Due to the small benefits in a specific population of men with LUTS and ED, the Committee decided that it was inappropriate to extrapolate the evidence to a LUTS only population, and that PDE5Is should not be offered to men with LUTS alone. It was discussed that more, high quality research on the use of PDE5Is in men with LUTS alone (without ED) was needed, and therefore PDE5Is should only be offered to men with LUTS as part of a randomised controlled trial (RCT) which fulfil the criteria set out in the research recommendation associated with this evidence review.
Trade-off between net health benefits and resource use/ Economic considerations	No published economic evaluations were identified in the literature. An original model was developed for the 2010 guideline that compared alpha-blockers with alpha-blockers plus 5-alpha-reductase-inhibitors. The 2010 model used an improvement in IPSS of 3 points to distinguish between treatment success and treatment failure. The meta-analysis of all PDE5Is for the present systematic review found a mean improvement in IPSS of 1.78 (95% CI 1.01 to 2.55). The 2010 model was not adapted for the present guideline update to include PDE5Is because none of the simulated cohort would have been considered a treatment success. The Committee considered that one study, McVary et al. (2007c), found a 4.4 (95% CI 1.87 to 6.93) point improvement in IPSS for sildenafil compared with placebo. The findings of this study were of limited usefulness

	because they were inconsistent with the 9 studies on other PDE5Is that reported this outcome, it is of very low quality, and there is likely to be confounding with improvements in erectile dysfunction (ED) as opposed to improvements in LUTS alone. This study was considered by the 2010 Guideline Development Group and PDE5Is were excluded from the economic modelling conducted at the time. The Committee considered the cost of PDE5Is, alpha-blockers and 5-alpha-reductase inhibitors. Tadalafil 5mg once-per-day is the only medicine currently licensed for benign prostatic hyperplasia. The annual cost of this treatment is £716.83 which is more costly than alpha-blockers and 5-alpha-reductase inhibitors. Vardenafil has a similar cost as tadalafil. Sildenafil, which is not currently licensed for LUTS, has an annual cost of £102.20 to £114.06 (25 mg to 100 mg). This is more costly than all, but one, alpha-blockers and more costly than one 5-alpha-reductase inhibitor. The Committee concluded that PDE5Is are highly likely to not be cost-effective compared with currently recommended alpha-blockers because they have not been shown to be clinically effective and are more costly.
Other considerations	Pharmacological treatment of LUTS is generally offered to men with bothersome LUTS when conservative management (for example, lifestyle advice) is not appropriate or unsuccessful. Patient view of the use of PDE5Is for LUTS: the patient representative discussed with the Committee that they would be willing to try PDE5Is if there was demonstrable benefit with the treatment. It was also discussed that a balanced view of the benefits and harms of the medications should be fully explained to a person considering PDE5I treatment, and that the patient should be fully involved in the decision making process with regards to their treatment. Links to other relevant recommendations and NICE guidance: this topic links to several other pieces of NICE guidance, which can be accessed through the nice pathway http://pathways.nice.org.uk/pathways/lower-urinary-tract-symptoms-in-men This update was focussed on whether PDE5Is were clinically effective in the treatment of men with LUTS alone. The Committee discussed the fact that they could not make recommendations on the use of PDE5Is unless more high- quality research with the correct population was undertaken, the Committee decided that it was appropriate to make a research recommendation for this evidence review. The research recommendation made by the Commitee was: What is the clinical and cost effectiveness of the use of PDE5Is alone compared to standard care in people with LUTS without erectile dysfunction (ED). This was because the Committee felt that the mixed population (LUTS and ED) of the studies in this review were not appropriate to enable a recommendation to be made on the use

	of PDE5Is in men with LUTS alone.

1.13 Recommendations

Do not offer phosphodiesterase-5-inhibitors (PDE5Is) to treat lower urinary tract symptoms in men, except as part of a randomised controlled trial.

1.14 Research recommendations

What is the clinical and cost effectiveness of phosphodiesterase-5 inhibitors (PDE5Is) for treating LUTS in men who do not have erectile dysfunction?

Why is this important?

There is a gap in the evidence about the effectiveness of PDE5Is in men with LUTS who do not have erectile dysfunction. The current evidence includes men with LUTS and erectile dysfunction. Therefore the standing Committee decided that it was not appropriate to make a recommendation about the routine use of PDE5Is in clinical practice. More evidence is needed to enable a recommendation to be made on the use of PDE5Is in all men with LUTS, including those without erectile dysfunction. The study should be a randomised controlled trial comparing PDE5Is with usual care in men over 45 years with LUTS without erectile dysfunction. Outcomes should include IPSS symptom score, IPSS quality of life, maximal urinary flow, residual urine volume, postural hypotension, headaches and withdrawals due to adverse events.

Table 4: Criteria for selecting high-priority research recommendations

PICO	**Population:** men with LUTS (without erectile dysfunction), >45 years **Intervention:** PDE5Is alone **Comparison:** Usual care **Outcomes:** IPSS symptom score IPSS quality of life Maximal urinary flow Residual urine volume Postural hypotension Headaches Withdrawals due to adverse events
Current evidence base	The current evidence base consists of 21 trials of PDE5Is compared to placebo, alpha blocker or antimuscarinic. The population of these trials is composed of men with LUTS and the majority also have ED. The Committee considered that they were currently unable to make a recommendation on the use of PDE5Is for the treatment of LUTS alone, as the population of the evidence base did not reflect accurately the population of men with LUTS seen in clinical practise in the UK, and therefore it would be inappropriate to extrapolate the evidence to this population.
Study design	Randomised controlled trials
Other comments	Men with LUTS and ED should be excluded from the trial, as there is already an evidence base on this population.

1

21 References

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3 Glossary and abbreviations

Please refer to the NICE glossary.

1 Appendices

2 Appendix A: Committee members and 3 NICE teams

A.1 4 Standing Committee members

Name	Role
Damien Longson (Chair)	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust
Catherine Briggs	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Senior Research Fellow, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Nuala Lucas (until December 2014)	Consultant Anaesthetist, Northwick Park Hospital, Middlesex
Kath Nuttall	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset
Philippa Williams	Lay Member
Sophie Wilne	Paediatric Oncologist, Nottingham Children's Hospital

A.2 5 Topic-specific Committee members

Name	Role
Jan Farrell	Nurse Consultant Urology, Rotherham NHS Foundation Trust
Vikky Morris	Consultant Physician – Care of Older People and General Medicine, Musgrove Park Hospital, Somerset
Raj Persad	Professor and Consultant Urological Surgeon, North Bristol NHS Trust
John Taylor	Lay Member

A.3 6 NICE project team

Name	Role
Mark Baker	Clinical Advisor
Christine Carson	Guideline Lead
James Hall	Editor
Bhash Naidoo	Technical Lead (Health Economics)
Beth Shaw	Technical Lead
Louise Shires	Guideline Commissioning Manager
Jennifer Wells	Guideline Co-ordinator

Name	Role
Erin Whittingham	Public Involvement Advisor

A.4 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Sara Buckner	Technical Analyst
Paul Crosland	Health Economist
Nicole Elliott	Associate Director
Sarah Glover	Information Specialist
Susannah Moon	Programme Manager
Rebecca Parsons	Project Manager
Charlotte Purves	Administrator
Toni Tan	Technical Adviser

1 Appendix B: Declarations of interest

Committee member	Interest declared	Type of interest	Decision taken
Damien Longson	Family member employee of NICE	Personal family non-specific	Declare and participate
Damien Longson	Director of Research & Innovation, Manchester Mental Health & Social Care NHS Trust	Personal non-specific pecuniary	Declare and participate
Catherine Briggs	Husband is a consultant anaesthetist at the University Hospital of South Manchester.	Personal family non-specific	Declare and participate
Catherine Briggs	Member of the Royal College of Surgeons, the Royal College of General Practitioners, the Faculty of Sexual and Reproductive Health and the BMA.	Personal non-specific pecuniary	Declare and participate
John Cape	Trustee of the Anna Freud Centre, a child and family mental health charity which applies for and receives grants from the department of health and the national institute for health research.	Personal non-specific non-pecuniary	Declare and participate
John Cape	Member of British Psychological Society & British Association for Behaviour & Cognitive Psychotherapists who seek to influence policy towards psychology & psychological therapies.	Personal non-specific non-pecuniary	Declare and participate
John Cape	Clinical Services Lead half-day a week to Big Health, a digital health company that has one commercial product; an online CBT self-help programme for insomnia with online support	Personal non-specific financial	Declare and participate
Alun Davies	Research grant funding: Commercial: Vascular Insights; Acergy Ltd; Firstkind; URGO laboratoires; Sapheon Inc (terminated 2013). All administered by Imperial College London as Sponsor and Prof Davies as CI.	Personal non-specific pecuniary	Declare and participate
Alun Davies	Non-commercial: NIHR, BHF, Royal	Personal non-specific pecuniary	Declare and participate

Committee member	Interest declared	Type of interest	Decision taken
	College of Surgeons, Circulation foundation, European Venous Forum.		
Alun Davies	Non-commercial: Attendance at numerous national & international meetings as an invited guest to lecture where the organising groups receive funding from numerous sources including device and pharmaceutical manufacturers. Organising groups pay expenses and occasionally honoraria - the exact source of funding is often not known.	Personal non-specific pecuniary	Declare and participate
Alun Davies	Non-commercial: Has received travel expenses to attend the Veith Meeting NY 2013 November to give lectures by Vascutek.	Personal non-specific pecuniary	Declare and participate
Alison Eastwood	Member of an independent academic team at Centre for Review & Dissemination, University of York commissioned by NICE through NIHR to undertake technology assessment reviews.	Non-personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Organises workshops for physiotherapists treating pelvic girdle pain. Paid for this work.	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Receives payment and expenses from the Nursing and Midwifery Council as a lay panellist of the Fitness to Practise Investigating Committee.	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Lay reviewed with the Local Supervising Authority auditing supervision of midwives - receives payment and expenses for this work.	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Lay reviewer for the NIHR; has reviewed a number of research proposals being considered for funding. Paid for carrying out	Personal non-specific pecuniary	Declare and participate

Committee member	Interest declared	Type of interest	Decision taken
	these reviews.		
Sarah Fishburn	Chair of the Pelvic Partnership, a support group for women with pregnancy-related pelvic girdle pain. This is a voluntary position.	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Trained as a chartered physiotherapist and qualified in 1988 but have not been in clinical practice since 1997. Remains a non-practicing member of the Chartered Society of Physiotherapy.	Personal non-specific pecuniary	Declare and participate
Sarah Fishburn	Recently appointed by Mott MacDonald to carry out reviews as a lay reviewer on behalf to the Nursing and Midwifery Council of Local Supervising Authorities and Universities providing courses for nurses and midwives. This is paid work.	Personal non-specific pecuniary	Declare and participate
Jim Gray	Deputy Editor, Journal of Hospital Infection (receive income for this work indirectly through primary employer)	Personal financial non-specific	Declare and participate
Jim Gray	Co-investigator in four major trials (3 HTA-funded; 1 British Council funded). Associate Editor, International Journal of Antimicrobial Agents. Associate Editor, Journal of Pediatric Infectious Diseases. Expert Advisor, British National Formulary for Children.	No-personal financial non-specific	Declare and participate
Jim Gray	My Department is in receipt of an Educational Grant from Pfizer Ltd to develop improved diagnosis of invasive fungal infections in immunocompromised children	Non-personal financial non-specific	Declare and participate
Nuala Lucas	Member Obstetric Anaesthetists' Association Executive Committee	Personal non-specific non-pecuniary	Declare and participate

Committee member	Interest declared	Type of interest	Decision taken
Nuala Lucas	Member NICE – Intra-partum Care GDG	Personal non-specific non-pecuniary	Declare and participate
Nuala Lucas	Member, Editorial Board, International Journal of Obstetric Anesthesia	Personal non-specific non-pecuniary	Declare and participate
Kath Nuttall	None		No action
Tilly Pillay	None		No action
Nick Screaton	Attended Thorax meeting – travel expenses paid.	Non-specific personal pecuniary	Declare and participate
Lindsay Smith	None		No action
Philippa Williams	None		No action
Sophie Wilne	Recipient of NHS Innovation Challenge Award for clinical awareness campaign to reduce delays in diagnosis of brain tumours in children & young adults. Award will be used to develop the campaign.	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Co-investigator for RFPB grant to undertake systematic reviews in childhood brain tumours.	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Co-investigator for grant awards from charity to evaluate impact of brain tumour awareness campaign.	Personal non-specific non-pecuniary	Declare and participate
Sophie Wilne	Funding for travel and accommodation from Novartis to attend a conference on the management of tuberous sclerosis	Personal non-specific financial	Declare and participate
Topic-specific member (LUTS)	**Interest declared**	**Type of interest**	**Decision**
Jan Farrell	None		No action
Vikky Morris	Speaker fee from Astellas pharma.	Non-specific personal pecuniary	Declare and participate
Vikky Morris	Speaker fee from Astellas pharma.	Non-specific personal pecuniary	Declare and participate
Raj Persad	None		No action
John Taylor	None		No action

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1 Appendix C: Review protocol

	Details
Review Question	What is the clinical and cost-effectiveness of phosphodiesterase 5 inhibitors alone in the treatment of LUTS?
Objectives	Tadalafil is the only phosphodiesterase 5 inhibitor licensed for treatment of LUTS associated with benign prostatic hyperplasia. In the original guideline GG97, the use of PDE5 inhibitors was not recommended because there was insufficient evidence to address the use of PDE5-Inhinitors in men with LUTS. In addition, at the time CG97 was developed, there was no PDE5 - inhibitor licensed for use in LUTS. Tadalafil was the subject of a technology appraisal (TA273) in 2013, however this was terminated. Guidance is now required on the use of Tadalafil in men with LUTS.
Type of Review	Intervention
Language	English
Study Design	Systematic reviews, RCTs
Status	Published papers only
Population	Men with lower urinary tract symptoms, including benign prostatic hyperplasia (studies with a mixed population of men with LUTS and ED will be included, as LUTS can be associated with ED) Subgroups: - Men of African family origin
Intervention	Phosphodiesterase 5 inhibitors (tadalafil, sildenafil, vardenafil, avanafil) as monotherapy, not in combination with any other pharmacological intervention.
Comparator	-Alpha blockers (BNF lists: Alfuzosin, Doxazosin, Indoramin, Prazosin, Tamsulosin and Terazosin), -5-alpha reductase inhibitors (Dutasteride, Finasteride) -Placebo, -Antimuscuranics (BNF lists: Oxybutynin, Tolteradine, Danfenacin, Fesoterodine, Propiverine, Solifenacin, Trospium), -Combination therapy (excluding any combination therapy with a PDE5 inhibitor) -NSAIDS, -Desmopressin, -Diuretics, -Surgery, -Conservative therapy.
Outcomes	Outcomes reported at longest follow up point: • Symptom scores (IPSS, BII),, • QOL (including IPSS), • Maximal urinary flow rate (QMax),

	Details
	• Voiding frequency, • Nocturia, • Postural hypotension • Flushing, • Dizziness, • Headaches , • Withdrawal due to adverse events, • Discontinuation due to AEs/ serious AEs Note: PDE5Is can be associated with serious adverse events such as sudden deafness and eye problems (Non-arteric anterior ischemic neuropathy , NAION). As these are very rare it is unlikely that studies would report these events, however, these events will be extracted and discussed where they are reported.
Other criteria for inclusion / exclusion of studies	Studies with Erectile Dysfunction (ED) population will be excluded. Observational studies will be excluded as there is sufficient high quality RCT trial data available for this question. Population solely with ED and ED outcomes will not be included in this review. Note: Baseline characteristics for age, comorbidities and polypharmacy will be extracted where they are reported by the studies identified.
Search strategies	Please see Appendix D.
Review strategies	Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytical approach will be used to give an overall summary effect. All key outcomes from the evidence will be presented in GRADE profiles or and further summarized in evidence statements

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Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in table 5. The Medline search strategy is shown in table 5. The same strategy was translated for the other databases listed in table 4.

Table 5: Clinical search summary

Database	Date searched	Number retrieved
CDSR (Wiley)	27/08/2014	2
Database of Abstracts of Reviews of Effects – DARE (Wiley)	27/08/2014	5
HTA database (Wiley)	27/08/2014	0
CENTRAL (Wiley)	27/08/2014	123
MEDLINE (Ovid)	27/08/2014	258
MEDLINE In-Process (Ovid)	27/08/2014	30
EMBASE (Ovid)	27/08/2014	398
PubMed	27/08/2014	13

Table 6: Clinical search terms (Medline/ Medline in Process)

Line number	Search term	Number retrieved
1	exp Lower Urinary Tract Symptoms/	(29709)
2	(LUTS or LUTD).tw.	(2011)
3	(Lower urinary tract adj4 (symptom* or disease* or disorder* or dysfunction*)).tw.	(5350)
4	Prostatic Hyperplasia/	(18287)
5	(prostat* adj4 (benign or hyperplas* or enlarg* or hypertroph* or obstruct* or adenoma*)).tw.	(18939)
6	hyperplasia.tw.	(67028)
7	(BPH or BPH-LUTS).tw.	(7424)
8	prostatism.tw.	(541)
9	Urinary Retention/	(3341)
10	(retent* adj4 (chronic* or urin* or acute*)).tw.	(7835)
11	Urinary bladder, overactive/	(2498)
12	Urinary incontinence/	(18072)
13	(urin* adj4 incontinen*).tw.	(18257)
14	(residual* adj4 urin*).tw.	(3385)
15	(storage adj4 symptom*).tw.	(502)
16	exp Enuresis/	(4306)

Line number	Search term	Number retrieved
17	enuresis.tw.	(3908)
18	((micturition or urin* or bladder or voiding) adj4 (disorder* or dysfunct* or symptom* or urgen* or incontinen*)).tw.	(37687)
19	(nocturia or pollakisuria or bedwett*).tw.	(2444)
20	((weak* or overactiv* or over-activ* or obstruct* or incomplet* or impair* or irritabl*) adj4 (bladder* or detrusor*)).tw.	(8846)
21	(post adj4 micturition adj4 dribbl*).tw.	(35)
22	(haematuria or hematuria).tw.	(14789)
23	(male or man or men).tw.	(1054489)
24	1 or 2 or 3 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	(79790)
25	23 and 24	(13400)
26	4 or 5 or 6 or 7 or 8 or 25	(91618)
27	Phosphodiesterase 5 Inhibitors/	(1558)
28	phosphodiesterase 5 inhibitor*.tw.	(843)
29	(pde 5 or pde5 or pde-5).tw.	(2075)
30	(pde v or pdev or pde-v).tw.	(112)
31	Phosphodiesterase Inhibitors/	(11549)
32	(Phosphodiesteras* adj4 Inhibitor*).tw.	(10490)
33	Piperazines/	(38510)
34	Carbolines/	(4264)
35	(piperazine* or carboline*).tw.	(8067)
36	(tadalafil* or sildenafil* or vardenafil* or avanafil*).tw.	(5272)
37	(cialis or nipatra or viagra or revatio or spedra or levitra).tw.	(1035)
38	or/27-37	(61403)
39	26 and 38	(600)
40	animals/ not humans/	(3904075)
41	39 not 40	(510)
42	Meta-Analysis.pt.	(50945)
43	Meta-Analysis as Topic/	(14000)
44	Review.pt.	(1907692)
45	exp Review Literature as Topic/	(7758)
46	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.	(60241)
47	(review$ or overview$).ti.	(269545)

Line number	Search term	Number retrieved
48	(systematic$ adj5 (review$ or overview$)).tw.	(55292)
49	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.	4355)
50	((studies or trial$) adj2 (review$ or overview$)).tw.	(24955)
51	(integrat$ adj3 (research or review$ or literature)).tw.	(5436)
52	(pool$ adj2 (analy$ or data)).tw.	(14149)
53	(handsearch$ or (hand adj3 search$)).tw.	(5421)
54	(manual$ adj3 search$).tw.	(3113)
55	or/42-54	(2067622)
56	animals/ not humans/	(3904075)
57	55 not 56	(1932292)
58	Randomized Controlled Trial.pt.	(385551)
59	Controlled Clinical Trial.pt.	(89638)
60	Clinical Trial.pt.	(494092)
61	exp Clinical Trials as Topic/	(285419)
62	Placebos/	(33293)
63	Random Allocation/	(81875)
64	Double-Blind Method/	(128853)
65	Single-Blind Method/	(19824)
66	Cross-Over Studies/	(35186)
67	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.	(744897)
68	(random$ adj3 allocat$).tw.	(20920)
69	placebo$.tw.	(154760)
70	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.	(126423)
71	(crossover$ or (cross adj over$)).tw.	(57460)
72	or/58-71	(1394924)
73	animals/ not humans/	(3904075)
74	72 not 73	(1300575)
75	57 or 74	(2993975)
76	41 and 75	(311)
77	limit 76 to english language	(258)

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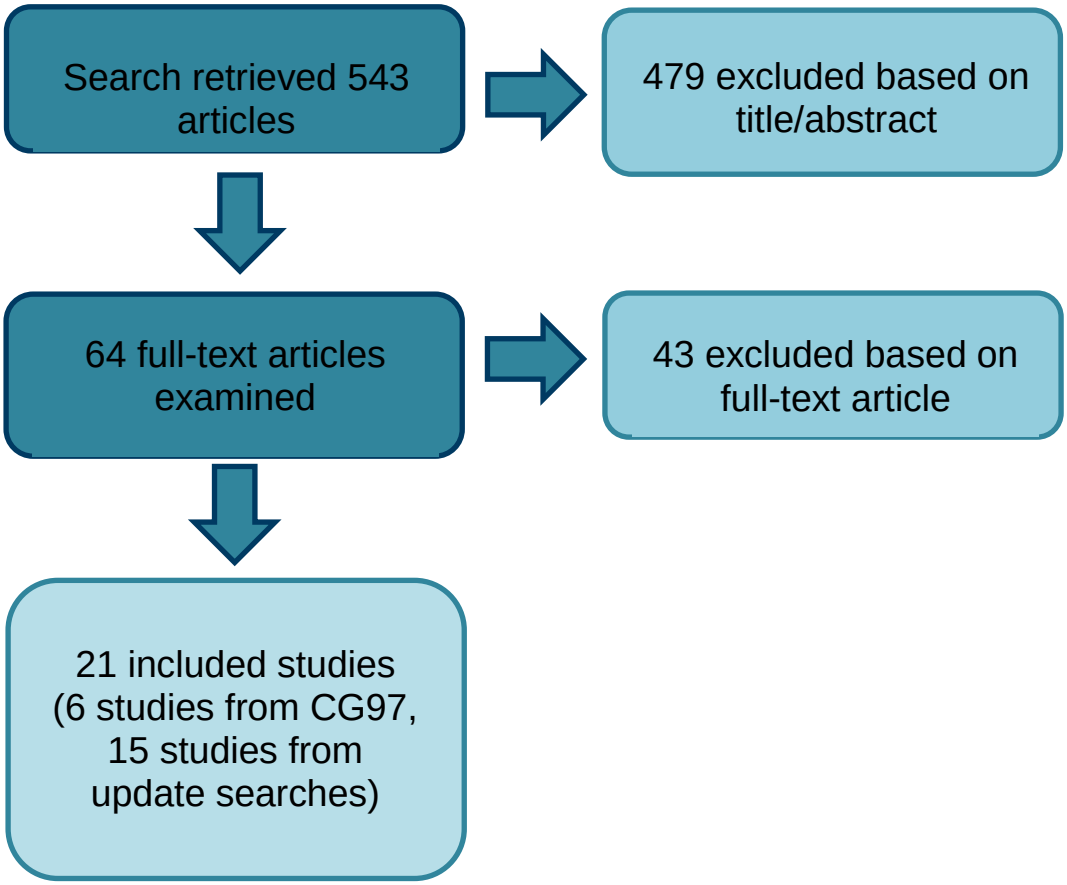
Appendix E: Review flowchart



1 Appendix F:Excluded studies

2 **Table 7: PDE5I excluded studies list – Clinical papers**

Reference	Reason for exclusion
Erratum (2013) Efficacy and safety of tadalafil 5 mg once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: Subgroup analyses of pooled data from 4 multinational, randomized, placebocontrolled clinical studies. Urology, 83, 684-, 2014	Publication type excluded in review protocol: erratum
Angalakuditi,Mallik, Seifert,Rita F., Hayes,Risa P., O'Leary,Michael P., Viktrup,Lars, (2010) Measurement properties of the benign prostatic hyperplasia impact index in tadalafil studies. Health and quality of life outcomes. 8: 131	Post hoc analysis of MacVary (2007) and Roehrborn (2008) assessing use of BII assessment
Auerbach,Stephen M., Gittelman,Marc, Mazzu,Arthur, Cihon,Frank, Sundaresan,Pavur, White,William B. (2004) Simultaneous administration of vardenafil and tamsulosin does not induce clinically significant hypotension in patients with benign prostatic hyperplasia. Urology. 64: 998-4,	Intervention not included in review protocol: vardenafil + tamsulosin in combination vs tamsulosin placebo
Bechara,Amado, Casabe,Adolfo, Rodriguez Baigorri,Gustavo, Cobreros,Christian. (2014) Effectiveness of tadalafil 5 mg once daily in the treatment of men with lower urinary tract symptoms suggestive to benign prostatic hyperplasia with or without erectile dysfunction: results from naturalistic observational TadaLutsEd study. The journal of sexual medicineJ Sex Med. 11: 498-505	Study type not included in review protocol: naturalistic observational study, not an RCT
Brock,G., Broderick,G., Roehrborn,C.G., Xu,L., Wong,D., Viktrup,L. (2013) Tadalafil once daily in the treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) in men without erectile dysfunction, BJU international. 112: 990-997	Post hoc analysis of 3 trials already included in review
Brock,G., Glina,S., Moncada,I., Watts,S., Xu,L., Wolka,A., Kopernicky,V. (2009) Likelihood of Tadalafil-associated Adverse Events in Integrated Multiclinical Trial Database: Classification Tree Analysis in Men With Erectile Dysfunction. Urology. 73: 756-761	Population does not match review protocol: Pooled data from 21 RCTs of tadalafil related adverse events in men with ED References were checked for any studies with LUTS + ED population
Brock,Gerald B., McVary,Kevin T., Roehrborn,Claus G., Watts,Steven, Ni,Xiao, Viktrup,Lars, Wong,David G., Donatucci,Craig. (2014) Direct effects of tadalafil on lower urinary tract symptoms versus indirect effects mediated through erectile dysfunction symptom improvement: integrated data analyses from 4 placebo controlled clinical studies. The Journal of urology. 191: 405-411	Post hoc analysis of studies already included in review.
Capitanio,U., Salonia,A., Briganti,A., Montorsi,F. (2013) Silodosin in the management of lower urinary tract symptoms as a result of benign prostatic hyperplasia: who are the best candidates. International journal of clinical practice. Int J Clin Pract. 67: 544-551	Publication type excluded in review protocol: Clinical review of silodosin only
Choi,H., Kim,J.H., Shim,J.S., Park,J.Y., Kang,S.H., Moon,D.G., Cheon,J., Lee,J.G., Kim,J.J., Bae,J.H. (2014) Comparison of the efficacy and safety of 5-mg once-daily versus 5-mg alternate-day tadalafil in men with erectile dysfunction and lower urinary tract symptoms, International journal of impotence research. Int J Impot Res.	Comparison not relevant to review protocol: tadalafil once daily vs alternate daily dose

Reference	Reason for exclusion
Curran,Monique P. (2012) Tadalafil: in the treatment of signs and symptoms of benign prostatic hyperplasia with or without erectile dysfunction. Drugs & aging. 29: 771-781	Publication type excluded in review protocol: Clinical review, lack of detail
Donatucci,Craig F., Brock,Gerald B., Goldfischer,Evan R., Pommerville,Peter J., Elion-Mboussa,Albert, Kissel,Jay D., Viktrup,Lars. (2011) Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. BJU international. 107: 1110-1116	Study type not included in review protocol: Open label extension of included study Roehrborn 2008
Dong,Yang, Hao,Lin, Shi,Zhenduo, Wang,Gang, Zhang,Zhiguo, Han,Conghui,. (2013) Efficacy and safety of tadalafil monotherapy for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a meta-analysis. Urologia internationalis. 91: 10-18	Does not include all studies or all outcomes of interest. No adequate detail to assess outcome quality using GRADE. Only used to cross check for other studies.
Gacci,M., Corona,G., Monami,M., Serni,S., Mirone,V., Carini,M., Maggi,M. (2012) Meta-analysis on the use of PDE5 inhibitors for lower urinary tract symptoms due to benign prostatic hyperplasia, according to the recommendations of the Cochrane. European urology. 62 (e36-e38): 2	Systematic review: only compared to placebo, only 7 studies included. Only used to cross check for studies.
Gales,Barry J., Gales,Mark A. (2008) Phosphodiesterase-5 inhibitors for lower urinary tract symptoms in men. The Annals of pharmacotherapy. 42: 111-115	Intervention not included in review protocol: (included combination treatments of PDE5I), more up to date SR available.
Giuliano,F., Oelke,M., Jungwirth,A., Hatzimouratidis,K., Watts,S., Cox,D., Viktrup,L. (2013) Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo- and tamsulosin-controlled, 12-week double-blind study. Journal of Sexual Medicine. 10: 857-865	Post hoc analysis of Oelke 2012
Giuliano,Francois, Oelke,Matthias, Jungwirth,Andreas, Hatzimouratidis,Konstantinos, Watts,Steven, Cox,David, Viktrup,Lars,. (2013) Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo- and tamsulosin-controlled, 12-week double-blind study. The journal of sexual medicine. 10: 857-865	Post hoc analysis of Oelke 2012
Kraus,S.R., Dmochowski,R., Albo,M.E., Xu,L., Klise,S.R., Roehrborn,C.G. (2010) Urodynamic standardization in a large-scale, multicenter clinical trial examining the effects of daily tadalafil in men with lower urinary tract symptoms with or without benign prostatic obstruction. Neurourology and urodynamics. 29: 741-747	Post hoc analysis of urodynamic standardisation
Laydner,Humberto K., Oliveira,Paulo, Oliveira,Carlos Roberto, Makarawo,Tafadzwa P., Andrade,Weslley S., Tannus,Matheus, Araujo,Jose Luciano,. (2011) Phosphodiesterase 5 inhibitors for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a systematic review. BJU international. 107: 1104-1109	Includes only 4 studies, not up to date, only compared to placebo, Only IPSS outcome reported. Onlu used to check for other studies.
Lee,Sung Won, Paick,Jae Seung, Park,Hyun Jun, Won,Ji Eon, Morisaki,Yoji, Sorsaburu,Sebastian, Viktrup,Lars,. (2014) The Efficacy and Safety of Tadalafil 5 mg Once Daily in Korean Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia: An Integrated Analysis. The world journal of men's	Post hoc analysis of Yokoyama (2012), Takeda (2014) and Kim (2011)

Reference	Reason for exclusion
health. 32: 28-35	
Lewis,Ronald W., Sadovsky,Richard, Eardley,Ian, O'Leary,Michael, Seftel,Allen, Wang,Wei Christine, Shen,Wei, Walker,Daniel J., Wong,David G., Ahuja,Sanjeev,. (2005) The efficacy of tadalafil in clinical populations. The journal of sexual medicine. 2: 517-531	Population does not match that specified in review protocol: A review of ED outcomes in ED population
Madani,Ali Hamidi, Afsharimoghaddam,Amin, Roushani,Ali, Farzan,Alireza, Asadollahzade,Ahmad, Shakiba,Maryam,. (2012) Evaluation of Tadalafil effect on lower urinary tract symptoms of benign prostatic hyperplasia in patients treated with standard medication. International braz j urol: official journal of the Brazilian Society of Urology. 38: 33-39	Intervention not included in review protocol: intervention groups received tadalafil + alpha blocker or tadalafil + alpha blocker + finasteride vs placebo
Mavuduru,Ravimohan S., Pattanaik,Smita, Panda,Arabind, Agarwal,Mayank M., Mathew,Joseph L., Singh,Shrawan K., Mandal,Arup K. (2012) Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia. Cochrane Database Syst Reviews.	Publication type not relevant to review protocol: Protocol for review only.
McVary,Kevin T., Siegel,Richard L., Carlsson,Martin,. (2008) Sildenafil citrate improves erectile function and lower urinary tract symptoms independent of baseline body mass index or LUTS severity. Urology. 72: 575-579	Post hoc analysis of McVary 2007
Miller,Mindi S. (2013) Role of phosphodiesterase type 5 inhibitors for lower urinary tract symptoms. The Annals of pharmacotherapy. 47: 278-283	Quality of included studies not adequately reported, included abstracts. References checked for relevant studies.
Nieminen,Tuomo, Tammela,Teuvo L.J., Koobi,Tiit, Kahonen,Mika,. (2006) The effects of tamsulosin and sildenafil in separate and combined regimens on detailed hemodynamics in patients with benign prostatic enlargement. The Journal of urology. 176: 2551-2556	No outcomes of use: all haemodynamic outcomes.
Oelke,M., Giuliano,F., Baygani,S.K., Melby,T., Sontag,A. (2014) Treatment Satisfaction with Tadalafil or Tamsulosin versus Placebo in Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia: Results from a Randomized, Placebo-controlled Study. BJU international.	Duplicate of Oelke 2012
Ozturk,M.I., Kalkan,S., Koca,O., Gunes,M., Akyuz,M., Karaman,M.I. (2012) Efficacy of alfuzosin and sildenafil combination in male patients with lower urinary tract symptoms. Andrologia. 44 (S1): 791-795.	Intervention not relevant to review protocol: sildenafil + alfusozin combined.
Park,Hyun Jun, Won,Ji Eon Joanne, Sorsaburu,Sebastian, Rivera,Paul David, Lee,Seung Wook,. (2013) Urinary Tract Symptoms (LUTS) Secondary to Benign Prostatic Hyperplasia (BPH) and LUTS/BPH with Erectile Dysfunction in Asian Men: A Systematic Review Focusing on Tadalafil. The world journal of men's health. 31: 193-207	Used to check for included studies. The systematic review did not contain sufficient information on the included studies to use this publication within the evidence base (i.e. no mean, median or 95%CI reported). There was not adequate information to assess study the quality using GRADE approach.The study had a clinical focus on the treatment of Asian men
Pisansky,T.M., Pugh,S.L., Greenberg,R.E., Pervez,N., Reed,D.R., Rosenthal,S.A., Mowat,R.B., Raben,A., Buyyounouski,M.K.,	Population not relevant to review protocol: men

Reference	Reason for exclusion
Kachnic,L.A., Bruner,D.W. (2014) Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: The Radiation Therapy Oncology Group [0831] randomized clinical trial. JAMA. 311: 1300-1307	receiving tadalafil for ED after radiotherapy for prostate cancer
Porst,Hartmut, McVary,Kevin T., Montorsi,Francesco, Sutherland,Peter, Elion-Mboussa,Albert, Wolka,Anne M., Viktrup,Lars,. (2009) Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. European urology. 56: 727-735	Post hoc analyses of Roehborn 2008
Porst,Hartmut, Oelke,Matthias, Goldfischer,Evan R., Cox,David, Watts,Steven, Dey,Debashish, Viktrup,Lars,. (2013) Efficacy and safety of tadalafil 5 mg once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: subgroup analyses of pooled data from 4 multinational, randomized, placebo-controlled clinical studies. Urology. 82: 667-673	Post hoc analyses of 4 trials already included in the review
Porst,Hartmut, Roehrborn,Claus G., Secrest,Roberta J., Esler,Anne, Viktrup,Lars, Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia and on erectile dysfunction in sexually active men with both conditions: analyses of pooled data from four randomized, placebo-controlled tadalafil clinical studies, The journal of sexual medicineJ Sex Med, 10, 2044-2052, 2013	Post hoc analysis of 4 trials already included in review
Regadas,Rommel Prata, Reges,Ricardo, Cerqueira,Joao Batista Gadelha, Sucupira,Daniel Gabrielle, Josino,Iatagan Rocha, Nogueira,Emmanuel Almeida, Jamacaru,Francisco Vagnaldo, de Moraes,Manoel Odorico, Silva,Lucio Flavio Gonzaga,. (2013) Urodynamic effects of the combination of tamsulosin and daily tadalafil in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: a randomized, placebo-controlled clinical trial. International urology and nephrology. 45: 39-43	Intervention not relevant to review protocol: tadalafil tamsulosin ve tamsulosin placebo
Roehrborn,Claus G., Chapple,Christopher, Oelke,Matthias, Cox,David, Esler,Anne, Viktrup,Lars, (2014) Effects of tadalafil once daily on maximum urinary flow rate in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. The Journal of urologyJ Urol. 191: 1045-1050	Post hoc analysis of 4 other studies already included in review
Roehrborn,Claus G., Kaminetsky,Jed C., Auerbach,Stephen M., Montelongo,Rafael Martinez, Elion-Mboussa,Albert, Viktrup,Lars,. (2010) Changes in peak urinary flow and voiding efficiency in men with signs and symptoms of benign prostatic hyperplasia during once daily tadalafil treatment. BJU international. 105: 502-507	Duplicate of Roehrborn 2008
Viktrup,Lars, Hayes,Risa P., Wang,Ping, Shen,Wei,. (2012) Construct validation of patient global impression of severity (PGI-S) and improvement (PGI-I) questionnaires in the treatment of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. BMC urology/ 12: 30	Secondary analysis of 4 other RCTS for questionnaire validation
Yalcinkaya,F.R., Davarci,M., Akcin,S., Gokce,A., Guven,E.O., Inci,M., Balbay,M.D. (2012) Urodynamic evaluation of acute effects of sildenafil on voiding among males with erectile dysfunction and symptomatic benign prostate. Turkish Journal of Medical Sciences. 42: 951-956	Intervention not relevant to review protocol: urodynamic study - participants only given 2 doses of drug
Yamaguchi,Kenya, Aoki,Yutaka, Yoshikawa,Tetsuo, Hachiya,Takahiko, Saito,Tadanori, Takahashi,Satoru,. (2013) Silodosin versus naftopidil for the treatment of benign prostatic hyperplasia: a multicenter randomized trial. International journal of urology : official journal of the Japanese Urological Association. 20: 1234-1238	Intervention not relevant to review protocol: comparison of alpha blockers (silodosin vs naftopidil).
Yan,Huilei, Zong,Huantao, Cui,Yuanshan, Li,Nan, Zhang,Yong,. (2014) The efficacy of PDE5 inhibitors alone or in combination with	Intervention not relevant to review protocol:

Reference	Reason for exclusion
alpha-blockers for the treatment of erectile dysfunction and lower urinary tract symptoms due to benign prostatic hyperplasia: a systematic review and meta-analysis. The journal of sexual medicine. 11: 1539-1545	Comparison of PDE5I in combination vs PDE5I alone in treatment of LUTS and ED
Zhao,Chen, Kim,Suhn Hee, Lee,Sung Won, Jeon,Ju Hong, Kang,Kyung Ku, Choi,Sung Beom, Park,Jong Kwan. (2011) Activity of phosphodiesterase type 5 inhibitors in patients with lower urinary tract symptoms due to benign prostatic hyperplasia. BJU international. 107: 1943-1947	Population/ intervention not relevant to review protocol: histology study, no outcomes of interest

Appendix G: Evidence tables

G.1 PDE5Is vs placebo, alpha blockers or antimuscarinics

<table>
<tr><td>Bibliographic reference</td><td>Abolyosr,Ahmed, Elsagheer,Gamal A., Abdel-Kader,Mohammad S., Hassan,Ahmed M., Abou-Zeid,Abdel Monem, Evaluation of the effect of sildenafil and/or doxazosin on Benign prostatic hyperplasia-related lower urinary tract symptoms and erectile dysfunction, Urology annalsUrol Ann, 5, 237-240, 2013</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Aim</td><td>To verify the association between LUTS and ED and evaluate influence of sildenafil and doxazosin as wither single or combined agents on both symptoms.</td></tr>
<tr><td>Patient characteristics</td><td>Patient characteristics
Study only reported IPSS, IIEF, mean urine flow rate and mean PVR urine at baseline; these characteristics were well balanced except PVR, where the doxazosin group had 62.72mL compared to 66.80mL in the sildenafil group. No other baseline characteristics were reported.

Key baseline characteristics:
<table>
<tr><td></td><td>Sildenafil:</td><td>Doxazosin:</td></tr>
<tr><td>IPSS (mean, SD)</td><td>17.36 (4.82)</td><td>15.78 (5.21)</td></tr>
<tr><td>IIEF (mean, SD)</td><td>15.04 (5.53)</td><td>14.10 (5.55)</td></tr>
<tr><td>Urine flow rate (mean, SD)</td><td>8.82 (2.90)</td><td>10.02 (2.83)</td></tr>
<tr><td>Postvoid residual volume (mean, SD)</td><td>66.80 (4.75)</td><td>62.72 (4.85)</td></tr>
</table>
Inclusion criteria
Aged 45 years or more, complaining of LUTS caused by BPH (after exclusion of other causes of LUTS) for 3 months or more with IPSS more than 7 associated with clinically diagnosed ED (for 3 months or more), with IIEF <25.

Exclusion criteria</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Abolyosr,Ahmed, Elsagheer,Gamal A., Abdel-Kader,Mohammad S., Hassan,Ahmed M., Abou-Zeid,Abdel Monem, Evaluation of the effect of sildenafil and/or doxazosin on Benign prostatic hyperplasia-related lower urinary tract symptoms and erectile dysfunction, Urology annalsUrol Ann, 5, 237-240, 2013</td></tr>
<tr><td></td><td>Patients who had previously had prostate surgery or other less invasive surgical interventions for BPH, those with active urinary tract disease that may cause LUTS (e.g. cystitis), those ith a PSA >10 and men who are not candidates for medical treatment for ED.

All participants underwent pre-treatment assessment which included complete medical history, assessment of degree of LUTS and ED assessed with IPSS and IIEF, physical examination including neurological assessment, laboratory investigations including CBC, blood sugar level, lipid profile, creatinine, PSA, testosterone, LH and prolactin, uroflowmetry and PVR urine.
There was a 3rd group which received combination therapy of Sildenafil and Doxazosin, this group is not included in this analysis as this is an excluded intervention.</td></tr>
<tr><td>Number of Patients</td><td>N=150, n=100 in sample of interest (combination therapy group not included in this analysis)</td></tr>
<tr><td>Intervention</td><td>Sildenafil 50g as monotherapy (N=50)</td></tr>
<tr><td>Comparison</td><td>Doxazosin 2mg (nN=50)</td></tr>
<tr><td>Length of follow up</td><td>4 months</td></tr>
<tr><td>Location</td><td>Egypt</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores

<table>
<tr><td>IPSS score (mean, SD):</td><td>Sildenafil:</td><td>Doxazosin:</td></tr>
<tr><td>Pre-treatment:</td><td>17.36 (4.82)</td><td>15.78 (5.21)</td></tr>
<tr><td>Post treatment:</td><td>15.1 (4.11)</td><td>12.42 (4.50)</td></tr>
</table>

Quality of Life
Not reported</td></tr>
</table>

Bibliographic reference	**Abolyosr,Ahmed, Elsagheer,Gamal A., Abdel-Kader,Mohammad S., Hassan,Ahmed M., Abou-Zeid,Abdel Monem, Evaluation of the effect of sildenafil and/or doxazosin on Benign prostatic hyperplasia-related lower urinary tract symptoms and erectile dysfunction, Urology annalsUrol Ann, 5, 237-240, 2013**
	QMax Unclear whether data is for Qmax – just states “Urine flow rate” **Voiding frequency** Not reported **Nocturia** Not reported **Adverse events** Not reported
Source of funding	None
Comments	**Study dates** April 2010- April 2011 **Overall Risk of Bias** -randomisation and allocation concealment not reported. -Lack of detail on baseline characteristics -lack of detail on administration of sildenafil (once/ day, alternate days?) -Not reported whether ITT analysis -Number of dropouts not reported -does not state proportion of population with ED **Other information** Study reported Urine flow rate reported, it is not stated whether it is Qmax and the units are not reported, therefore outcome not meta-analysed.

<table>
<tr><td>Bibliographic reference</td><td>Abolyosr,Ahmed, Elsagheer,Gamal A., Abdel-Kader,Mohammad S., Hassan,Ahmed M., Abou-Zeid,Abdel Monem, Evaluation of the effect of sildenafil and/or doxazosin on Benign prostatic hyperplasia-related lower urinary tract symptoms and erectile dysfunction, Urology annalsUrol Ann, 5, 237-240, 2013</td></tr>
<tr><td></td><td>Urine flow rate (mean, SD):
<table>
<tr><td></td><td>Sildenafil:</td><td>Doxazosin:</td></tr>
<tr><td>Pre-treatment:</td><td>8.82 (2.90)</td><td>10.02 (2.83)</td></tr>
<tr><td>Post treatment:</td><td>10.58 (2.40)</td><td>13.32 (2.74)</td></tr>
</table>
Repeated IPSS assessed by Qui-squared test</td></tr>
</table>

1

<table>
<tr><td>Bibliographic reference</td><td>Dmochowski,R., Roehrborn,C., Klise,S., Xu,L., Kaminetsky,J., Kraus,S., Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-week clinical trial, Journal of UrologyJ.Urol., 183, 1092-1097, 2010</td></tr>
<tr><td>Study type</td><td>Randomised, double blind placebo controlled trial.</td></tr>
<tr><td>Aim</td><td>Impact of tadalafil on urodynamic measures in men with LUTS secondary to BPH.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
Men at least 40 years old, with a greater than 6 month history of BPH-LUTS (with or without bladder obstruction) and an IPSS of 13 or ore at screening visit. PSA less than 10 ng/mL (if PSA 4-10ng/mL were eligible only with prostate biopsy negative for malignancy within 12 months or stable PSA since the biopsy) or PVR 350mL or less at the screening visit

Exclusion criteria
5-alpha reductase inhibitor use within 4 months prior to study, history of penile or pelvic surgery or radiotherapy, lower urinary tract malignancy, trauma or recent instrumentation; urinary retention or bladder stones; urethral obstruction; urinary tract infection or inflammation; prostate cancer; bladder calculi; stonic, decompensated or hypocontractile bladder; detrusor-sphincter dyssynergia; intravesical obstruction. Clinically significant renal or hepatic insufficiency; cardiovascular conditions e.g. angina, recent MI, stroke, spinal cord injury, current therapy with nitrates, cancer chemotherapy, antiandrogens, uncontrolled diabetes.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Dmochowski,R., Roehrborn,C., Klise,S., Xu,L., Kaminetsky,J., Kraus,S., Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-week clinical trial, Journal of UrologyJ.Urol., 183, 1092-1097, 2010</td></tr>
<tr><td></td><td>Details
There was a 4 week washout period for men reporting use of other BPH or ED therapies. After the 4 week washout participants underwent a week of baseline assessment and urodynamics (UDS). After this they were randomised into intervention groups. Post- treatment UDS were completed at treatment completion (12 weeks) or at early study discontinuation.

Key baseline details
<table>
<tr><td></td><td>Tadalafil</td><td>Placebo</td></tr>
<tr><td>PVR (mean (SD))</td><td>45.7mL (49.6)</td><td>59.3mL (60.9)</td></tr>
<tr><td>Patients with ED</td><td>58.6%</td><td>59.4%</td></tr>
</table>
Baseline characteristics were well balanced between groups apart from PVR.</td></tr>
<tr><td>Number of Patients</td><td>N=200</td></tr>
<tr><td>Intervention</td><td>20mg tadalafil once daily for 12 weeks

N=99, 10 discontinued, 89 completed and 6 were non-evaluable.
N=83 analysed</td></tr>
<tr><td>Comparison</td><td>Placebo once daily for 12 weeks

N=101, 9 discontinued, 92 completed and 3 were non-evaluable.
N=89 analysed</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>USA and Canada</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores
<table>
<tr><td>Mean (SD)</td><td>IPSS total</td><td>Obstructive subscore</td><td>Irritative subscore</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Dmochowski,R., Roehrborn,C., Klise,S., Xu,L., Kaminetsky,J., Kraus,S., Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-week clinical trial, Journal of UrologyJ.Urol., 183, 1092-1097, 2010

Placebo - baseline (N=89)	22.0 (5.8)	11.9 (4.0)	10.1 (2.7)
Placebo - change (N=89)	-5.1 (7.0)	-2.8 (4.5)	-2.3 (3.2)
Tadalafil - baseline (N=82)	21.3 (5.5)	11.6 (4.2)	9.7 (2.9)
Tadalafil - change (N=82)	-9.2 (6.9)	-5.6 (4.6)	-3.6 (3.2)
Difference of change (tadalafil - placebo)	-4.2 (1.1)	-2.8 (0.7)	-1.4 (0.5)
p Value	<0.001	<0.001	0.006

Quality of Life
Not reported

QMax

	Placebo - baseline (mean, SD)	Placebo – change (mean, SD)	Tadalafil - baseline (mean, SD)	Tadalafil - change (mean, SD)	Difference of change (tadalafil - placebo)	p value
Qmax - pressure flow	9.5 (4.9)	0.5 (2.9)	10.3 (4.5)	0.4 (2.9)	-0.1 (0.5)	0.79
Qmax - non-invasive uroflow	13.3 (7.5)	0.5 (8.0)	15.5 (11.1)	-0.1(9.3)	-0.6 (1.5)	0.67

Voiding frequency
Not reported

Nocturia
Not reported

Adverse events
Discontinuation due to AE:
Tadalafil: 2 (2%)
Placebo: 1 (1%)
Treatment emergent adverse events:

Bibliographic reference	Dmochowski,R., Roehrborn,C., Klise,S., Xu,L., Kaminetsky,J., Kraus,S., Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-week clinical trial, Journal of UrologyJ.Urol., 183, 1092-1097, 2010
	Headaches: Tadalafil: 7 (7.1%) Placebo: 3 (3.0%)
Source of funding	Eli Lilly assisted with study design, implementation and data interpretation.
Comments	**Overall Risk of Bias** • Randomisation and allocation concealment not reported • Analysed on an available case analysis (ACA) basis: the study sates that analysis was undertaken on all men who were randomised, started study medication, had a valid baseline and end of study PFS and had at least 37 days between randomisation and end point PFS. They state ITT not appropriate because a lack of time that a drug is taken would reduce the potential for measuring impact of study drug on urodynamic safety end points. • ANOVA models used to compare treatment groups for change from baseline to end point. . The model included therapy, randomisation stratum, interaction of therapy and randomisation stratum. (strata were baseline BOOI and LUTS severity) • Analysis of safety included all participants randomly assigned who received study treatment. **Other information** This study was powered to detect a difference in PdetQmax (detrusor pressure at maximum urinary flow rate) from baseline to week 12, total sample size of 190 subjects.

1

Bibliographic reference	Egerdie,Russell Blair, Auerbach,Stephen, Roehrborn,Claus G., Costa,Pierre, Garza,Martin Sanchez, Esler,Anne L., Wong,David G., Secrest,Roberta J., Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study, The journal of sexual medicineJ Sex Med, 9, 271-281, 2012
Study type	Randomised, double blind,placebo controlled, multinational trial

Bibliographic reference	Egerdie,Russell Blair, Auerbach,Stephen, Roehrborn,Claus G., Costa,Pierre, Garza,Martin Sanchez, Esler,Anne L., Wong,David G., Secrest,Roberta J., Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study, The journal of sexual medicineJ Sex Med, 9, 271-281, 2012
Aim	To assess the effects of 2.5mg or 5mg tadalafil once daily on ED and BPH-LUTS in men with both conditions during 12 weeks of double blind therapy
Patient characteristics	Patient characteristics were relatively well balanced at baseline, with similar Qmax and IPSS scores across all groups. The mean age was well balanced between groups, though there were slightly fewer men aged ≤65 years in the tadalafil 5mg group (60.1%) compared to the tadalafil 2.5mg (66.7%) and placebo groups (61.5%) and there were slightly more men aged ≥75 years in the tadalafil 2.5mg group (6.1%) compared to tadalafil 5mg (10.1%) and placebo (11.5%). The majority of study participants were of white family origin (≥90%), with less than 5% of participants of black or African American ethnicity. More people in the tadalafil 5mg group had previously use α blockers (26.9%, n=56) compared to tadalafil 2.5mg (20.2%, N=39) ad placebo (23.0%, N=46) **Inclusion** Sexually active men ≥45 years of age, had a ≥3 month history of ED and PBH-LUTS for >6 months, clinically diagnosed by a qualified physician were eligible for screening. Histological confirmation of BPH not required. To continue to the placebo lead in period men were required to have IPSS ≥13 and Qmax ≥4-≤15mL/second obtained from valid uroflowmetry assessment, were required to make ≥4 intercourse attempts with an adult female partner (recorded in SEP diary) and be at least 70% compliant with dosing to be eligible for randomisation. **Exclusion** History of ED cause by other primary sexual disorders, untreated endocrine disease or prior non-responsiveness to PDE5I therapy, certain cardiac conditions e.g. conduction defects, PSA >10ng/mL (or 4-10ng/mL if malignancy had not been ruled out), post void residual volume ≥300mL, use of finasteride or dutasteride within3 or 6 months respectively, LUT instrumentation within 30 days, history of urethral or intravesical obstruction, urinary retention or LUT stones within 6 months, neurogenic bladder, renal insufficiency or hepatic impairment. **Details**

<table>
<tr><td>Bibliographic reference</td><td>Egerdie,Russell Blair, Auerbach,Stephen, Roehrborn,Claus G., Costa,Pierre, Garza,Martin Sanchez, Esler,Anne L., Wong,David G., Secrest,Roberta J., Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study, The journal of sexual medicineJ Sex Med, 9, 271-281, 2012</td></tr>
<tr><td></td><td>Screening/ washout period of 4 weeks followed by 4 week placebo lead in period (participant blinded), followed by 12 weeks of double blind randomised therapy.
Men reporting other use of treatment for ED, BPH or overactive bladder were required to complete a 4 week washout period prior to entering the placebo lead in period. Those not requiring washout could enter the placebo lead in period after screening results were assessed.
Participants randomly assigned in 1:1:1 ratio by computer generated random sequence using an interactive voice-response system. Randomisation stratified using baseline ED severity (mild, moderate or severe on IIEF), baseline LUTS severity (total IPSS <20 or≥20) and region (USA/Canada, Mexico or Europe).

Key baseline characteristics
<table>
<tr><td></td><td>Placebo</td><td>Tadalafil 2.5mg</td><td>Tadalafil 5mg</td></tr>
<tr><td>Age (mean, range)</td><td>62.9 (45.4-83.2)</td><td>62.2 (45.3-80.7)</td><td>62.5 (45.7-82.0)</td></tr>
<tr><td>≤65 years (%)</td><td>61.5</td><td>66.7</td><td>60.1</td></tr>
<tr><td>>65-<75 years (%)</td><td>27.0</td><td>27.2</td><td>29.8</td></tr>
<tr><td>≥75 years (%)</td><td>11.5</td><td>6.1</td><td>10.1</td></tr>
<tr><td colspan="4">Race (%)</td></tr>
<tr><td>White</td><td>95.0</td><td>91.4</td><td>93.3</td></tr>
<tr><td>Black/ African American</td><td>4.0</td><td>4.5</td><td>2.9</td></tr>
<tr><td>Asian</td><td>1.0</td><td>3.1</td><td>2.9</td></tr>
<tr><td>Other</td><td>0</td><td>1.0</td><td>1.0</td></tr>
<tr><td colspan="4">Baseline LUTS severity (%)</td></tr>
<tr><td>Moderate (<20 IPSS)</td><td>61.0</td><td>62.4</td><td>59.6</td></tr>
<tr><td>Severe (≥20 IPSS)</td><td>39.0</td><td>37.6</td><td>40.4</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>N= 606</td></tr>
<tr><td>Intervention</td><td>Tadalafil (oral) 2.5mg, once daily (N=198)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Egerdie,Russell Blair, Auerbach,Stephen, Roehrborn,Claus G., Costa,Pierre, Garza,Martin Sanchez, Esler,Anne L., Wong,David G., Secrest,Roberta J., Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study, The journal of sexual medicineJ Sex Med, 9, 271-281, 2012</td></tr>
<tr><td></td><td>Tadalafil (oral) 5mg, once daily (N=208)</td></tr>
<tr><td>Comparison</td><td>Placebo (N=200)</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>54 urology sites in 9 countries; USA, Canada, Mexico and Europe</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores
<table>
<tr><td></td><td colspan="2">Placebo (N=200)</td><td colspan="4">Tadalafil 2.5mg (N=198)</td><td colspan="4">Tadalafil 5mg (N=208)</td></tr>
<tr><td>Measures</td><td>Baseline</td><td>Change from BL</td><td>Baseline</td><td>Change from BL</td><td>Change vs placebo</td><td>P value</td><td>Baseline</td><td>Change from BL</td><td>Change vs placebo</td><td>P value</td></tr>
<tr><td>Total IPSS</td><td>18.2 (5.3)</td><td>-3.8 (0.5) (N=194)</td><td>18.2 (5.6)</td><td>-4.6 (0.4) (N=191)</td><td>-0.8 (0.6)</td><td>0.18</td><td>18.5 (5.8)</td><td>-6.1 (0.4) (N=206)</td><td>-2.3 (0.6)</td><td><0.001</td></tr>
</table>
Baseline values are mean ±SD, change values are least squares mean ±SE
*not interpreted for significance based on rules of the gatekeeping procedure
IPSS= international prostate symptom score;

Patient global impression of improvement (PGI-I) & Clinical global impression of improvement (CGI-I)
<table>
<tr><td>Outcomes</td><td>Placebo (N, %)</td><td>Tadalafil 2.5mg (N, %)</td><td>Tadalfil 5mg (N, %)</td></tr>
<tr><td colspan="4">PGI-I</td></tr>
<tr><td>Better</td><td>106/185 (57.3)</td><td>136/185 (73.5)</td><td>158/197 (80.2)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Egerdie,Russell Blair, Auerbach,Stephen, Roehrborn,Claus G., Costa,Pierre, Garza,Martin Sanchez, Esler,Anne L., Wong,David G., Secrest,Roberta J., Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study, The journal of sexual medicineJ Sex Med, 9, 271-281, 2012

No change	61/185 (33.0)	34/185 (18.4)	34/197 (17.3)
Worse	18/185 (9.7)	15/185 (8.1)	5/197 (2.5)
CGI-I			
Better	106/184 (57.3)	130/181 (71.8)	152/197 (77.2)
No change	64/184 (34.8)	41/181 (22.7)	42/197 (21.3)
Worse	14/184 (7.6)	10/181 (5.5)	3/197 (1.5)

IPSS Quality of Life

	Placebo	Tadalafil 2.5mg (N=198)			Tadalafil 5mg (N=208)		
measures	Change from BL	Change from BL	Change vs placebo	P value	Change from BL	Change vs placebo	P value
IPSS QoL index	-0.8 (0.1) (N=194)	-0.9 (0.1) (N=192)	-0.1 (0.1)	0.38	-1.0 (0.1) (N=205)	-0.3 (0.1)	0.082

Values are least squares mean ±SE

BII (BPH Impact Index)

	Placebo (N=200)		Tadalafil 2.5mg (N=198)				Tadalafil 5mg (N=208)			
Measures	Baseline	Change from BL	Baseline	Change from BL	Change vs placebo	P value	Baseline	Change from BL	Change vs placebo	P value
BII	6.0 (3.0)	-1.2 (0.2) (N=190)	5.8 (22.9)	-1.6 (0.2) (N=190)	-0.4 (0.3)	0.16*	5.6 (3.1)	-2.1 (0.2) (N=203)	-0.9 (0.3)	<0.001

Bibliographic reference	Egerdie,Russell Blair, Auerbach,Stephen, Roehrborn,Claus G., Costa,Pierre, Garza,Martin Sanchez, Esler,Anne L., Wong,David G., Secrest,Roberta J., Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study, The journal of sexual medicineJ Sex Med, 9, 271-281, 2012

Baseline values are mean ±SD, change values are least squares mean ±SE

QMax (mean, SD), mL/second

	Placebo	Tadalafil 2.5mg (N=198)	Tadalafil 5mg (N=208)
Baseline	10.1 (3.8)	10.4 (4.6)	10.3 (3.5)
Change from BL	1.2 (4.5)	1.7 (4.5)	1.6 (4.2)

Voiding frequency

The study only reported the voiding sub-score of IPSS, these results have not been reported here as it is a composite of symptoms, not just frequency.

Nocturia

	placebo	Tadalafil 2.5mg (N=198)			Tadalafil 5mg (N=208)		
Measures	Change from BL	Change from BL	Change vs placebo	P value	Change from BL	Change vs placebo	P value
Nocturia question of IPSS	-0.5 (0.1) (N=194)	-0.5 (0.1 (N=192)	0.0 (0.1)	0.76	-0.6 (0.1) (N=206)	-0.2 (0.1)	0.075

Values are least squares mean ±SE

Adverse events

TEAEs (N, %)	Placebo	Tadalafil 2.5mg (N=198)	Tadalafil 5mg (N=208)
Headache	6 (3)	5 (2.5)	12 (5.8)

Bibliographic reference	Egerdie,Russell Blair, Auerbach,Stephen, Roehrborn,Claus G., Costa,Pierre, Garza,Martin Sanchez, Esler,Anne L., Wong,David G., Secrest,Roberta J., Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study, The journal of sexual medicineJ Sex Med, 9, 271-281, 2012
	≥1 AE leading to discontinuation: 3 (1.5) / 3 (1.5) / 6 (2.9) Met ≥1 criteria for positive orthostatic test*: 42 (21.0) / 41 (20.7) / 38 (18.3) **criteria were: systolic bp decrease ≥20mmHg, diastolic bp decrease ≥10mmHg, heart rate increase ≥20 beats per minute, or unable to remain standing*
Source of funding	Eli Lilly provided funds for the trial
Comments	Subject, study site personnel and sponsor were blinded **Risk of bias** Analyses performed on an ITT basis for all subjects who were randomised and started double blind study medication. For continuous measures, efficacy was analysed as the mean difference in the change from baseline to end point between each tadalafil group and placebo using ANCOVA models with terms for therapy, region and a baseline covariate. Region by treatment group interaction and baseline covariate by treatment group terms included if p<0.1. Data reported as LSM Minimum sample size estimated at 184 subjects per treatment arm based on alpha levels specified in the gatekeeping procedure and 80% power to detect a placebo adjusted mean difference in IIEF of 2.6 points (SD 8.0) and IPSS of -1.9 points (assuming SD of 6 points) Safety analysis consisted of all randomised subjects. Differences in event rate between treatment groups analysed using Fisher's exact test. Changes in Qmax and PVR analysed by a ranked ANOVA model with a term for treatment group. There were 170 dropouts in the placebo group (15%), 26 in tadalafil 2.5mg (13.1%) and 24 in tadalafil 5mg group (11.5%).

1

<table>
<tr><td>Bibliographic reference</td><td>Giuliano, Francois A., Lamb, Janice, Crossland, Anna, Haughie, Scott, Ellis, Peter, Tamimi, Nihad A.M., A placebo-controlled exploratory study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with storage lower urinary tract symptoms associated with a clinical diagnosis of overactive bladder, BJU internationalBJU Int, 106, 666-673, 2010</td></tr>
<tr><td>Study type</td><td>Multicentre double blind, placebo controlled, parallel group study</td></tr>
<tr><td>Aim</td><td>To evaluate the safety and efficacy of UK369003 modified release (MR) for the treatment of LUTS storage symptoms in men with and without ED.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Men aged ≥18 years with a clinical diagnosis of OAB, (a voiding frequency of ≥8 times/24hours, urgency episode frequency once or more per 24hours (with or without urinary incontinence), and a mean voided volume of <300mL, confirmed with a 3 day bladder diary and Qmax of <5mL/s in a voided volume of >150mL.

Exclusion
Men who had a history, evidence or suspicion of prostate cancer, PVR of >200mL, history of catheterisation for BOO in the previous 12 months, documented UTI, history of chronic persistent local lower urinary tract pathology or relevant urological procedures, primary neurological conditions such as spinal cord injury, MS. Poorly controlled diabetes, loss of vision in one eye due to NAION, family history of long QT syndrome, current treatment with nitrates, antiandrogens, and potent cytochrome P450 3A4 inhibitors or treatment with α blocker, antimuscarinic or PDE5I within 4 weeks of randomisation

Details
2 week, single blind placebo run-in, patients then stratified into 2 groups of men with or without ED, based on their IIEF score of ≥25 (ED) or <25 (no ED). No more than 210 patients would be randomised to the LUTS with ED stratum and no more than 150 would be randomised to the LUTS without ED stratum. Within each stratum patients were randomised to one of five treatment groups according to the ratio 1:1:1:1:1

Baseline characteristics were generally well balanced between the 4 groups, with voiding frequency, urgency episodes and incontinence episodes being similar between all groups. Characteristics of note, or that differed between groups are presented below:

The study did not report numbers of participants with or without ED
<table>
<tr><td></td><td>UK369,003 10mg</td><td>UK369,003 25mg</td><td>UK369,003 50mg</td><td>UK369,003 100mg</td><td>Placebo</td></tr>
<tr><td>Age (yrs.) (mean (SD))</td><td>60.2 (10.4)</td><td>59.8 (9.7)</td><td>60.1 (8.4)</td><td>59.3 (11.0)</td><td>60.5 (9.6)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Giuliano, Francois A., Lamb, Janice, Crossland, Anna, Haughie, Scott, Ellis, Peter, Tamimi, Nihad A.M., A placebo-controlled exploratory study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with storage lower urinary tract symptoms associated with a clinical diagnosis of overactive bladder, BJU internationalBJU Int, 106, 666-673, 2010</td></tr>
<tr><td></td><td>
<table>
<tr><td>White ethnicity</td><td>53</td><td>52</td><td>59</td><td>58</td><td>57</td></tr>
<tr><td>Other ethnicity</td><td>6</td><td>5</td><td>8</td><td>6</td><td>5</td></tr>
<tr><td>Voided volume/ void (mean (SD))</td><td>180.4 (52.59)</td><td>174.7 (53.30)</td><td>191.1 (43.65)</td><td>180.1 (46.63)</td><td>188.6 (49.62)</td></tr>
<tr><td>Nocturnal frequency (mean (SD))</td><td>?N=51
1.8 (0.94)</td><td>?N=52
2.0 (1.20)</td><td>?N=58
1.7 (1.04)</td><td>?N=58
1.5 (1.0)</td><td>?N=58
1.8 (1.17)</td></tr>
<tr><td>Total IPSS (mean (SD))</td><td>? N=40
12.1 (8.03)</td><td>? N=40
12.3 (7.45)</td><td>? N=47
9.9 (8.09)</td><td>? N=45
14.0 (7.70)</td><td>? N=37
10.6 (9.03)</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>N=310</td></tr>
<tr><td>Intervention</td><td>Modified release UK369,003 10mg (N=60, 59 treated, 54 completed)

Modified release UK369,003 25mg (N=57, 57 treated, 51 completed)

Modified release UK369,003 50mg (N=67, 67 treated, 63 completed)

Modified release UK369,003 100mg (N=63, 64 treated, 55 completed)

The modified release form of this drug has an 18 hour release profile, providing24 hour coverage through once daily administration.</td></tr>
<tr><td>Comparison</td><td>Placebo (N=63, 62 treated, 57 completed)</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>50 centres in North and South America, Europe and Australia, August 2007- June 2008</td></tr>
<tr><td>Outcomes measures and effect size</td><td>All outcomes at week 12 follow up

Symptom scores

IPSS (changes from baseline, with estimates of treatment difference)</td></tr>
</table>

Bibliographic reference	Giuliano, Francois A., Lamb, Janice, Crossland, Anna, Haughie, Scott, Ellis, Peter, Tamimi, Nihad A.M., A placebo-controlled exploratory study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with storage lower urinary tract symptoms associated with a clinical diagnosis of overactive bladder, BJU internationalBJU Int, 106, 666-673, 2010

	UK369,003 10mg	UK369,003 25mg	UK369,003 50mg	UK369,003 100mg	Placebo
Week 12, N patients	53	50	61	55	56
LS mean (SE)	-3.38 (0.63)	-3.07 (0.65)	-4.97 (0.59)	-3.56 (0.63)	-3.49 (0.61)
Mean (90%CI) diff vs placebo	0.11 (-1.32, 1.54)	0.41 (-1.04, 1.87)	-1.48 (-2.86, -0.10)	-0.07 (-1.50, -1.35)	NA

Quality of Life

Not reported

QMax

Not reported

Voiding frequency (per 24 hours)

	UK369,003 10mg	UK369,003 25mg	UK369,003 50mg	UK369,003 100mg	Placebo
N patients	44	46	54	49	54
LS mean (SE)	-0.68 (0.30)	-1.12 (0.30)	-0.85 (0.27)	-1.13 (0.29)	-0.93 (0.27)
Mean (90%CI) diff vs placebo	0.25 (-0.41, 0.92)	-0.19 (-0.85, 0.47)	0.08 (-0.55, 071)	-0.20 (-0.84, 0.45)	NA

Nocturia (frequency/ 24 hours)

	UK369,003 10mg	UK369,003 25mg	UK369,003 50mg	UK369,003 100mg	Placebo
N patients	39	44	47	44	51

Bibliographic reference

Giuliano, Francois A., Lamb, Janice, Crossland, Anna, Haughie, Scott, Ellis, Peter, Tamimi, Nihad A.M., A placebo-controlled exploratory study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with storage lower urinary tract symptoms associated with a clinical diagnosis of overactive bladder, BJU internationalBJU Int, 106, 666-673, 2010

LS mean (SE)	-0.36 (0.13)	-0.55 (0.12)	-0.30 (0.12)	-0.55 (0.12)	-0.26 (0.11)
Mean (90%CI) diff vs placebo	-0.09 (-0.37, 0.18)	-0.28 (-0.55, -0.02)	-0.04 (-0.30, 0.22)	-0.29 (-0.55, -0.02)	NA

Adverse events (n, %)

	UK369,003 10mg	UK369,003 25mg	UK369,003 50mg	UK369,003 100mg	Placebo
Headache	7 (12)	2 (4)	5 (8)	7 (11)	4 (7)
Discontinued due to AEs	3 (5.1)	4 (7.1)	2 (3.0)	6 (9.4)	2 (3.2)

Source of funding

Pfizer

Comments

- Randomisation and allocation concealment not adequately described. Blinding not described.
- Efficacy data analysed on Full Analysis Set (FAS): patients who has been randomised, received double blind treatment, and had at least one efficacy measure after baseline.
- Analyses of bladder diary endpoints, IPSS used mixed effects models with repeated measures. Each model included time point, baseline value, ED status, treatment group and time point by treatment interaction term as fixed effects and individual patient identifiers as random effects. Least squares means for each treatment and the treatment differences between UK369003 MR doses and placebo at each on-treatment time point were estimated with 90%CI
- Safety analysis set was used for the analyses of safety endpoints and included all randomised patients who had taken at least one dose of study medication.
- Sample size adequately powered to detect changes from baseline in IPSS, voiding frequency, 54 patients per group.

1

Bibliographic reference	Kaplan,Steven A., Gonzalez,Ricardo R., Te,Alexis E., Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction, European urologyEur Urol, 51, 1717-1723, 2007
Study type	RCT, open label
Aim	
Patient characteristics	**Patient group:** consecutive men with moderate to severe untreated LUTS and erectile dysfunction **Inclusion criteria**: • Moderate to severe untreated LUTS and self-reported erectile dysfunction (not specific cut off points) **Exclusion criteria:** • Contraindications to the study Key patient characteristics

	Sildenafil	Alfuzosin
N	21	20
Mean (S) age	64 ± 5.9	62.6 ± 8.2
Duration LUTS (months)	14.3 ± 2.4	12.4 ± 2.3
Duration ED (months)	25.6 ± 5.4	22.5 ± 4.9
Frequency	9.3 ± 2.6	8.9 ± 2.5
Nocturia	2.9 ± 0.6	3.1 ± 1.1
IPSS mean (SD)	17.3 ± 4.3	16.9 ± 4.1
IPSS moderate (8-19)	43%	45%
IPSS severe (>20)	57%	55%

<table>
<tr><td>Bibliographic reference</td><td>Kaplan,Steven A., Gonzalez,Ricardo R., Te,Alexis E., Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction, European urologyEur Urol, 51, 1717-1723, 2007</td></tr>
<tr><td></td><td>
<table>
<tr><td>IIEF-EF domain (mean, SD)</td><td>14.3 ± 5.2</td><td>17.4 ± 4.9</td></tr>
<tr><td>Qmax (mean, SD) mL/s</td><td>9.7 ± 3.7</td><td>9.4 ± 2.2</td></tr>
<tr><td>dropouts</td><td>2</td><td>2</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>N=62</td></tr>
<tr><td>Intervention</td><td>Group 1: Sildenafil citrate 25 mg one daily at night</td></tr>
<tr><td>Comparison</td><td>Group 2: Alfuzosin 10mg once daily after the same meal

Group 3: Sildenafil citrate 25 mg/day + Alfuzosin 10 mg/day (combination excluded from review, therefore not further information on this combination.</td></tr>
<tr><td>Length of follow up</td><td>3 months</td></tr>
<tr><td>Location</td><td>single-centre, Department of Urology, Weill Cornell Medical College, NY, USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores- IPSS
<table>
<tr><td></td><td>Sildenafil</td><td>Alfuzosin</td></tr>
<tr><td>12 weeks follow up (mean, SD)
P value calculated by NGC as t-test with equal variances</td><td>14.9 ± 4.2</td><td>14.6 ± 3.7</td></tr>
<tr><td>IPSS change from baseline at 12 weeks
(p change from baseline t-test)</td><td>-2.40 ±4.25 (11.8%) p=0.03</td><td>-2.30 ±3.91(15.6%) p=0.01</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Kaplan,Steven A., Gonzalez,Ricardo R., Te,Alexis E., Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction, European urologyEur Urol, 51, 1717-1723, 2007

Change (mean ±sd) calculated by NCGC from the difference in baseline and follow up values. % values as reported		

Quality of Life

Not reported

QMax

	Sildenafil	Alfuzosin
Mean (SD) at 12 weeks	10.3 ± 2.4	10.5 ± 2.3
Change from baseline	0.3±3.1	1.1±2.3

Voiding frequency

	Sildenafil	Alfuzosin
Mean (SD) at 12 weeks	7.8 ± 1.7	6.4 ± 2.1

Nocturia

	Sildenafil	Alfuzosin
Mean (SD) at 12 weeks	2.1 ± 0.9	1.8 ± 0.9
Change from baseline	-0.8±0.8	-1.3±1.0

Bibliographic reference	Kaplan,Steven A., Gonzalez,Ricardo R., Te,Alexis E., Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction, European urologyEur Urol, 51, 1717-1723, 2007
	Adverse events (N)

	Sildenafil	Alfuzosin
Withdrawals due to AEs	2	2
Dizziness	0	2
Flushing	1	0

Source of funding	
Comments	Randomisation was performed according to a code generated by Bayer, balanced blocks of treatment group allocation and 1:1 ratio between the two treatment groups. The packaging site was provided with copies of the randomisation code and investigators received sealed, patient specific “code break” envelopes. Double blind Patients, investigators and researchers masked to treatment allocation Outcome measures with standard deviations were not reported. Sample size based on projected treatment difference of 15% between Tolterodine ER + Tamsulosin group compared to placebo for number of patients reporting treatment benefit at week 12. Missing data imputed for treatment benefit question (YES/NO), bladder diary variables, IPSS and IPSS QoL using Last observation carried forward (LOCF) % of IIEF change from baseline had been updated to correct publication error in original article. **Erectile Dysfunction assessed using the Erectile Function domain score of the 15-question IIEF, ie , ie Q1-5 and Q15 (Maximum score 30).

1

Bibliographic reference	Kim,S.C., Park,J.K., Kim,S.W., Lee,S.W., Ahn,T.Y., Kim,J.J., Paick,J.S., Park,N.C., Park,K., Min,K.S., Kraus,S.R., Secrest,R.J., Elion-Mboussa,A., Viktrup,L., Tadalafil Administered Once Daily for Treatment of Lower Urinary Tract Symptoms in Korean men with Benign Prostatic Hyperplasia: Results from a Placebo-Controlled Pilot Study Using Tamsulosin as an Active Control, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 3, 86-93, 2011

<table>
<tr><td>Bibliographic reference</td><td>Kim,S.C., Park,J.K., Kim,S.W., Lee,S.W., Ahn,T.Y., Kim,J.J., Paick,J.S., Park,N.C., Park,K., Min,K.S., Kraus,S.R., Secrest,R.J., Elion-Mboussa,A., Viktrup,L., Tadalafil Administered Once Daily for Treatment of Lower Urinary Tract Symptoms in Korean men with Benign Prostatic Hyperplasia: Results from a Placebo-Controlled Pilot Study Using Tamsulosin as an Active Control, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 3, 86-93, 2011</td></tr>
<tr><td>Study type</td><td>RCT (randomised, double blind, placebo and active controlled, pilot clinical trial)</td></tr>
<tr><td>Aim</td><td>To assess the efficacy of once-daily tadalafil or tamsulosin vs placebo during 12 weeks on LUTS symptoms in Korean men with BPH</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Men ≥45 years age, with BPH and a >6 month history of LUTS at visit 1, BOO of intermediate severity (Qmax ≥4 to ≤15/ sec at visit 2), total IPSS of ≥13 at visit 2.

Exclusion
PSA at visit 1 of >10ng/mL, PVR >300mL, history of symptomatic orthostatic hypotension, dizziness, vertigo, and loss of consciousness or syncope. Men with PSA levels of 4-10ng/mL must have had a prostate biopsy negative for malignancy within 12 months of visit 1. Use of finasteride or dutasteride within 3 and 6 months prior to visit 2 respectively ,

Details
Men reporting the use of ED or BPH treatments upon study entry underwent 4 week treatment free washout period before beginning a 4 week placebo run-in period. All other participants began a 4 week placebo run-in period immediately after screening results were reviewed. After the placebo run in period subjects were randomly assigned (1:1:1) to received once daily tadalafil, tamsulosin or placebo. Randomisation stratified by prior alpha blocker use (within 12 months of visit 1) and LUTS severity at baseline (moderate <20 or severe, ≥20)

Baseline characteristics of note or not balanced at baseline:
<table>
<tr><td></td><td>Tadalafil 5mg</td><td>Tamsulosin 0.2mg</td><td>Placebo</td></tr>
<tr><td>Age (mean, SD)</td><td>61.2 (6.6)</td><td>61.5 (6.4)</td><td>62.2 (6.8)</td></tr>
<tr><td>IPSS (mean, SD)</td><td>17.1 (5.4)</td><td>17.7 (5.0)</td><td>17.3 (5.0)</td></tr>
<tr><td>LUTS – moderate severity (<20)</td><td>68.6</td><td>67.3</td><td>68.6</td></tr>
<tr><td>LUTS – severe</td><td>31.4</td><td>32.7</td><td>31.4</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Kim,S.C., Park,J.K., Kim,S.W., Lee,S.W., Ahn,T.Y., Kim,J.J., Paick,J.S., Park,N.C., Park,K., Min,K.S., Kraus,S.R., Secrest,R.J., Elion-Mboussa,A., Viktrup,L., Tadalafil Administered Once Daily for Treatment of Lower Urinary Tract Symptoms in Korean men with Benign Prostatic Hyperplasia: Results from a Placebo-Controlled Pilot Study Using Tamsulosin as an Active Control, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 3, 86-93, 2011</td></tr>
<tr><td></td><td>
<table>
<tr><td>(IPSS ≥20)</td><td></td><td></td><td></td></tr>
<tr><td>ED (Yes) (%)</td><td>58.8</td><td>49.0</td><td>70.6</td></tr>
<tr><td>PSA (ng/mL) (mean, SD)</td><td>1.0 (0.7)</td><td>1.7 (1.0)</td><td>1.2 (1.0)</td></tr>
</table>
Of note, the number of men with ED is higher in the placebo group compared to tadalafil and tamsulosin</td></tr>
<tr><td>Number of Patients</td><td>N=151</td></tr>
<tr><td>Intervention</td><td>Tadalafil 5mg once daily (n=51, 48 completed)</td></tr>
<tr><td>Comparison</td><td>Tamsulosin 0.2mg (N=49, 48 completed)

Placebo (N=51, 47 completed)</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>10 centres in South Korea</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores
<table>
<tr><td></td><td colspan="2">Tadalafil 5mg</td><td colspan="2">Tamsulosin 0.2mg</td><td>Placebo</td></tr>
<tr><td></td><td>Mean (SE)</td><td>P value</td><td>Mean (SE)</td><td>P value</td><td>Mean (SE)</td></tr>
<tr><td>IPSS total</td><td>-5.8 (0.6)</td><td>0.07</td><td>-5.4 (0.7)</td><td>0.19</td><td>-4.2 (0.6)</td></tr>
<tr><td>IPSS obstructive</td><td>-3.7 (0.4)</td><td>0.10</td><td>-3.6 (0.5)</td><td>0.15</td><td>-2.7 (0.4)</td></tr>
<tr><td>IPSS irritative</td><td>-1.8 (0.3)</td><td>0.52</td><td>-2.1 (0.3)</td><td>0.15</td><td>-1.5 (0.3)</td></tr>
<tr><td>BII</td><td>-2.2 (0.3)</td><td>0.69</td><td>-1.6 (0.3)</td><td>0.42</td><td>-2.0 (0.3)</td></tr>
</table>
Quality of Life</td></tr>
</table>

Bibliographic reference	Kim,S.C., Park,J.K., Kim,S.W., Lee,S.W., Ahn,T.Y., Kim,J.J., Paick,J.S., Park,N.C., Park,K., Min,K.S., Kraus,S.R., Secrest,R.J., Elion-Mboussa,A., Viktrup,L., Tadalafil Administered Once Daily for Treatment of Lower Urinary Tract Symptoms in Korean men with Benign Prostatic Hyperplasia: Results from a Placebo-Controlled Pilot Study Using Tamsulosin as an Active Control, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 3, 86-93, 2011

	Tadalafil 5mg		Tamsulosin 0.2mg		Placebo
	Mean (SE)	**P value**	**Mean (SE)**	**P value**	**Mean (SE)**
IPSS QoL	-1.2 (0.2)	0.21	-1.0 (0.2)	0.59	-0.9 (0.2)
PGI-I					
Worse (%)	2.0		6.3		2.1
No change (%)	10.2		14.6		20.8
Better (%)	87.8		79.2		77.1
CGI-I					
Worse (%)	0.0		8.3		0.0
No change (%)	16.3		8.3		10.4
Better (%)	83.7		83.3		89.6

QMax

	Tadalafil 5mg		Tamsulosin 0.2mg		Placebo
	Mean (SE)	**P value**	**Mean (SE)**	**P value**	**Mean (SE)**
Qmax (mL/sec)	2.5 (0.7)	0.84	2.1 (0.7)	0.83	2.3 (0.7)

Voiding frequency

Not reported

Nocturia (IPSS nocturia question)

Bibliographic reference	Kim,S.C., Park,J.K., Kim,S.W., Lee,S.W., Ahn,T.Y., Kim,J.J., Paick,J.S., Park,N.C., Park,K., Min,K.S., Kraus,S.R., Secrest,R.J., Elion-Mboussa,A., Viktrup,L., Tadalafil Administered Once Daily for Treatment of Lower Urinary Tract Symptoms in Korean men with Benign Prostatic Hyperplasia: Results from a Placebo-Controlled Pilot Study Using Tamsulosin as an Active Control, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 3, 86-93, 2011

	Tadalafil 5mg		Tamsulosin 0.2mg		Placebo
	Mean (SE)	**P value**	**Mean (SE)**	**P value**	**Mean (SE)**
Nocturia (IPSS nocturia question)	-0.5 (0.1)	0.77	-0.5 (0.1)	0.73	-0.4 (0.1)

Adverse events (n,%)

	Tadalafil 5mg (N=51)	Tamsulosin 0.2mg (N=49)	Placebo (N=51)
Headache	1 (2%)	0	1 (2%)
Flushing	1 (2%)	0	0
Withdrawals due to AEs	1 (2%)	1 (2%)	0

Source of funding	Eli Lilly
Comments	Randomisation, allocation concealment and blinding not reported in paper. - Study reported to be adequately powered to detect change from baseline to endpoint of 2.5 in total IPSS, N=45 in each arm. - Efficacy analyses on ITT basis; included all randomised subjects with at least one post baseline measurement. Safety analyses included all randomised subjects. - ANCOVA model which included all effects for treatment, prior alpha blocker use, and a baseline covariate (baseline of parameter being analysed) to analyse IPSS, BII and Qmax). A baseline by treatment model was evaluated and included in the model if it was significant. - Fisher's exact text was used to compare reported treatment emergent adverse events

1

Bibliographic reference	Kumar,S., Kondareddy,C., Ganesamoni,R., Nanjappa,B., Singh,S.K., Randomized controlled trial to assess the efficacy of the combination therapy of alfuzosin and tadalafil in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 6, 35-40, 2014
Study type	RCT

<table>
<tr><td>Bibliographic reference</td><td>Kumar,S., Kondareddy,C., Ganesamoni,R., Nanjappa,B., Singh,S.K., Randomized controlled trial to assess the efficacy of the combination therapy of alfuzosin and tadalafil in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 6, 35-40, 2014</td></tr>
<tr><td>Aim</td><td>To find out whether concurrent admiration of alfusozin and tadalafil to people with LUTS due to BPH improves the beneficial effects of each drug alone.</td></tr>
<tr><td>Patient characteristics</td><td>Patient characteristics.
Patient characteristics were well balanced between groups at baseline for age (mean (SD) age 60.1 (11.4) and 63.1 (9.5) for alfusozin and tadalafil respectively), duration of LUTS, prostate volume, IPSS total and sub scores, Qmax, PVR and IPSS QoL.
<table>
<tr><td></td><td>Alfuzosin</td><td>Tadalafil</td></tr>
<tr><td>Sexually active males with ED</td><td>38%</td><td>28%</td></tr>
</table>
Inclusion
Men >50 years of age, with IPSS ≥8

Exclusion
According to contraindications of the study drugs. No further details given.

Details
Patients advised to take alfusozin each day after the same meal and tadalafil at bed time. Patients were assessed at baseline, 6 weeks and 12 weeks of treatment.</td></tr>
<tr><td>Number of Patients</td><td>N=50 in intervention arms of interest (N=75 in total)</td></tr>
<tr><td>Intervention</td><td>Tadalafil 10mg once daily (N=25)</td></tr>
<tr><td>Comparison</td><td>Alfusozin 10mg once daily (N=25)

Tadalafil 10mg + alfusozin 10mg once daily (N=25) – comparison not included in this analysis, therefore data not presented here.</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores</td></tr>
</table>

Bibliographic reference	Kumar,S., Kondareddy,C., Ganesamoni,R., Nanjappa,B., Singh,S.K., Randomized controlled trial to assess the efficacy of the combination therapy of alfuzosin and tadalafil in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 6, 35-40, 2014

IPSS total (not stated in publication what units the figures are)

Time point	Tadalafil	Alfusozin
Baseline	17.4 (3.9)	17.1 (2.3)
6 weeks	12.9 (3.9)	10.2 (2.9)
P value	0.001	<0.001
12 weeks	11.1 (3.9)	7.6 (3.4)
P value	<0.001	<0.001
Change from baseline to 12 weeks	6.3 (1.5)	9.5 (3.5)

IPSS storage (not stated in publication what units the figures are)

Time point	Tadalafil	Alfusozin
Baseline	6.9 (1.6)	7.1 (1.2)
6 weeks	5.2 (1.9)	3.8 (1.1)
P value	<0.001	<0.001
12 weeks	4.4 (1.9)	3.1 (1.7)
Change from baseline to 12 weeks	<0.001	<0.001

IPSS voiding (not stated in publication what units the figures are)

Time point	Tadalafil	Alfusozin
Baseline	10.4 (2.6)	10.1 (1.6)

Bibliographic reference	Kumar,S., Kondareddy,C., Ganesamoni,R., Nanjappa,B., Singh,S.K., Randomized controlled trial to assess the efficacy of the combination therapy of alfuzosin and tadalafil in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 6, 35-40, 2014

6 weeks	7.8 (2.4)	6.2 (1.7)
P value	<0.001	<0.001
12 weeks	6.6 (2.2)	4.6 (1.9)
Change from baseline to 12 weeks	<0.001	<0.001

Quality of Life (not stated in publication what units the figures are)

Time point	Tadalafil	Alfusozin
Baseline	5.2 (0.4)	5.3 (0.5)
6 weeks	3.6 (0.6)	2.8 (0.8)
P value	<0.001	<0.001
12 weeks	2.80	2.0 (0.9)
Change from baseline to 12 weeks	<0.001	<0.001

Qmax (not stated in publication what units the figures are)

Time point	Tadalafil	Alfusozin
Baseline	9.3 (3.8)	11.3 (6.1)
6 weeks	10.2 (3.7)	13.4 (6.2)
P value	<0.001	<0.001
12 weeks	10.9 (3.8)	14.2 (6.2)
Change from baseline to	<0.001	<0.001

Bibliographic reference	Kumar,S., Kondareddy,C., Ganesamoni,R., Nanjappa,B., Singh,S.K., Randomized controlled trial to assess the efficacy of the combination therapy of alfuzosin and tadalafil in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, LUTS: Lower Urinary Tract SymptomsLUTS: Lower Urin.Tract Symptoms, 6, 35-40, 2014
	12 weeks **Voiding frequency** Not reported **Nocturia** Not reported **Adverse events** Tadalafil 10mg – 2 patients had occasional headache Alfusozin 10mg – no reports of adverse events No dropout due to AEs.
Source of funding	Not reported
Comments	-Normality of data tested by Kolmogorov Smirnov test All 3 groups compared for normally distributed data by ANOVA followed by post hoc test student Newman Kuel procedure for pairwise comparisons -Within the same group the variables were compared by paired t test and variables between the groups were compared using unpaired t test. The skewed data were analysed for all 3 groups using Kruskal Wallis test, ANOVA followed by Mann Whitney test for pairwise comparisons. -All classified/ categorical data analysed for all 3 groups using chi squared. -No loss to follow up or discontinuations. -Method of randomisation not reported. Allocation concealment and blinding not described. -All patients who entered the trial competed it, therefore ITT analysis (n=50) -not stated whether figures are mean(SD), therefore data not metanalysed due to lack of clarity of what figures reported are

1

<table>
<tr><td>Bibliographic reference</td><td>Liguori,Giovanni, Trombetta,Carlo, De Giorgi,Gioacchino, Pomara,Giorgio, Maio,Giuseppe, Vecchio,Daniele, Ocello,Giuseppe, Ollandini,Giangiacomo, Bucci,Stefano, Belgrano,Emanuele, Efficacy and safety of combined oral therapy with tadalafil and alfuzosin: an integrated approach to the management of patients with lower urinary tract symptoms and erectile dysfunction. Preliminary report, The journal of sexual medicineJ Sex Med, 6, 544-552, 2009</td></tr>
<tr><td>Study type</td><td>Randomised open label three armed study</td></tr>
<tr><td>Aim</td><td>To evaluate the efficacy of combined therapy with alfusozin and tadalafil in patients with ED and LUTS</td></tr>
<tr><td>Patient characteristics</td><td>No significant differences reported between groups at baseline. IPSS and Qmax scores similar between groups, with incidence of diabetes, hypertension and ischaemic heart disease remaining similar between groups.

The age distribution of the groups is as follows:

<table>
<tr><td></td><td>Tadalafil</td><td>Alfusisozin</td></tr>
<tr><td>Age (years) (mean, D)</td><td>60.8 (8)</td><td>61.3 (6.8)</td></tr>
<tr><td><60 n,(%)</td><td>11 (56.2)</td><td>8 (46.6)</td></tr>
<tr><td>60-70</td><td>6 (31.2)</td><td>6 (33.3)</td></tr>
<tr><td>>70</td><td>2 (12.5)</td><td>4 (20)</td></tr>
</table>

Inclusion
Men presenting to a urologic outpatient clinic complaining of both ED and LUTS who were PDE5I and alpha blocker treatment naïve.
-Aged 50-75 years, previously untreated ED of any grade, history of LUTS secondary to BPH of ≥6 months, IPSS of >8

Exclusion
Contraindications of both drugs, , use of medications to control bladder symptoms, bladder tumours, urethral strictures, neurogenic bladder dysfunction, history of prostatitis, prostate cancer, PSA level of >20ng/mL, history of prostate surgery of radiotherapy, cute urinary retention, or an indwelling catheter, evidence of acute urinary infection on urinalysis, or if they had ever taken 5ARIs, alpha blockers of PDE5Is</td></tr>
<tr><td>Number of Patients</td><td>N=43 in study arms of interest (N=66 in all three study arms)
Mean age: 61 years (range 50 to 75)
Drop outs: 8/66 (Baseline data excluded patients who dropped out of study)</td></tr>
<tr><td>Intervention</td><td>Tadalafil 20mg every other day (N=21)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Liguori,Giovanni, Trombetta,Carlo, De Giorgi,Gioacchino, Pomara,Giorgio, Maio,Giuseppe, Vecchio,Daniele, Ocello,Giuseppe, Ollandini,Giangiacomo, Bucci,Stefano, Belgrano,Emanuele, Efficacy and safety of combined oral therapy with tadalafil and alfuzosin: an integrated approach to the management of patients with lower urinary tract symptoms and erectile dysfunction. Preliminary report, The journal of sexual medicineJ Sex Med, 6, 544-552, 2009</td></tr>
<tr><td>Comparison</td><td>Alfusozin 10g retarded release with Geomatrix once/ day (N=22)

Tadalafil + alfusozin (not reported here as excluded intervention)</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>5 centres in Italy, February – December 2007</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores

IPSS total (mean, not clear from publication whether SD or SE)
<table>
<tr><td></td><td>Tadalafil (N=18)</td><td>Alfusozin (N=19)</td></tr>
<tr><td>Baseline</td><td>13.8 (5.6)</td><td>15.7 (4.8)</td></tr>
<tr><td>12 weeks</td><td>12.5 (5.6)</td><td>10.5 (3.6)</td></tr>
<tr><td>% change</td><td>-8.4 (p=ns)</td><td>-27.2 (p=0.003)</td></tr>
</table>
Quality of Life- IPSS (mean, not clear from publication whether SD or SE)
<table>
<tr><td></td><td>Tadalafil (N=18)</td><td>Alfusozin (N=19)</td></tr>
<tr><td>Baseline</td><td>3.5 (1.1)</td><td>3.4 (0.9)</td></tr>
<tr><td>12 weeks</td><td>2.5 (1.2)</td><td>2.1 (0.9)</td></tr>
<tr><td>% change</td><td>-28.8 (p=0.04)</td><td>-27.2 (p=0.000)</td></tr>
</table>
Qmax (mean, not clear from publication whether SD or SE)
<table>
<tr><td></td><td>Tadalafil (N=18)</td><td>Alfusozin (N=19)</td></tr>
<tr><td>Baseline</td><td>13.1 (4.3)</td><td>12.3 (5.4)</td></tr>
<tr><td>12 weeks</td><td>14.3 (5.2)</td><td>14.0 (3.7)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Liguori,Giovanni, Trombetta,Carlo, De Giorgi,Gioacchino, Pomara,Giorgio, Maio,Giuseppe, Vecchio,Daniele, Ocello,Giuseppe, Ollandini,Giangiacomo, Bucci,Stefano, Belgrano,Emanuele, Efficacy and safety of combined oral therapy with tadalafil and alfuzosin: an integrated approach to the management of patients with lower urinary tract symptoms and erectile dysfunction. Preliminary report, The journal of sexual medicineJ Sex Med, 6, 544-552, 2009

% change	9.5 (p=0.044)	21.7 (p=0.006)

Voiding frequency

Not reported

Nocturia (IPSS question) (mean, not clear from publication whether SD or SE)

	Tadalafil (N=18)	Alfusozin (N=19)
Baseline	1.7 (1.0)	1.9 (0.9)
12 weeks	1.4 (1.1)	1.0 (0.7)
% change	-14.4 (p=ns)	-38.1 (p=0.006)

Adverse events (withdrawals)
Tadalafil:1 dropped out due to back pain and headaches
Alfusozin: 3 dropped out due to dizziness and constipation.

No severe or serious adverse events were reported during the study.

Source of funding	Not stated
Comments	- No details of randomisation or allocation concealment, study was open label - 66 patients were enrolled. 8 patients dropped out, so study population consisted of N= 58 (tadalafil N=19, alfusozin N=18). Demographics and outcomes reported for per protocol population. - Changes in IPSS and Qmax were expressed in terms of % of improvement. Differences regarding the parameters in question within the groups were evaluated with the Wilcoxon test.

1

Bibliographic reference	Maselli,G., Bergamasco,L., Silvestri,V., Gualà,L., Pace,G., Vicentini,C., Tadalafil versus solifenacin for persistent storage symptoms after prostate surgery in patients with erectile dysfunction: a prospective randomized study, International Journal of UrologyInt.J.Urol., 18, 515-520, 2011
Study type	Prospective randomised study

Bibliographic reference	Maselli,G., Bergamasco,L., Silvestri,V., Gualà,L., Pace,G., Vicentini,C., Tadalafil versus solifenacin for persistent storage symptoms after prostate surgery in patients with erectile dysfunction: a prospective randomized study, International Journal of UrologyInt.J.Urol., 18, 515-520, 2011
Aim	To compare tadalafil with solifenacin in modifying symptoms and uroflowmetric parameters in patients with ED and residual storage symptoms after surgery.
Patient characteristics	Evaluated patients surgically treated for BPH-LUTS in the previous 3 year, suffering ED and residual storage symptoms at least 6 months after surgery **Inclusion** men aged 50–70 years with mild to moderate ED (International Index of Erectile Function-5 [IIEF-5]: 12–16 and IPSS: 8–19, Qmax > 12 mL/s) who were able to give written informed consent and comply with study procedures **Exclusion** Postvoid residual (PVR) > 50 mL, any findings in urodynamics, and retrograde and voiding cystourethrography, which might be suspected for neurogenic bladder, detrusor over-activity, urethral stricture, sclerosis of bladder neck, acute or chronic urinary tract infection, total serum prostate-specific antigen > 4 ng/mL, history of prostate cancer, lower urinary tract instrumentation, and use of any 5-a-reductase inhibitors or androgens, anti-androgens, phytotherapic drugs within the past 6 months from the randomization visit, use of any 5-a-adrenoreceptor blockers or any PDE5-I within 2 weeks of the randomization visit. We excluded patients receiving treatment with nitrates or nitric oxide (NO) donors, anticoagulants, cytochrome P-450 3A4 inhibitors, cardiovascular diseases (unstable angina, recent myocardial infarction, uncontrolled blood pressure) and with laboratory evidence of significant renal or hepatic insufficiency, history of stroke or spinal cord injury, diabetic neuropathy, uncontrolled diabetes (glycosylated HbA1c greater than 9%), uncontrolled narrow-angle glaucoma, ulcerative colitis, toxic megacolon, myasthenia gravis or any clinical conditions or hypersensitivity that make taking anti-cholinergic or PDE5-I drugs not recommended. **Details** Medical history, electrocardiogram, urodynamics, and retrograde and voiding cystourethrography were obtained at study entry. A physical examination and laboratory examinations were carried out at the beginning and after 12 weeks or at study discontinuation. Eligible subjects were randomized to receive tadalafil 5 mg/day (group 1) or solifenacin 5 mg/day (group 2) for 12 weeks. Patients were instructed to take the assigned medication approximately at the same time every day without any restriction in food intake. Patients were considered dose compliant if at least 75 of the daily doses were taken in each 84-day period (89.3%) and if the days of therapy discontinuation were not consecutive. Baseline characteristics of the two groups were comparable at baseline for IPSS, Qmax and PVR. The median (range) age was 63.1 (4.9 and 61.3 (5.7) for tadalafil and solifenacin respectively.

<table>
<tr><td>Bibliographic reference</td><td>Maselli,G., Bergamasco,L., Silvestri,V., Gualà,L., Pace,G., Vicentini,C., Tadalafil versus solifenacin for persistent storage symptoms after prostate surgery in patients with erectile dysfunction: a prospective randomized study, International Journal of UrologyInt.J.Urol., 18, 515-520, 2011</td></tr>
<tr><td>Number of Patients</td><td>N=56</td></tr>
<tr><td>Intervention</td><td>Tadalafil 5mg once daily (N=28, 2 dropped out)</td></tr>
<tr><td>Comparison</td><td>Solifenacin 5mg once daily (N=28, 4 dropped out)</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>Italy, May 2007 – April 2009</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
Symptom scores- IPSS (Mean, not clear from publication whether SD or SE)
<table>
<tr><td></td><td>Tadalafil</td><td>Solifenacin</td></tr>
<tr><td>Baseline</td><td>8.8 (0.9)</td><td>8.7 (0.7)</td></tr>
<tr><td>12 weeks</td><td>3.8 (1.1)</td><td>3.5 (0.9)</td></tr>
<tr><td>change</td><td></td><td></td></tr>
</table>
Reduction in IPSS mainly due to IPSS irritative domain tadalafil group change 3.1 (0.4), solifenacin change 3.4 (0.3)
Quality of Life - IPSS (Mean, not clear from publication whether SD or SE)
<table>
<tr><td></td><td>Tadalafil</td><td>Solifenacin</td></tr>
<tr><td>Baseline</td><td>2.2 (0.4)</td><td>2.4 (0.5)</td></tr>
<tr><td>12 weeks</td><td>1.3 (0.3)</td><td>1.3 (0.4)</td></tr>
<tr><td>change</td><td></td><td></td></tr>
</table>
QMax (Mean, not clear from publication whether SD or SE)
<table>
<tr><td></td><td>Tadalafil</td><td>Solifenacin</td></tr>
<tr><td>Mean variation</td><td>-3.8 (2.3) mL/s</td><td>1.2 (1.8) mL/s</td></tr>
</table>
Voiding frequency (daytime frequency) (Mean, not clear from publication whether SD or SE)
<table>
<tr><td></td><td>Tadalafil</td><td>Solifenacin</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Maselli,G., Bergamasco,L., Silvestri,V., Gualà,L., Pace,G., Vicentini,C., Tadalafil versus solifenacin for persistent storage symptoms after prostate surgery in patients with erectile dysfunction: a prospective randomized study, International Journal of UrologyInt.J.Urol., 18, 515-520, 2011

Baseline	7.8 (2.3)	8.1 (2.6)
12 weeks	6.6 (2.1)	6.4 (2.3)
p	<0.05	<0.05

Nocturia (Mean, not clear from publication whether SD or SE)

	Tadalafil	Solifenacin
Baseline	1.7 (0.9)	1.5 (0.6)
12 weeks	1.3 (0.6)	1.2 (0.5)
p	>0.05	>0.05

Adverse events

Tadalafil: 5 reports of headache (minor adverse event)

Withdrawals due to AEs – not reported.

Source of funding	Not reported
Comments	- tadalafil group: 2 dropouts - Solifenacin: 4 dropouts - Not stated whether analysis on ITT or per protocol basis - Randomisation, allocation concealment and blinding not reported. - Wilcoxon matched pairs signed- rank test was applied to compare IPSS from baseline to end of treatment. Mann Whitney sum rank test was used to compare variables of 2 groups. - Figures in publication for results state mean, but do not state whether SD or SE. Assumed figures mean (SD) as that is what baseline demographics are reported as. However, not that this is an assumption only, and the study will be downgraded for lack of explicit reporting of figures as assumptions about results have had to be made.

1

Bibliographic reference	McVary,K.T., Kaufman,J., Young,J.M., Tseng,L.J., Sildenafil citrate improves erectile function: a randomised double-blind trial with open-label extension, International journal of clinical practiceInt J Clin Pract, 61, 1843-1849, 2007c
Study type	RCT
Aim	
Patient characteristics	**Patient group:** men with erectile dysfunction and LUTS/BPH from 41 urology clinics and clinical research centres. **Inclusion criteria**: Men≥45 years, had a clinical diagnosis of ED (score≤25 on the erectile function domain of the International Index of Erectile Function) and IPSS ≥12 **Exclusion criteria:** Men with confirmed or suspected prostate malignancy, serum prostate-specific antigen >10ng/ml, previous invasive intervention for BPH, ore previous prostate or bladder/pelvic rations or surgery. Those with PSA between 4-10ng/ml required two additional forms of documentation to confirm the absence of clinically evident malignancy. Men with acute urinary tract disease or cystoscopy with in 4 weeks of the trial, calculi in the urinary tract or acute urinary retention within 6 months of the trial, recurrent urinary tract infections or catheterisation for outflow obstruction in the year before the trial, or other known or suspected causes of urinary symptoms other than BPH, hypotension, hypertension orthostatic hypotension or significant cardiovascular disease. Men were excluded if they used nitrates, had hepatic or renal dysfunction, poorly controlled diabetes or a history of retinitis pigmentosa. Use of antimuscarinics, 5-alpha-reductase inhibitors within 6 months or alpha blockers within 4 weeks during study. PDE5 inhibitor or any other treatment for ED must have terminated therapy 4 weeks or more before the study.
Number of Patients	**N:** 370 **Mean age**: 60 (9) **Drop outs:** 1 not treated/withdrew
Intervention	**Group 1: Sildenafil citrate** Sildenafil citrate: 50mg once daily with each night at bedtime or 30 minutes to 1hr before sexual activity. After 2 weeks the does increased to 100mg but could be decreased to 50mg if the higher dose was not tolerated.
Comparison	**Group 2: Placebo**
Length of follow up	12 weeks
Location	USA
Outcomes measures and effect size	**Symptom scores- IPSS** Group 1 (N=182): -6.3 (-8.1, -4.6) Group 2 (N=178): -1.9 (-3.7, -0.2)

<table>
<tr><td>Bibliographic reference</td><td>McVary,K.T., Kaufman,J., Young,J.M., Tseng,L.J., Sildenafil citrate improves erectile function: a randomised double-blind trial with open-label extension, International journal of clinical practiceInt J Clin Pract, 61, 1843-1849, 2007c</td></tr>
<tr><td></td><td>P<0.001

Quality of Life
Group 1: -0.97 (-1.32, -0.62)
Group 2: -0.29 (-0.64, 0.05)
P<0.001

QMax
Group 1: 0.31 (-1.6, 2.2)
Group 2: 0.16 (-1.7, 2.1)
P=0.8

Voiding frequency

Not reported

Nocturia
Not reported

Adverse events
<table>
<tr><td></td><td>Sildenafil</td><td>placebo</td></tr>
<tr><td>Headache</td><td>21/189 (11%)</td><td>6/180 (3%)</td></tr>
<tr><td>Flushing</td><td>9/189 (5%)</td><td>1/180 (1%)</td></tr>
<tr><td>Discontinuations due to AEs</td><td>10/189 (2%)</td><td>2/180 (1%)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Supported by Pfizer, Inc.</td></tr>
<tr><td>Comments</td><td>Randomisation adequately reported.
- Study powered at 90% to detect change of 2.5±6.5 points on IPSS score, required 300 study completers
-ITT analysis
-ANCOVA used for IPSS, covariates included study site, treatment group, baseline values, baseline values, patient age, duration and etiology of ED and smoking status.
- Actual figures and SD not provided for IPSS, Qmax and IPSS QoL question.</td></tr>
</table>

Bibliographic reference	McVary,K.T., Kaufman,J., Young,J.M., Tseng,L.J., Sildenafil citrate improves erectile function: a randomised double-blind trial with open-label extension, International journal of clinical practiceInt J Clin Pract, 61, 1843-1849, 2007c
	In previous guideline, Least square means calculations used for analysis. NCGC calculated SD for meta-analysis from Cochrane calculations.

1

Bibliographic reference	McVary,K.T., Roehrborn,C.G., Kaminetsky,J.C., Auerbach,S.M., Wachs,B., Young,J.M., Esler,A., Sides,G.D., Denes,B.S., Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia, Journal of UrologyJ.Urol., 177, 1401-1407, 2007b
Study type	RCT
Aim	
Patient characteristics	**Patient group:** Men 45 years and older with a history of LUTS secondary to BPH of 6 months or longer were recruited from 21 centres in US from November 2004 to July 2005. Patients agreed not to use other BPH medications during this study. **Inclusion criteria**: IPSS of 13 or greater and a Qmax of 4-15ml/s on a voided volume of 125ml or greater was required. **Exclusion criteria:** patients without treatment compliance during run in phase (<70%) were excluded. Men with PSA >10ng/ml, recent finasteride or dutasteride treatment, history of radical prostatectomy or other pelvic surgery; neurological condition affecting bladder function; recent lower urinary tract instrumentation, urinary retention or bladder stones; history of urethral obstruction due to strictures, valves, sclerosis or tumour; detrusor-sphincter dyssynergia; urinary tract inflammation or infection; intravesical obstruction secondary to the prostate median lobe; prostate cancer; PVR 200ml or greater; certain cardiovascular diseases, clinically significant renal or hepatic insufficiency; recent history of stroke or spinal cord injury; current treatment with nitrates, cancer chemotherapy, antiandrogens or a potent cytochrome P450 3A4 inhibitor; or uncontrolled diabetes. Key baseline characteristics

	Tadalafil	Placebo
N	138	143
Ethnicity/ race	Black 10.9%, white 79%,	Black 8.4%, white 83.2%,

Bibliographic reference	McVary,K.T., Roehrborn,C.G., Kaminetsky,J.C., Auerbach,S.M., Wachs,B., Young,J.M., Esler,A., Sides,G.D., Denes,B.S., Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia, Journal of UrologyJ.Urol., 177, 1401-1407, 2007b
	<table><tr><td></td><td>Hispanic 6.5%, other 3.6%</td><td>Hispanic 7%, other 1.4%</td></tr><tr><td>Mean (range) age</td><td>62 (45.1-82.4)</td><td>61 (45.0-82.3)</td></tr><tr><td>dropouts</td><td>13 (adverse events=5, lost to follow up=1, patient decision=2, other =5)</td><td>17 (adverse events=2, lack of efficacy=1, lost to follow up=5, patient decision=6, other=3)</td></tr><tr><td>ED (%)</td><td>71.7%</td><td>59.2%</td></tr></table>
Number of Patients	281
Intervention	**Group 1: Tadalafil 5mg** Tadalafil 5mg once daily for six weeks, followed by dose escalation to 20mg for remaining 6 weeks. Medication ingested at same time every day.
Comparison	**Group 2: placebo**
Length of follow up	12 weeks
Location	USA
Outcomes measures and effect size	**Symptom scores- IPSS** **Mean (SE) IPSS at 12 weeks** **Baseline** Group1 (N=138): 17.5 Group 2 (N=143): 18.3 **12 weeks** Group1 (N =136): 13.3 Group 2 (N=138): 16.1

Bibliographic reference	McVary,K.T., Roehrborn,C.G., Kaminetsky,J.C., Auerbach,S.M., Wachs,B., Young,J.M., Esler,A., Sides,G.D., Denes,B.S., Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia, Journal of UrologyJ.Urol., 177, 1401-1407, 2007b
	Change: Group 1: -3.8 (0.5) Group 2: -1.7 (0.5); p<0.001 **Difference between change from baseline**: 2.1 (95% CI: 0.9-3.3); p<0.001 **Quality of Life** **Mean (SE) IPSS quality of life question at 12 weeks** **Baseline** Group1 (N=136): 3.6 Group 2 (N=138) : 3.8 **12 weeks** Group1 (N=136): 2.8 Group 2 (N=138): 3.3 **Change from baseline:** Group1: -0.7 (0.1) Group 2: -0.3 (0.1); p=0.004 **QMax** **Mean (SE) Qmax, ml/sec at 12 weeks** **Baseline** Group1 (N=116): 11.8 Group 2 (N=121) : 11.1 **12 weeks** Group1 (N=116): 12.3 Group 2 (N=121): 12.1 **Change from baseline:** Group1: 0.5 (0.5) Group 2: 0.9 (0.5); p=0.72 **Voiding frequency**

Bibliographic reference	McVary,K.T., Roehrborn,C.G., Kaminetsky,J.C., Auerbach,S.M., Wachs,B., Young,J.M., Esler,A., Sides,G.D., Denes,B.S., Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia, Journal of UrologyJ.Urol., 177, 1401-1407, 2007b
	Not reported **Nocturia** Not reported **Adverse events** **Discontinuation due to treatment emergent adverse events** Group 1: 3.6% Group 2: 1.4% **Treatment emergent adverse events with a frequency of 2% or greater at 12 weeks** **Headache** Group 1: 4 (2.9%) Group 2: 1 (0.7%)
Source of funding	Not reported
Comments	NCGC calculated SD Analyses of 12 week data used LOCF convention. Safety analyses on all randomised patients. ANCOVA model for IPSS end points BII and uroflowmetry: terms for baseline IPSS, previous a blocker therapy, treatment group, geographic region and baseline by treatment group interaction (if significant <0.1) Randomisation method and allocation concealment unclear.

1

Bibliographic reference	Oelke, Matthias, Giuliano, Francois, Mirone, Vincenzo, Xu, Lei, Cox, David, Viktrup, Lars, Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial, European urologyEur Urol, 61, 917-925, 2012
Study type	Randomised, parallel placebo controlled trial
Aim	To assess tadalafil or tamsulosin vs placebo for LUTS/BPH
Patient characteristics	**Inclusion**

Bibliographic reference	Oelke, Matthias, Giuliano, Francois, Mirone, Vincenzo, Xu, Lei, Cox, David, Viktrup, Lars, Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial, European urologyEur Urol, 61, 917-925, 2012

Men, aged ≥45 years who had had LUTS for >6 months at screening ad with IPSS of ≥13 and Qmax of ≥4 to ≤15 mL/s prior to the placebo lead-in period; subjects with improvements in IPSS or Qmax during the lead in period were not excluded. Compliance of ≥70% during the lead in period was required for randomisation.

Exclusion

Use of finasteride or dutasteride in the previous 3 or 6 months respectively. Other exclusion criteria described previously. Tamsulosin specific exclusions of men with planned cataract surgery, history of symptomatic orthostatic hypertension or recurrent dizziness, vertigo, loss of consciousness or syncope.

Details

Following screening and a 4 week washout for BPH, OAB and ED drugs as needed, participants began a 4 week single blind placebo lead-in period followed by randomisation (1:1:1 ratio).

Key baseline characteristics:

	Placebo (N=172)	Tadalafil (N=171)	Tamsulosin 0.4mg (N=168)
Age (mean, range)	63.7 (45.9-88.6)	63.5 (45.1-83.1)	63.5 (45.5 – 83.4)
≤65 (N, %)	95 (55.2)	96 (56.1)	96 (57.1)
>65-<75 (n, %)	54 (31.4)	62 (36.3)	56 (33.3)
≥75 (N, %)	23 (13.4)	13 (7.6)	16 (9.5)
Race (N, %)			
White	131 (76.2)	130 (76.0)	131 (78.0)
Black or African American	0	1 (0.6)	0
American Indian/ Alaska native	41 (23.8)	40 (23.4)	37 (22.0)
LUTS severity (N, %)			
Mild (IPSS <8)	6 (3.5)	3 (1.8)	4 (2.4)
Moderate (IPSS ≥8 to <20)	112 (65.1)	120 (70.2)	115 (68.5)
Severe (IPSS ≥20)	54 (31.4)	48 (28.1)	49 (29.2)

<table>
<tr><td>Bibliographic reference</td><td>Oelke, Matthias, Giuliano, Francois, Mirone, Vincenzo, Xu, Lei, Cox, David, Viktrup, Lars, Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial, European urologyEur Urol, 61, 917-925, 2012</td></tr>
<tr><td></td><td>
<table>
<tr><td>ED history (N, %)</td><td>120 (69.8)</td><td>121 (70.8)</td><td>116 (69.0)</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>N=511, 454 completed study, 510 took at least one dose of study drug and made up the efficacy population</td></tr>
<tr><td>Intervention</td><td>Tadalafil 5mg once daily (N=171, 156 completed)</td></tr>
<tr><td>Comparison</td><td>Tamsulosin 0.4mg (N=168, 150 completed)
Dosing to occur approximately 30 minutes after eating as per recommendations.

Placebo (N= 172, 148 completed)</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>44 urology sites in Australia, Austria, Belgium, France, Germany, Greece Italy Mexico, The Netherlands and Poland.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
Symptom scores (LS mean ± SE)
<table>
<tr><td></td><td>Tadalafil 5mg (N=171)</td><td>Tamsulosin 0.4mg (N=165)</td><td>Placebo (N=172)</td></tr>
<tr><td colspan="4">IPSS total</td></tr>
<tr><td>Change from baseline</td><td>-6.3±0.5</td><td>-5.7±0.5</td><td>-4.2±0.5</td></tr>
<tr><td>Change vs placebo</td><td>-2.1±0.6 (-3.3, -0.8)</td><td>-1.5±0.6 (-2.8, -0.2)</td><td>-</td></tr>
<tr><td>P value vs placebo</td><td>0.001</td><td>0.023</td><td>-</td></tr>
</table>
Symptom scores differences from placebo (least squares mean, 95%CI) change from baseline to 12 weeks (LOCF)
<table>
<tr><td></td><td>Tadalafil 5mg</td><td>Tamsulosin 0.4mg</td></tr>
<tr><td>IPSS total</td><td>-2.1 (-3.3, -0.8)</td><td>-1.5 (-2.8, -0.2)</td></tr>
<tr><td>BII</td><td>-0.8 (-1.3, -0.3)</td><td>-0.6 (-1.1, -0.1)</td></tr>
</table>
Quality of Life- IPSS (LS mean ±SE (95%CI)
</td></tr>
</table>

Bibliographic reference	Oelke, Matthias, Giuliano, Francois, Mirone, Vincenzo, Xu, Lei, Cox, David, Viktrup, Lars, Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial, European urologyEur Urol, 61, 917-925, 2012

	Tadalafil 5mg (N=171)	Tamsulosin 0.4mg (N=167)	Placebo (N=172)
Change from baseline	-1.3 ±0.1	-1.1±0.1	-1.0±0.1
Change vs placebo	-0.3±0.1 (-0.6, 0.0)	-0.1±0.1 (-0.4, 0.2)	-
P value vs placebo	0.022	0.546	-

QMax (mL/s)

	Tadalafil 5mg (N=171)	Tamsulosin 0.4mg (N=168)	Placebo (N=172)
Baseline	9.9±3.6	9.4±3.3	10.5 ±4.1
Mean change	2.4±5.5	2.2±4.1	1.2±4.8
Median change	1.6	1.6	0.3
P value vs placebo	0.009	0.014	-

Unless otherwise noted data are mean (SD)

Voiding frequency

Not reported

Nocturia (IPSS nocturia question)

	Tadalafil 5mg (N=171)	Tamsulosin 0.4mg (N=167)	Placebo (N=172)
Change from baseline, LS mean ±SE	-0.5±0.1	-0.5±0.1	-0.3±0.1
Change vs placebo, LS mean ±SE (95% CI)	-0.2±0.1 (-0.4, 0.0)	-0.2±0.1 (-0.4, 0.0)	-

Bibliographic reference	Oelke, Matthias, Giuliano, Francois, Mirone, Vincenzo, Xu, Lei, Cox, David, Viktrup, Lars, Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial, European urologyEur Urol, 61, 917-925, 2012

P value	0.080	0.118	-

Adverse events (N, %)

	Tadalafil:	Tamsulosin:	Placebo:
Discontinuations due to AEs	2 (1.2%)	1 (0.6%)	2 (1.2%)
Headache	5 (2.9)	7 (4.2)	2 (1.2)
Dizziness	4 (2.3)	6 (3.6)	3 (1.7)

Source of funding	Study supported by Eli Lilly
Comments	- Study not designed for statistical testing of non-inferiority or superiority between tadalafil and tamsulosin, study was adequately powered for the comparison of each active treatment with placebo. - Analysis undertaken used last observation carried forward. - Dropouts similar between groups. - Continuous efficacy measures uroflowmetry evaluated as change from baseline to week 12, LOCF end point. - Continuous efficacy measures assessed using ANCOVA with terms for treatment group, region, and baseline, and baseline by treatment interaction and treatment by region interaction (removed where p≤0.1) - Changes from baseline to end of therapy for Qmax analysed using ANOVA with a term for treatment group.

1

Bibliographic reference	Pinggera, Germar Michael, Frauscher, Ferdinand, Paduch, Darius A., Bolyakov, Alex, Efros, Mitchell, Kaminetsky, Jed, Da Pozzo, Luigi, Esler, Anne, Cox, David, Effect of Tadalafil Once Daily on Prostate Blood Flow and Perfusion in Men With Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Randomized, Double-blind, Multicenter, Placebo-controlled Trial, Urology, 84, 412-420, 2014
Study type	Multicentre, randomised, double blind, parallel, placebo controlled trial.
Aim	To assess the effect of tadalafil vs placebo on prostatic blood flow in men with moderate to severe BPH-LUTS
Patient characteristics	**Inclusion**

<table>
<tr><td>Bibliographic reference</td><td>Pinggera, Germar Michael, Frauscher, Ferdinand, Paduch, Darius A., Bolyakov, Alex, Efros, Mitchell, Kaminetsky, Jed, Da Pozzo, Luigi, Esler, Anne, Cox, David, Effect of Tadalafil Once Daily on Prostate Blood Flow and Perfusion in Men With Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Randomized, Double-blind, Multicenter, Placebo-controlled Trial, Urology, 84, 412-420, 2014</td></tr>
<tr><td></td><td>Men aged ≥45 years with clinically diagnosed BPH-LUTS diagnosed ≥6 months before screening, with IPSS ≥13 and a Qmax ≥4 to ≤15 mL/s

Exclusion
History of prostate saturation biopsy or evidence of any conditions that could reduce tolerance to transrectal ultrasound (TRUS). Study refers to other exclusion criteria in Porst (2011).

Details
A screening and washout of ≤ 4 weeks was followed by a 2 week baseline TRUS assessment period. Eligible patients were then randomised in 1:1 ratio to oral tadalafil 5mg once daily or placebo, followed by an 8 week double blind treatment period. Randomisation was stratified by baseline LUTS severity, geographic region (EU, non-EU) and the presence or absence of pre-existing disease or risk factors.

Groups balanced at baseline for demographics.
<table>
<tr><td></td><td>Tadalafil</td><td>Placebo</td></tr>
<tr><td>Patients with mild, moderate or severe ED (N, %)</td><td>33, (61.7%)</td><td>29 (66%)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>N=97 (84 completed 8 weeks of treatment)</td></tr>
<tr><td>Intervention</td><td>Tadalafil 5mg once daily (N=47)</td></tr>
<tr><td>Comparison</td><td>Placebo (N=50)</td></tr>
<tr><td>Length of follow up</td><td>8 weeks</td></tr>
<tr><td>Location</td><td>Various</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores
Not reported

Quality of Life
Not reported

QMax
Not reported</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Pinggera, Germar Michael, Frauscher, Ferdinand, Paduch, Darius A., Bolyakov, Alex, Efros, Mitchell, Kaminetsky, Jed, Da Pozzo, Luigi, Esler, Anne, Cox, David, Effect of Tadalafil Once Daily on Prostate Blood Flow and Perfusion in Men With Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Randomized, Double-blind, Multicenter, Placebo-controlled Trial, Urology, 84, 412-420, 2014</td></tr>
<tr><td></td><td>Voiding frequency
Not reported

Nocturia
Not reported

Adverse events (n,%)
<table>
<tr><td></td><td>Tadalafil 5mg (N=47)</td><td>Placebo (N=50)</td></tr>
<tr><td>Headache</td><td>4 (8.5)</td><td>1 (2.0)</td></tr>
<tr><td>AE leading to discontinuation</td><td>4 (8.5)</td><td>3 (6.0)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Eli Lilly funded the study</td></tr>
<tr><td>Comments</td><td>- Randomisation, allocation concealment and blinding not described.
- Analysis undertaken using modified ITT model – all patients who were randomised and received ≥1 dose of study medication. Patients analysed by the assigned treatment group; only patients who has a baseline and >1 evaluable post- baseline measurement were analysed for efficacy.
- Study required a total of 96 patients to give 80% power to detect mean difference in change from baseline in RI of 0.07</td></tr>
</table>

1

<table>
<tr><td>Bibliographic reference</td><td>Porst, Hartmut, Kim, Edward D., Casabe, Adolfo R., Mirone, Vincenzo, Secrest, Roberta J., Xu, Lei, Sundin, David P., Viktrup, Lars, LVHJ study team, Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial, European urologyEur Urol, 60, 1105-1113, 2011</td></tr>
<tr><td>Study type</td><td>Multicentre, double blind placebo controlled parallel design trial (RCT)</td></tr>
<tr><td>Aim</td><td>To assess efficacy, including onset and safety of tadalafil on BPH-LUTS</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Men ≥45 years of ag, e with BPH LUTS for ≥6 months at screening, digital rectal examination was performed at screening. Subjects reporting use of BPH OAB or ED therapy underwent a 4 week treatment free washout period, otherwise a 4 week single blind placebo lead-in period commenced after screening. Inclusion criteria prior to</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Porst, Hartmut, Kim, Edward D., Casabe, Adolfo R., Mirone, Vincenzo, Secrest, Roberta J., Xu, Lei, Sundin, David P., Viktrup, Lars, LVHJ study team, Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial, European urologyEur Urol, 60, 1105-1113, 2011</td></tr>
<tr><td></td><td>placebo lead in period included a total IPSS of ≥13 and a Qmax of ≥4 to ≤15 mL/s. During the placebo period subjects needed to be >70% compliant with dosing to qualify for randomisation. Subjects whose IPSS or Qmax improved were not excluded

Exclusion
PSA >10ng/mL, PVR ≥300mL at screening, finasteride or dutasteride use within 3 or 6 months respectively of visit 2, lower urinary tract instrumentation within prior 30 days, urinary retention or lower urinary tract stones within 6 months, history of urethral and/ or proven bladder neck obstruction; neurogenic bladder, , low creatinine clearance, severe hepatic impairment, certain cardiovascular conditions, or current nitrate therapy.

Details
Randomisation stratified by baseline LUTS severity geographic region, history of ED.

Key baseline characteristics
<table>
<tr><td></td><td>Placebo (N=164)</td><td>Tadalafil (N=161)</td></tr>
<tr><td>Age (mean, SD)</td><td>64.6 (10.0)</td><td>65.1 (8.4)</td></tr>
<tr><td><75 yrs (N, %)</td><td>129 (78.7)</td><td>131 (81.4)</td></tr>
<tr><td>≥75 yrs (N, %)</td><td>35 (21.3)</td><td>30 (18.6)</td></tr>
<tr><td>Ethnicity (N,%)</td><td></td><td></td></tr>
<tr><td>Hispanic or latino</td><td>44 (26.8)</td><td>46 (28.6)</td></tr>
<tr><td>Not Hispanic or latino</td><td>120 (73.2)</td><td>115 (71.4)</td></tr>
<tr><td>ED history (N, %)</td><td>112 (68.3)</td><td>112 (69.6)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>N=325</td></tr>
<tr><td>Intervention</td><td>Tadalafil 5mg</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>28 Urology sites across Argentina, Germany, Italy, Mexico, USA</td></tr>
</table>

Bibliographic reference	Porst, Hartmut, Kim, Edward D., Casabe, Adolfo R., Mirone, Vincenzo, Secrest, Roberta J., Xu, Lei, Sundin, David P., Viktrup, Lars, LVHJ study team, Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial, European urologyEur Urol, 60, 1105-1113, 2011
Outcomes measures and effect size	**Symptom scores**

	Placebo (N=164) LSM change (SE)	Tadalafil 5mg (N=161) LSM change (SE)	LS mean treatment difference	P value
Total IPSS	-3.6 (0.47)	-5.6 (0.47)	-1.9 (-3.2, -0.6)	0.004
BII	-1.3 (0.21)	-1.8 (0.21)	-0.6 (-1.2, 0.0)	0.057
IPSS voiding subscore	-2.3 (0.31)	-3.3 (0.31)	-1.0 (-1.9, -0.2)	0.020
IPSS storage subscore	-1.3 (0.21)	-2.3 (0.22)	-0.9 (-1.5, -0.3)	0.002
PGI-I				0.003
Better	91/158 (57.6)	115/155 (74.2)		
No change	57/158 (36.1)	30/155 (19.4)		
Worse	10/158 (6.3)	10/155 (6.5)		
CGI-I				0.009
Better	87/158 (55.1)	110/155 (71.0)		
No change	59/158 (37.3)	36/155 (23.2)		
worse	12/158 (7.6)	9/155 (5.8)		

Quality of Life (IPSS)

	Placebo (N=164) LSM change (SE)	Tadalafil 5mg (N=161) LSM change	LS mean treatment difference	P value

Bibliographic reference	Porst, Hartmut, Kim, Edward D., Casabe, Adolfo R., Mirone, Vincenzo, Secrest, Roberta J., Xu, Lei, Sundin, David P., Viktrup, Lars, LVHJ study team, Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial, European urologyEur Urol, 60, 1105-1113, 2011

		(SE)		
IPSS QoL	-0.7 (0.10)	-1.0 (0.10)	-0.4 (-0.6, -0.1)	0.013

QMax (mean SD)

	Placebo (N=not stated)	Tadalafil 5mg (N=not stated)	P value
Qmax	1.1mL/s (4.6)	1.6 mL/s (4.6)	0.30

Voiding frequency
Not reported

Nocturia

	Placebo (N=164) LSM change (SE)	Tadalafil 5mg (N=161) LSM change (SE)	LS mean treatment difference	P value
IPSS nocturia	-0.4 (0.08)	-0.5 (0.08)	-0.1 (-0.3, 0.1)	0.233

Adverse events (N, %)

	Placebo (N=164)	Tadalafil 5mg (N=161)
Headache	1 (0.6)	6 (3.7)
Discontinuation due to AEs	1 (0.6)	3 (1.9)*
Positive orthostatic test		
SBP decrease ≥20mmHg	12 (7.3)	12 (7.5)
DBP decrease ≥10mmHg	29 (17.7)	21 (13.0)
HR increase ≥20bpm	5 (3.0)	3 (1.9)
Unable to remain standing	0	0

*includes one subject who died

Source of funding	Eli Lilly helped design, conduct and support the trial

Bibliographic reference	Porst, Hartmut, Kim, Edward D., Casabe, Adolfo R., Mirone, Vincenzo, Secrest, Roberta J., Xu, Lei, Sundin, David P., Viktrup, Lars, LVHJ study team, Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial, European urologyEur Urol, 60, 1105-1113, 2011
Comments	- Efficacy analysis included all randomised subjects who started double blind study drug, - Study adequately powered (143 subjects per arm would provide 80% power for a mean treatment difference in IPSS of 2.0 assuming a SD of 6). - For continuous efficacy outcomes, last observation carried forward was used. - Changes for continuous endpoints were analysed using ANCOVA, with terms for baseline, treatment group, region, baseline by treatment interaction, and treatment bby region interaction. Interaction terms were removed if p≤0.1 - Change from baseline and the treatment difference of changes were estimated using least squares mean, - Safety analyses included all randomised subjects - Changes from baseline to end of therapy in Qmax were analysed using a non-parametric model. - Randomisation, allocation concealment and blinding were not reported.

1

Bibliographic reference	Roehrborn,Claus G., McVary,Kevin T., Elion-Mboussa,Albert, Viktrup,Lars, Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study, The Journal of urologyJ Urol, 180, 1228-1234, 2008
Study type	RCT
Aim	
Patient characteristics	**Patient group:** Men with a history of LUTS secondary to BPH of 6 months longer. **Inclusion criteria**: • At least 45 years old • IPSS of 13 or greater • Qmax of 4-15ml/s from pre-void bladder volume between 150-550ml with a voided volume of 125ml or greater. **Exclusion criteria:** • PSA > 10ng/ml

Bibliographic reference	Roehrborn,Claus G., McVary,Kevin T., Elion-Mboussa,Albert, Viktrup,Lars, Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study, The Journal of urologyJ Urol, 180, 1228-1234, 2008
	• PVR volume was 300ml or greater at screening visit 1 • Patients reporting use of other BPH or ED treatments underwent a 4 week treatment free screening/ washout period. • Penile or pelvic surgery, radiotherapy, lower urinary tract malignancy, trauma or recent instrumentation, urinary retention or bladder stones, • History of urethral obstruction • Neurological condition • Detrusor sphincter dyssynergia, intravesical obstruction secondary to the prostate median lobe, • Urinary tract inflammation or infection • Prostate cancer. • Renal or hepatic insufficiency, Cardiovascular conditions, history of stroke or spinal cord injury, cancer chemotherapy, uncontrolled diabetes **Group 1** **N:** 209 **Mean Age**: 62.03 **Ethnicity/race**: White 88.46%, Hispanic 9.62%, black 1.44%, other 0.48% **Mean % ED history**: 64.9% **Dropouts**: 27 **Group 2** **N:** 212 **Mean Age**: 61.95 **Ethnicity/race**: White 84.43%, Hispanic 11.79%, black 3.30%, other 0.47% **Mean % ED history**: 67.92% **Dropouts:** 30 **Group 3** **N:** 216 **Mean Age**: 62.22 **Ethnicity/race**: White 86.11%, Hispanic 11.11%, black 2.31%, other 0.46% **Mean % ED history**: 69.44% **Dropouts**: 41

Bibliographic reference	Roehrborn,Claus G., McVary,Kevin T., Elion-Mboussa,Albert, Viktrup,Lars, Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study, The Journal of urologyJ Urol, 180, 1228-1234, 2008
	Group 4 **N:** 209 **Mean Age**: 62.55 **Ethnicity/race**: White 84.21%, Hispanic 11.96%, black 2.39%, other 1.44% **Mean % ED history**: 69.38% **Dropouts**: 47 **Group 5** **N:** 212 **Mean Age**: 61.75 **Ethnicity/race**: White 84.83%, Hispanic 13.74%, black 1.42%, other 0% **Mean % ED history**: 67.30% **Dropouts**: 27
Number of Patients	**N:** 1058
Intervention	**Group 1:** Tadalafil 2.5mg once daily **Group2:** Tadalafil 5 mg once daily **Group 3:** Tadalafil 10 mg once daily **Group 4:** Tadalafil 20 mg once daily
Comparison	**Group 5: Placebo** once daily
Length of follow up	12 weeks
Location	92 centres in 10 countries
Outcomes measures and effect size	**Symptom scores IPSS** **Least squares mean (SE) IPSS change from baseline**

Bibliographic reference	Roehrborn,Claus G., McVary,Kevin T., Elion-Mboussa,Albert, Viktrup,Lars, Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study, The Journal of urologyJ Urol, 180, 1228-1234, 2008
	Group1 (N=208): -3.88 (0.50) Group 2 (N=212): -4.87 (0.49) Group 3 (N=216): -5.17 (0.49) Group 4 (N=208): -5.21 (0.50) Group 5 (N=210): -2.27 (0.49) P<0.001 (tad v placebo) **BII (mean (SE)** Group 1: -0.96 (0.21) Group 2:-1.40 (0.21) Group 3:-1.38 (0.20) Group 4: -1.45 (0.21) Group 5:-0.83 (0.21) **Quality of Life, Least squares mean (SE) IPSS quality of life change from baseline** Group1 (N=208): -0.74 (0.11) Group 2 (N=212): -0.86 (0.11) Group 3 (N=216): -0.92 (0.10) Group 4 (N=208): -0.88 (0.11) Group 5 (N=210): -0.49 (0.11) P<0.01 (tad v placebo) **Qmax, Least squares mean (SE) Qmax change from baseline** Group1 (N=208): 1.41 (0.39) Group 2 (N=212): 1.64 (0.39) Group 3 (N=216): 1.58 (0.38) Group 4 (N=208): 1.96 (0.39) Group 5 (N=210): 1.24 (0.40) P=Not sig. (tad v placebo)

Bibliographic reference	Roehrborn,Claus G., McVary,Kevin T., Elion-Mboussa,Albert, Viktrup,Lars, Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study, The Journal of urologyJ Urol, 180, 1228-1234, 2008
	Voiding frequency Not reported **Nocturia** Not reported **Adverse events** **Headache** Group1: 5/209 Group 2: 6/212 Group 3: 11/216 Group 4: 7/209 Group 5: 6/211 **Discontinuation due to adverse events** Group1: 4/209 Group 2: 12/212 Group 3: 11/216 Group 4: 14/209 Group 5: 5/211
Source of funding	Eli Lilly and Co.
Comments	Method of randomisation and allocation concealment unclear.

1

Bibliographic reference	Singh,Dig Vijay, Mete,Uttam Kumar, Mandal,Arup Kumar, Singh,Shrawan Kumar, A comparative randomized prospective study to evaluate efficacy and safety of combination of tamsulosin and tadalafil vs. tamsulosin or tadalafil alone in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, The journal of sexual medicineJ Sex Med, 11, 187-196, 2014

<table>
<tr><td>Bibliographic reference</td><td>Singh,Dig Vijay, Mete,Uttam Kumar, Mandal,Arup Kumar, Singh,Shrawan Kumar, A comparative randomized prospective study to evaluate efficacy and safety of combination of tamsulosin and tadalafil vs. tamsulosin or tadalafil alone in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, The journal of sexual medicineJ Sex Med, 11, 187-196, 2014</td></tr>
<tr><td>Study type</td><td>Prospective randomised study</td></tr>
<tr><td>Aim</td><td>To evaluate the efficacy and safety of tamsulosin and tadalafil in patients with LUTS due to BPH.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Men over the age of 45 years, presenting to urologic clinic with history of LUTS secondary to BPH of ≥6 months, IPSS of ≥8, PSA ≤4.0 ng/mL, Qmax >5mL/s with minimum voided volume of 125mL at screening
Patients agreed not to use BPH medications during the research other than the study medications.

Exclusion
Contraindication to investigational drugs, use of finasteride or dutasteride and other prohibited medications like α adrenergic agonist, history of syncope and orthostatic hypertension, BOO due to cancer, calculi or stricture, previous transurethral resection of the prostate, neurological conditions affecting storage and voiding function, prostatic disease like prostatitis or cancer, PSA >4ng/mL, episode of acute urinary retention within 4 weeks of study initiation, documented UTI, poorly controlled diabetes poorly controlled hypertension.

Details
Mean age 62 years; 48.9% ≤60 years, ≥ 60 years. IPSS, IIEF, Qmax, QoL well balanced between all groups.
Patients using BPH drugs or medications that could interfere with bladder function or PDE5Is underwent a 2 week medication free run- in period before study treatment period. After 2 weeks, digital rectal examination, US basiclab investigations serum PSA and uroflowmetry were performed.
An IPSS of ≥8 and Qmax 5-15 mL/s on a voided volume of 125mL or more were required for study continuation.
Treatments allocated according to computer generated random table to tamsulosin, tadalafil or combination treatment. Patients were instructed to take the study medication at approximately the same time every day without restriction of food intake or timing of sexual activity.

Key baseline characteristics (not stated whether mean or median)
<table>
<tr><td></td><td>Tamsulosin</td><td>Tadalafil</td></tr>
<tr><td>Age (years)</td><td>59.50 (6.05)</td><td>63.42 (8.09)</td></tr>
<tr><td>≤60 years (%)</td><td>53.3 (n=24)</td><td>47.7 (n=21)</td></tr>
<tr><td>>60 years (%)</td><td>46.7 (n=21)</td><td>52.3 (n=23)</td></tr>
<tr><td>IPSS</td><td>20.93</td><td>20.33</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Singh,Dig Vijay, Mete,Uttam Kumar, Mandal,Arup Kumar, Singh,Shrawan Kumar, A comparative randomized prospective study to evaluate efficacy and safety of combination of tamsulosin and tadalafil vs. tamsulosin or tadalafil alone in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, The journal of sexual medicineJ Sex Med, 11, 187-196, 2014</td></tr>
<tr><td></td><td>
<table>
<tr><td>IIEF</td><td>10.08</td><td>11.77</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>N=133 (population for efficacy comparison is n=125)</td></tr>
<tr><td>Intervention</td><td>Tadalafil 10mg/ day (n=44, n=40 for primary outcome assessment*)</td></tr>
<tr><td>Comparison</td><td>Tamsulosin 0.4mg/ day (n=45, n= 43 for primary outcome analysis*)

Combination therapy (n=44)- no further details of this intervention will be reported here as this is an excluded combination.</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>India, single centre, October 2010 – December 2012.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
Symptom scores- IPSS (mean, not stated whether SD or SE in study)
<table>
<tr><td></td><td>Tamsulosin</td><td>Tadalafil</td></tr>
<tr><td>Baseline</td><td>20.93 (4.607)</td><td>20.33 (5.662)</td></tr>
<tr><td>3 months</td><td>10.26 (3.218)</td><td>13.50 (3.856)</td></tr>
<tr><td>% change</td><td>-50.90 (p<0.05)</td><td>-33.50 (p<0.05)</td></tr>
</table>
Quality of Life- IPSS (mean, not stated whether SD or SE in study)
<table>
<tr><td></td><td>Tamsulosin</td><td>Tadalafil</td></tr>
<tr><td>Baseline</td><td>5.59 (0.501)</td><td>5.75 (0.442)</td></tr>
<tr><td>3 months</td><td>1.48 (0.509)</td><td>1.71 (0.550)</td></tr>
<tr><td>% change</td><td>-73.35 (p<0.05)</td><td>-70.26 (p<0.05)</td></tr>
</table>
QMax (mean, not stated whether SD or SE in study)
<table>
<tr><td></td><td>Tamsulosin (N=43)</td><td>Tadalafil (N=40)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Singh,Dig Vijay, Mete,Uttam Kumar, Mandal,Arup Kumar, Singh,Shrawan Kumar, A comparative randomized prospective study to evaluate efficacy and safety of combination of tamsulosin and tadalafil vs. tamsulosin or tadalafil alone in patients with lower urinary tract symptoms due to benign prostatic hyperplasia, The journal of sexual medicineJ Sex Med, 11, 187-196, 2014

Baseline	9.15 (3.022)	8.83 (3.535)
3 months	12.26 (3.537)	11.46 (3.867)
% change	+33.99 (p<0.05)	+29.78 (p<0.05)

Voiding frequency

Not reported

Nocturia

Not reported

Adverse events (N**)**

	Tadalafil	Tamsulosin
Discontinuation due to adverse events	4	0
Headache	2	0

Source of funding	Not stated
Comments	*IPSS, IPSS QoL Qmax -statistical significance determined by paired t test, subgroup analysis performed within the framework of one way ANOVA model. -study was designed to provide 80% power to detect a difference of 3.0 for change in IPSS and 2mL/s for Qmax assuming a SD of 5.0 and a one-sided alpha of 0.5. The purpose of this study was to establish proof of principle in anticipation of subsequent larger and more definitive trials, as such one sided tests of significance for evaluating the efficacy endpoints. Assuming that 85% of patients would complete the study, randomised sample of 123 subjects were required. -allocation concealment and blinding were not described. - Not clear whether figures reported in paper are mean (SD), therefore stud not included in metanalysis.

1

<table>
<tr><td>Bibliographic reference</td><td>Stief,Christian G., Porst,Hartmut, Neuser,Dieter, Beneke,Manfred, Ulbrich,Ernst, A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia, European urologyEur Urol, 53, 1236-1244, 2008</td></tr>
<tr><td>Study type</td><td>Randomised, double blind, placebo controlled parallel group phase 2b study</td></tr>
<tr><td>Aim</td><td></td></tr>
<tr><td>Patient characteristics</td><td>Characteristics of two groups balanced at baseline (age, weight, BMI, ethnicity, IPSS total and sub-scores, Qmax PVR volume and IIEF). Characteristics of interest are shown below (all mean, SD):
<table>
<tr><td></td><td>Vardenafil</td><td>Placebo</td></tr>
<tr><td>Age (yr.)</td><td>56.5 (5.4)</td><td>55.4 (5.7)</td></tr>
<tr><td>Ethnicity</td><td></td><td></td></tr>
<tr><td>White</td><td>108 (100%)</td><td>111 (98%)</td></tr>
<tr><td>Black</td><td>0</td><td>1 (0.9%)</td></tr>
</table>
Reported that there was little difference in medications taken by each group, though the figures are not reported in the paper. Baseline IIEF- EF score was 15.9 in both groups at baseline.

Inclusion
Men aged 45-64 years with history of LUTS for at least 6 months before commencing the study; IPSS ≥12 at screening

Exclusion
Contraindications to vardenafil, spinal cord injury, prostatitis, history of prostate or bladder cancer, bladder or urethra stricture, urinary retention (PVR ≥10mL, pelvic trauma or surgery, history of any malignancies, life expectancy of less than 3 years. Concomitant use of nitrates, NO donors, androgens or antiandrogens, anticoagulants, cytochrome P450 3A4 inhibitors and treatment for ED or α1 adrenoceptor antagonists was prohibited. If α blockers were withdrawn at screening subjects became ineligible for study entry. Previous or current use of 5ARI was prohibited,

Details
Upon enrolment, participants entered a 4 week run in phase during which no medication was administered.</td></tr>
<tr><td>Number of Patients</td><td>N=222</td></tr>
<tr><td>Intervention</td><td>Vardenafil propionate (N=109) (ITT population N=105, safety population N=108)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Stief,Christian G., Porst,Hartmut, Neuser,Dieter, Beneke,Manfred, Ulbrich,Ernst, A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia, European urologyEur Urol, 53, 1236-1244, 2008</td></tr>
<tr><td></td><td>Participants administered Vardenafil 10mg twice daily.</td></tr>
<tr><td>Comparison</td><td>Placebo (N=113) (ITT population N=110, safety population N=113)</td></tr>
<tr><td>Length of follow up</td><td>8 weeks</td></tr>
<tr><td>Location</td><td>Undertaken at 16 centres in Germany between October 2005 and June 2006</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores (Least square mean)
<table>
<tr><td></td><td colspan="2">Vardenafil (N=104)</td><td colspan="2">Placebo (N=110)</td><td>Between group difference in change from baseline (95%CI)</td></tr>
<tr><td></td><td>Baseline</td><td>8 weeks</td><td>Baseline</td><td>8 weeks</td><td></td></tr>
<tr><td>IPSS total</td><td>16.8</td><td>11.0</td><td>16.8</td><td>13.2</td><td>2.3 (0.90, 3.64) p=0.0013</td></tr>
</table>
Quality of Life
<table>
<tr><td></td><td colspan="2">Vardenafil (N=104)</td><td colspan="2">Placebo (N=110)</td><td>Between group difference in change from baseline (95%CI)</td></tr>
<tr><td></td><td>Baseline</td><td>8 weeks</td><td>Baseline</td><td>8 weeks</td><td></td></tr>
<tr><td>Urolife QoL 9 total score</td><td>42.8</td><td>54.5</td><td>42.3</td><td>45.2</td><td>P=<0.0001</td></tr>
</table>
Includes domain on interference with activities, wellbeing and perceived sexual life. P value significant for interference with activities and perceived sexual life.
QMax (Least squares mean)
<table>
<tr><td></td><td>Vardenafil (N=104)</td><td>Placebo (N=110)</td><td>Between group difference in change from baseline</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Stief,Christian G., Porst,Hartmut, Neuser,Dieter, Beneke,Manfred, Ulbrich,Ernst, A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia, European urologyEur Urol, 53, 1236-1244, 2008

					(95%CI)
	Baseline	8 weeks	Baseline	8 weeks	
Qmax	15.9	17.5	15.9	16.9	-0.6 (-2.62, 1.43), p=5614

Voiding frequency

Not reported

Nocturia

Not reported

Adverse events

	Vardenafil	Placebo
Headache	14 (13%)	2 (1.8%)
Flushing	7 (6.5%)	1 (0.9%)
Withdrawal due to adverse event	9	2

Source of funding	Bayer Healthcare AG sponsored the study
Comments	-sample size based on intention to test -Efficacy data analysed on ITT basis with last observation carried forward (LOCF) -ANCOVA used with baseline covariates and the LOCF as the dependent variable, -Adverse events were assessed on the safety population (all patients who received at least one dose of drug) -included in original guideline -No SD values provided for further analysis. [NCC emailed author for this information] * Least square means analysis reported for outcomes. NCGC calculated estimated SD for mean change in IPSS/Qmax from Cochrane handbook formula.

1

<table>
<tr><td>Bibliographic reference</td><td>Takeda, Masayuki, Yokoyama, Osamu, Lee, Sung Won, Murakami, Masahiro, Morisaki, Yoji, Viktrup, Lars, Tadalafil 5 mg once-daily therapy for men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results from a randomized, double-blind, placebo-controlled trial carried out in Japan and Korea, International journal of urology : official journal of the Japanese Urological AssociationInt J Urol, 21, 670-675, 2014</td></tr>
<tr><td>Study type</td><td>Randomised double blind placebo- controlled</td></tr>
<tr><td>Aim</td><td>To gain further evidence on the efficacy, safety and tolerability of tadalafil 5mg once daily in Japanese and Korean men</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Men aged ≥45 years, total IPSS ≥13, bladder outlet obstruction as indicated by Qmax ≥4 -≤15 mL/s from a pre-void bladder volume ≥150mL -≤550mL (minimum voided volume 125mL and prostate volume ≥20mL (determined by ultrasound)

Exclusion
PSA >10ng/mL or ≥4 ng/mL if prostate cancer could not be ruled out, bladder PVR ≥300mL at screening, treatment with the following for the indicated time before the placebo lead- in period: finasteride (3 months), dutasteride (6 months) antiandrogenic hormone therapy (12 months) and other BPH, ED or OAB therapies (4 weeks).

Details
There was a screening/ washout period for 4 weeks, followed by a single blind placebo lead in period, and a 12 week double blind 12 week treatment period. After the placebo lead in period, participants were randomised (1:1) to tadalafil 5mg or placebo. Randomisation stratified by BPH-LUTS severity at baseline (moderate <20 or severe ≥20, the placebo lead-in change in total IPSS (≤-2 or > -2) and previous α blocker therapy within 12 months of washout period.

Key demographic data is presented below, there were no details on the % of study population with ED.
<table>
<tr><td></td><td>Tadalafil</td><td>Placebo</td></tr>
<tr><td>Age, years (mean (SD))</td><td>60.8 (7.7)</td><td>60.9 (8.1)</td></tr>
<tr><td>Age ≥65 years, N (%)</td><td>108 (35.3)</td><td>103 (33.9)</td></tr>
<tr><td>Previous α blocker therapy (N,%)</td><td>39 (12.7)</td><td>43 (14.1)</td></tr>
<tr><td>other</td><td>22 (7.2)</td><td>21 (6.9)</td></tr>
<tr><td>Duration of LUTS, years (mean, SD)</td><td>4.1 (3.2)</td><td>4.0 (3.3)</td></tr>
<tr><td>Mild</td><td>6 (2.0)</td><td>5 (1.6)</td></tr>
<tr><td>Moderate</td><td>166 (54.2)</td><td>167 (54.9)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Takeda, Masayuki, Yokoyama, Osamu, Lee, Sung Won, Murakami, Masahiro, Morisaki, Yoji, Viktrup, Lars, Tadalafil 5 mg once-daily therapy for men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results from a randomized, double-blind, placebo-controlled trial carried out in Japan and Korea, International journal of urology : official journal of the Japanese Urological AssociationInt J Urol, 21, 670-675, 2014
	severe: 134 (43.8); 132 (43.4) Total IPSS: 18.7 (6.0); 18.7 (5.2) Qmax mL/s (mean, SD): 11.9 (4.5); 11.9 (4.5)
Number of Patients	N=610 (25 lost to follow up, n=585 completed study)
Intervention	Tadalafil 5mg once daily (n=306, n=292 completed treatment)
Comparison	Placebo (n= 304, n=293 completed treatment)
Length of follow up	12 weeks
Location	39 sites in Japan and Korea
Outcomes measures and effect size	**Symptom scores– IPSS**

	Tadalafil 5mg (N=306)		Placebo (N=304)		Difference in change	
	N	LS mean (SE)	N	LS mean (SE)	LS mean, SE (95%CI)	P value
Total IPSS	292	-6.0 (0.4)	294	-4.5 (0.4)	-1.5, 0.5 (-2.4, -0.6)	<0.001

Quality of Life

	Tadalafil 5mg (N=306)		Placebo (N=304)		Difference in change	
	N	LS mean (SE)	N	LS mean (SE)	LS mean,SE (95%CI)	P value
IPSS QoL	292	-1.1 (0.1)	294	-0.9 (0.1)	-0.2, 0.1 (-0.4, -0.0)	0.038

QMax

<table>
<tr><td>Bibliographic reference</td><td>Takeda, Masayuki, Yokoyama, Osamu, Lee, Sung Won, Murakami, Masahiro, Morisaki, Yoji, Viktrup, Lars, Tadalafil 5 mg once-daily therapy for men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results from a randomized, double-blind, placebo-controlled trial carried out in Japan and Korea, International journal of urology : official journal of the Japanese Urological AssociationInt J Urol, 21, 670-675, 2014</td></tr>
<tr><td></td><td>Not reported

Voiding frequency
Not reported

Nocturia
Not reported

Adverse events
<table>
<tr><td></td><td>Tadalafil 5mg (N=306)</td><td>Placebo (N=304)</td></tr>
<tr><td>Discontinued due to adverse events</td><td>4 (1.3%)</td><td>5 (1.6%)</td></tr>
<tr><td>Headache</td><td>9 (2.9%)</td><td>6 (2.0%)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Eli Lilly funded and assisted with trial</td></tr>
<tr><td>Comments</td><td>- Randomisation undertaken using computer generated random sequence using an interactive voice response system.
- Allocation concealment and blinding not reported
- Outcomes reported as Least squares mean and SE.
- Treatment differences for IPSS change was analysed using a mixed effects model repeated measures analysis with treatment, previous α blocker therapy (yes/no), country, visit, treatment by visit interaction, baseline total IPSS and placebo lead-in change in total IPSS as covariates. Same analysis for IPSS QoL and IPSS sub-scores.
- Study adequately powered (90%) to detect mean difference of 1.5 between tadalafil and placebo groups in the change in total IPSS from baseline to end point, assuming SD of 5.0.
- Efficacy population included all randomised participants who started study medication and completed at least one assessment after randomisation
- Safety population included all randomised participants who started study medication.</td></tr>
</table>

1

<table>
<tr><td>Bibliographic reference</td><td>Tamimi, Nihad A.M., Mincik, Ivan, Haughie, Scott, Lamb, Janice, Crossland, Anna, Ellis, Peter, A placebo-controlled study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia, BJU internationalBJU Int, 106, 674-680, 2010</td></tr>
<tr><td>Study type</td><td>Multicentre, double blind, placebo and active controlled parallel group study</td></tr>
<tr><td>Aim</td><td>To evaluate the safety and efficacy of the PDE5I UK369003 for the treatment of LUTS associated with BPH in men with and without ED</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion
Men aged ≥40 years with clinical diagnosis of BPH, total IPSS of ≥13 at screening and baseline and a Qmax 5-15, total voided volume ≥150mL at screening.

Exclusion
Key exclusion criteria: Men who had a history, evidence or suspicion of prostate cancer, PVR of >200mL, history of catheterisation for BOO in the previous 12 months, documented UTI, history of chronic persistent local lower urinary tract pathology or relevant urological procedures, primary neurological conditions such as spinal cord injury, MS. Poorly controlled diabetes, loss of vision in one eye due to NAION, family history of long QT syndrome, current treatment with nitrates, antiandrogens, and potent cytochrome P450 3A4 inhibitors or treatment with α blocker, antimuscarinic or PDE5I within 4 weeks of randomisation

Details
Two week single blind placebo run-in, eligible patients were stratified into two groups: with ED (≤25 on IIEF) or without ED (>25 IIEF). No more than 299 people would be randomised to LUTS- ED stratum and ≤207 to the LUTS without ED stratum.. Within each stratum, participants were randomised to one of the 7 groups (details in comments section).

Relevant demographics are below:
Age range of study population (mean (SD)): 60.5 (8.1) – 62.1 (7.8)
Race: white 84.9% - 92.1%; other 7.9% - 15.1%

Baseline IPSS
<table>
<tr><td>Mean (SD)</td><td>UK-369,003 10mg</td><td>UK-369,003 25mg MR</td><td>UK-369,003 50mg MR</td><td>UK-369,003 100mg MR</td><td>UK-369,003 40mg immediate</td><td>Tamsulosin 0.4mg prolonged release</td><td>Placebo (N=38)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Tamimi, Nihad A.M., Mincik, Ivan, Haughie, Scott, Lamb, Janice, Crossland, Anna, Ellis, Peter, A placebo-controlled study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia, BJU internationalBJU Int, 106, 674-680, 2010
	<table><tr><td></td><td></td><td></td><td></td><td></td><td>release</td><td></td><td></td></tr><tr><td>Baseline IPSS</td><td>16.7 (4.53)</td><td>17.9 (5.25)</td><td>17.3 (4.60)</td><td>16.8 (4.05)</td><td>17.2 (3.98)</td><td>18.1 (3.86)</td><td>18.8 (4.32)</td></tr></table>
Number of Patients	N=418 (n=415 in full analysis set (FAS))
Intervention	UK-369,003 10mg modified release (MR) (N=53) UK-369,003 25mg MR (N=56) UK-369,003 50mg MR (N=53) UK-369,003 100mg MR (N=90) UK-369,003 40mg immediate release (IR) (N=89)
Comparison	Tamsulosin 0.4mg prolonged release (N=36) Placebo (N=38)
Length of follow up	12 weeks
Location	45 centres in North and South America, Europe and Australia between May 2007 and April 2008.
Outcomes measures and effect size	**Symptom scores- IPSS** <table><tr><td>Mean (SD)</td><td>UK-369,003 10mg</td><td>UK-369,003 25mg MR</td><td>UK-369,003 50mg MR</td><td>UK-369,003 100mg MR</td><td>Placebo</td></tr></table>

Bibliographic reference	Tamimi, Nihad A.M., Mincik, Ivan, Haughie, Scott, Lamb, Janice, Crossland, Anna, Ellis, Peter, A placebo-controlled study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia, BJU internationalBJU Int, 106, 674-680, 2010

Number of patients	52	56	51	87	37
NDLM mean estimate	-5.70	-6.36	-6.81	-6.93	-4.12
NDLM estimate of difference vs placebo					
Mean	-1.57	-2.24	-2.69	-2.81	
90%CI	-3.14, -0.15	-3.82, -0.71	-4.28, -1.14	-4.22, -1.38	
Posterior probability difference	0.31	0.59	0.77	0.82	

Summary of Bayesian estimates and posterior probabilities vs placebo for change from baseline in IPSS

	UK369003 100mg MR	UK369003 40mg IR
N	124	125
Mean treatment difference vs placebo	-2.91	-2.50
(90%CI)	-4.55, -1.30	-3.95, -1.04
Posterior probability P (difference ≤2.5)	0.66	0.49

Summary of Bayesian estimates and posterior probabilities vs tamsulosin 0.4mg for change from baseline in IPSS

	UK369,003 10mg MR	UK369,003 25mg MR	UK369,003 50mg MR	UK369,003 100mg MR

Bibliographic reference	Tamimi, Nihad A.M., Mincik, Ivan, Haughie, Scott, Lamb, Janice, Crossland, Anna, Ellis, Peter, A placebo-controlled study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia, BJU international BJU Int, 106, 674-680, 2010

N	88	92	87	123
Mean treatment difference vs tamsulosin 0.4mg PR	0.09	-0.59	-1.18	-1.12
(90%CI)	-1.62, 1.77	-2.36, 1.17	-2.88, 0.57	-2.62, 0.39
Posterior probability P (difference <0)	0.49	0.71	0.87	0.89

Quality of Life

Not reported

QMax

Summary of Bayesian estimates and posterior probabilities vs placebo for change from baseline in Qmax

	100mg UK369003
N	127
Mean (90%CI) treatment difference vs placebo	2.10 (0.94, 3.28)
Posterior probability P (difference <0)	0.998

Voiding frequency
Stated that reported within diary, but results not reported as outcomes

Nocturia
Stated that reported within diary, but results not reported as outcomes

Bibliographic reference	Tamimi, Nihad A.M., Mincik, Ivan, Haughie, Scott, Lamb, Janice, Crossland, Anna, Ellis, Peter, A placebo-controlled study investigating the efficacy and safety of the phosphodiesterase type 5 inhibitor UK-369,003 for the treatment of men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia, BJU internationalBJU Int, 106, 674-680, 2010
	Adverse events N (%) / UK-369,003 10mg / UK-369,003 25mg MR / UK-369,003 50mg MR / UK-369,003 100mg MR / UK-369,003 40mg immediate release / Tamsulosin 0.4mg prolonged release / Placebo (n=38) Flushing: 1 (2) / 0 / 1 (2) / 2 (2) / 8 (9) / 0 / 0 Headache: 5 (9) / 2 (4) / 4(8) / 5 (6) / 5 (6) / 2(6) / 1 (3) Reported that "the frequency of TEAEs that led to discontinuation and serious TEAEs were low across all treatment groups". N was not reported.
Source of funding	Study funded by Pfizer
Comments	- Randomisation, allocation concealment and blinding not adequately described in the study. - Randomisation was undertaken on a ratio of 3:3:3:5:5:2:2. The reason for the unequal randomisation was the application of a Bayesian approach in the statistical design: - Change in total IPSS -model included terms for treatment, baseline IPSS and ED status. - Qmax was analysed in a similar way to the primary endpoint - For Qmax, only report the difference between 100mg UK369,003 and placebo

1

Bibliographic reference	Tuncel, Altug, Nalcacioglu, Varol, Ener, Kemal, Aslan, Yilmaz, Aydin, Omur, Atan, Ali, Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction, World journal of urologyWorld J Urol, 28, 17-22, 2010
Study type	RCT
Aim	To evaluate the efficacy of sildenafil citrate only 25mg 4/weekly, tamsulosin only 0.4mg once daily on LUTS symptoms suggestive of BPH and ED
Patient characteristics	**Inclusion** Clinical diagnosis of ED, Sexual Health Inventory for Male (SHIM) score ≤21 and an International Prostate Symptom Score (IPSS) score ≥12.

<table>
<tr><td>Bibliographic reference</td><td>Tuncel, Altug, Nalcacioglu, Varol, Ener, Kemal, Aslan, Yilmaz, Aydin, Omur, Atan, Ali, Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction, World journal of urologyWorld J Urol, 28, 17-22, 2010</td></tr>
<tr><td></td><td>Exclusion
History of drug use or surgical treatment or BPH and/or ED, prostate biopsy within the last 6 months, use of 5alpha-reductase inhibitors within 6 months, any urologic cancer, previous prostate or bladder/ pelvic radiation or surgery, urinary system stone disease, and/or active urinary system infection, acute urinary retention in the last 6 months and, thus, using urethral catheter
for the last one year, acute or chronic hepatic failure, acute or chronic renal dysfunction, diagnosis of poorly controlled diabetes mellitus, and nitrates usage.

Details
Patients underwent randomized allocation to receive a 8-week treatment with either sildenafil citrate only, 25 mg. p.o. 4 days/week (Group 1, n = 20), sildenafil citrate (Viagra®, Pfizer Inc.), 25 mg. p.o. 4 days/week plus tamsulosin (Flomax®, Boehringer Ingelheim) 0.4 mg/day p.o. (Group 2, n = 20), or tamsulosin (Flomax®, Boehringer Ingelheim) only 0.4 mg/day p.o (Group 3, n = 20). All the patients were followed up for 8 weeks and invited for weekly controls for the determination of any side effects of the drugs.

The mean age of the patients was 58.8 ± 6.5 (range 47–77) years. No further baseline demographics were reported in the study report.</td></tr>
<tr><td>Number of Patients</td><td>N=60, all patients completed the study – no dropouts</td></tr>
<tr><td>Intervention</td><td>Sildenafil citrate (N=20)</td></tr>
<tr><td>Comparison</td><td>Tamsulosin (N=20)

Combination (N=20) no further details of this intervention included here as an excluded comparison</td></tr>
<tr><td>Length of follow up</td><td>8 weeks</td></tr>
<tr><td>Location</td><td>Turkey, outpatient clinic</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores- IPSS (mean)
<table>
<tr><td></td><td>Sildenafil</td><td>Tamsulosin</td></tr>
<tr><td>Before treatment</td><td>14.75</td><td>15.05</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Tuncel, Altug, Nalcacioglu, Varol, Ener, Kemal, Aslan, Yilmaz, Aydin, Omur, Atan, Ali, Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction, World journal of urologyWorld J Urol, 28, 17-22, 2010

After treatment	10.8	9.7

P<0.001 within groups

Quality of Life (IPSS QoL)

	Sildenafill citrate only (N = 20)			Tamsulosin only (N = 20)		
	Before treatment	After treatment	*p* value	Before treatment	After treatment	*p* value
QoL	3.8 ± 0.8 (1–6)	2.2 ± 0.6 (1–6)	<0.001	3.6 ± 0.5 (1–6)	2.8± 0.5 (1–6)	<0.001

Data are presented as mean ± standard deviation with minimum and maximum values in parenthesis

QMax

	Sildenafill citrate only (N = 20)			Tamsulosin only (N = 20)		
	Before treatment	After treatment	*p* value	Before treatment	After treatment	*p* value
Qmax (mL/s)	14.8 ± 3.9 (8–24)	18.5 ± 4.3 (12–29)	<0.001	13.1 ± 3.4 (8–19)	16.3 ± 3.5 (10–24)	<0.001

Data are presented as mean ± standard deviation with minimum and maximum values in parenthesis

Voiding frequency
Not reported

Nocturia
Not reported

Adverse events – not reported

Source of funding	Not reported

Bibliographic reference	Tuncel, Altug, Nalcacioglu, Varol, Ener, Kemal, Aslan, Yilmaz, Aydin, Omur, Atan, Ali, Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction, World journal of urologyWorld J Urol, 28, 17-22, 2010
Comments	- No sample size calculation performed because a pilot study - No baseline demographics reported in paper - Randomisation, allocation concealment and blinding not reported in paper. - Age distribution analysed by using independent samples t- test - % change in each group before and after treatment were evaluated with dependent samples t test - Parameters of the groups before and after treatment were compared with one way ANOVA. - Only mean values reported for IPSS, no SD, SE reported.

1

Bibliographic reference	Yokoyama,Osamu, Yoshida,Masaki, Kim,Sae Chul, Wang,Chii Jye, Imaoka,Takeshi, Morisaki,Yoji, Viktrup,Lars, Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men, International journal of urology : official journal of the Japanese Urological AssociationInt J Urol, 20, 193-201, 2013
Study type	Prospective, multicentre, double blind, randomised, parallel group, placebo controlled study with active control
Aim	To examine the efficacy and safety of tadalafil in Asian men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia
Patient characteristics	**Inclusion** The main inclusion criteria were: Asian men aged ≥45 years, >6-month history of BPH-LUTS, total IPSS ≥13, intermediate bladder outlet obstruction per Qmax of 4–15 mL/s and prostate volume ≥20 mL (assessed by ultrasound). The symptom and Qmax severity thresholds at inclusion were similar to those in studies from Asian18,19 and non-Asian countries. **Exclusion** PSA >10.0 ng/mL or ≥4.0 and ≤10.0 ng/mL without clinical judgement of “negative prostate cancer”, bladder PVR ≤300 mL (assessed by ultrasound) or a history of symptomatic orthostatic hypotension, dizziness, vertigo and loss of consciousness or syncope (per warnings in Japanese, Korean and USA tamsulosin prescribing information7,8,20), clinical evidence of prostate cancer or any bladder or urinary tract conditions that might have affected LUTS, treatment with finasteride or dutasteride within 3 and 6 months, a history of severe renal or hepatic insufficiency, certain cardiac conditions or nitrate use.

<table>
<tr><td>Bibliographic reference</td><td>Yokoyama,Osamu, Yoshida,Masaki, Kim,Sae Chul, Wang,Chii Jye, Imaoka,Takeshi, Morisaki,Yoji, Viktrup,Lars, Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men, International journal of urology : official journal of the Japanese Urological AssociationInt J Urol, 20, 193-201, 2013</td></tr>
<tr><td></td><td>Details
The study comprised three periods: screening/wash-out, single-blind placebo lead-in and double-blind treatment (Fig. 1). Participants who had used BPH, ED or overactive bladder treatments underwent a 2-week wash-out period. Eligible participants entered a 4-week, single-blind, placebo lead-in period before being randomized (1:1:1:1) to oral placebo, tadalafil 2.5 mg, tadalafil 5.0 mg or tamsulosin 0.2 mg once-daily for 12 weeks. Randomization was stratified by LUTS severity at week 0 (moderate: total IPSS <20, severe: total IPSS ≥20), country and a1-blocker use within 12 months of screening. Participants were instructed to take their medication at the same time each day, 30 min after eating (per USA tamsulosin prescribing information).

Demographic and baseline characteristics were generally balanced between treatment groups (Table 1). The mean (±SD) age of participants was 63.1 ± 7.8 years; 39.5% of participants were aged ≥65 years. The proportion of patients aged _65 years in the tadalafil 5 mg treatment group was numerically lower than in the other treatment groups, but did not reach statistical significance (P = 0.140).
Of the 612 participants, 55.9% were Japanese, 29.4% were Korean and 14.7% were Taiwanese. The mean (± SD) duration of LUTS was 3.7 ±3.2 years. Approximately half (54.7%) of the participants had taken a1-blockers for BPH within the past year
No baseline demographics for ED – does not state whether people with ED are included in the study</td></tr>
<tr><td>Number of Patients</td><td>N=612 (51 discontinued study, NB data from 17 participants at one site were excluded from all analyses because of good clinical practice violations)</td></tr>
<tr><td>Intervention</td><td>Tadalafil 2.5mg daily (N=151, 136 completed treatment)

Tadalafil 5mg daily (N=155, 137 completed treatment)</td></tr>
<tr><td>Comparison</td><td>Tamsulosin 0.2mg daily (N=152, 143 completed treatment)

Placebo (N=154, 145 completed treatment)</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>34 study sites in Japan (N=19), Korea (n=10) and Taiwan (n=5)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Symptom scores
<table>
<tr><td></td><td>Placebo, N = 154</td><td>Tadalafil 2.5 mg N =</td><td>Tadalafil 5.0 mg, N =</td><td>Tamsulosin, N = 152</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Yokoyama,Osamu, Yoshida,Masaki, Kim,Sae Chul, Wang,Chii Jye, Imaoka,Takeshi, Morisaki,Yoji, Viktrup,Lars, Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men, International journal of urology : official journal of the Japanese Urological AssociationInt J Urol, 20, 193-201, 2013

			151		155			
	N	LS mean ± SE	N	LS mean ± SE	N	LS mean ± SE	N	LS mean ± SE
Total IPSS (primary)	154	-3.0 ± 0.4	151	-4.8 ± 0.4	154	-4.7 ± 0.4	152	-5.5 ± 0.4

Quality of Life

	Placebo, N = 154		Tadalafil 2.5 mg , N= 151		Tadalafil 5.0 mg, N = 155		Tamsulosin, N = 152	
	N	LS mean ± SE	N	LS mean ± SE	N	LS mean ± SE	N	LS mean ± SE
IPSS QoL index	154	-0.5 ± 0.1	151	-0.8 ± 0.1	154	-0.8 ± 0.1	152	-1.1 ± 0.1
BII score	152	-0.8 ± 0.2	147	-1.1 ± 0.2	153	-1.0 ± 0.2	150	-1.6 ± 0.2

QMax

	Placebo, N = 154		Tadalafil 2.5 mg , N = 151		Tadalafil 5.0 mg, N = 155		Tamsulosin, N = 152	
	N	LS mean ± SE	N	LS mean ± SE	N	LS mean ± SE	N	LS mean ± SE
Qmax	147	2.1 ± 0.4	145	1.6 ± 0.4	148	1.3 ± 0.4	148	2.1 ± 0.4

Voiding frequency
Not reported

Nocturia

<table>
<tr><td>Bibliographic reference</td><td>Yokoyama,Osamu, Yoshida,Masaki, Kim,Sae Chul, Wang,Chii Jye, Imaoka,Takeshi, Morisaki,Yoji, Viktrup,Lars, Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men, International journal of urology : official journal of the Japanese Urological AssociationInt J Urol, 20, 193-201, 2013</td></tr>
<tr><td></td><td>Not reported

Adverse events
<table>
<tr><th></th><th>Tadalafil 2.5mg</th><th>Tadalafil 5mg</th><th>Tamsulosin 0.2mg</th><th>Placebo</th></tr>
<tr><td>Discontinued due to AE (N, %)</td><td>5 (3.3)</td><td>7 (4.5)</td><td>2 (1.3)</td><td>1 (0.6)</td></tr>
<tr><td>Headache (N, %)</td><td>3 (2.0)</td><td>3 (1.9)</td><td>1 (0.7)</td><td>1 (0.6)</td></tr>
<tr><td>Dizziness (N,%)</td><td>3 (2.0)</td><td>0</td><td>2</td><td>0 (1.3)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Funded by Eli Lilly</td></tr>
<tr><td>Comments</td><td>A sample size of 137 participants per group was estimated to provide 90% power to detect an expected difference (2.36 points) in the change in total IPSS from baseline (week 0) to end-point (week 12 or last available observation) between the tadalafil 5.0 mg and placebo group (two-sided t-test, significance level: 0.05).

The ITT population included participants who were randomized (grouped by treatment assigned) and started medication. The PPS population included participants who completed the treatment period and took ≥70% of prescribed doses.
Participants were excluded from primary and secondary efficacy analyses if no post baseline data were available. All efficacy analyses were carried out using the ITT population, unless otherwise specified. Safety analyses included participants.

Total IPSS change, IPSS QoL, Qmax and BII based on LOCF; treatment differences assessed using ANCOVA model including treatment group, prior α blocker therapy, and country as fixed effects and baseline total IPSS as a covariate. Findings reported as least squares mean and SE</td></tr>
</table>

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Appendix H: GRADE profiles

H.1 PDE5I VS placebo

Table 8: PDE5Is vs placebo – continuous outcomes

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
Outcome: Symptom score (IPSS) – tadalafil (Evidence tables, appendix G1; Forest plots Figure 1)										
9	RCT	Very serious [a]	No serious	Very serious[c]	No serious[d]	No serious	2445	1464	1.73 lower (2.47 to 1 lower)	VERY LOW
Outcome: Symptom score (IPSS) - - sildenafil (Evidence tables, appendix G1; Forest plots Figure 1)										
1	RCT	Very serious [b]	No serious	No serious	Serious[e]	No serious	182	178	MD 4.4 lower (6.93 to 1.87 lower)	VERY LOW
Outcome: Symptom score (IPSS) - UK-369,003 (Evidence tables, appendix G1; Forest plots Figure 1)										
1	RCT	Very serious [m]	No serious	No serious	Serious[e]	No serious	172	37	MD 1.44 higher (1.70 lower to 4.58 higher)	VERY LOW
Outcome: Symptom score (IPSS) – PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 1)										
11	RCT	Very serious [a],[b],[m]	No serious	Very serious[n]	No serious	No serious	2627	1642	MD 1.78 lower (2.55 to 1.01 lower)	VERY LOW
Outcome: Symptom score (BII) – Tadalafil (Evidence tables, appendix G1; Forest plots Figure 2)										
4	RCT	Very serious (f)	No serious	No serious	Serious(e)	No serious	455	405	MD 0.51 lower (0.78 to 0.24 lower)	VERY LOW
Outcome: Symptom score (BII) – Sildenafil (Evidence tables, appendix G1; Forest plots Figure 2)										
1	RCT	Very serious	No serious	No serious	Serious(e)	No serious	187	179	MD 1.1 lower (2.08 to 0.12 lower)	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
		(b)								
Outcome: Symptom score (BII) - PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 2)										
5	RCT	Very serious (f),(b)	No serious	No serious	Serious(e)	No serious	642	584	0.55 (0.81 lower to 0.29 lower)	VERY LOW
Outcome: Quality of life (IPSS) – Tadalafil (Evidence tables, appendix G1; Forest plots Figure 3)										
9	RCT	Very serious (a)	No serious	No serious	No serious	No serious	2366	1337	MD 0.29 lower (0.38 to 0.19 lower)	LOW
Outcome: Quality of life (IPSS) – Sildenafil (Evidence tables, appendix G1; Forest plots Figure 3)										
1	RCT	Very serious (b)	No serious	No serious	Serious(e)	No serious	182	178	MD 0.68 lower (1.17 to 0.19 lower)	VERY LOW
Outcome: Quality of life (IPSS) - PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 3)										
10	RCT	Very serious (a),(b)	No serious	No serious	No serious	No serious	2548	1515	MD 0.30 lower (0.40 to 0.21 lower)	LOW
Outcome: Quality of Life (Urolife)- Vardenafil (Evidence tables, appendix G1; Forest plots Figure 4)										
1	RCT	Serious(g)	No serious	No serious	No serious	No serious	104	110	MD 9.30 lower (12.79 to 5.81 lower)	MODERATE
Outcome: Qmax- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 5)										
10	RCT	Very serious (a)	No serious	No serious	Serious(h)	No serious	2124	1154	MD 0.29 higher (0.09 lower to 0.67 higher)	VERY LOW
Outcome: Qmax- Sildenafil (Evidence tables, appendix G1; Forest plots Figure 5)										
1	RCT	Very serious (b)	No serious	No serious	Very serious(i)	No serious	182	178	MD 0.18 (2.47 lower to 2.83 higher)	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
Outcome: Qmax- UK-369,003 (Evidence tables, appendix G1; Forest plots Figure 5)										
1	RCT	Very serious (k)	No serious	No serious	Serious(j)	No serious	90	38	MD 2.1 higher (0.72 to 3.48 higher)	VERY LOW
Outcome: Qmax- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 5)										
12	RCT	Very serious (a),(b),(h)	No serious	Serious(l)	No serious	No serious	2396	1370	MD 0.40 (0.04 lower to 0.85 higher)	MODERATE
Outcome: Voiding frequency- UK369,003 (Evidence tables, appendix G1; Forest plots Figure 6)										
1	RCT	Very serious (m)	No serious	No serious	Very serious(i)	No serious	193	54	MD 0.02 lower (1.94 lower to 1.91 higher)	VERY LOW
Outcome: Nocturia- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 7)										
4	RCT	Very serious (f)	No serious	No serious	No serious	No serious	781	581	MD 0.11 lower (0.24 lower to 0.02 higher)	LOW

(a) *All studies did not adequately describe randomisation, allocation concealment or blinding. At least 3 studies were sponsored by Eli Lilly. Takeda, 2008 & Yokoyama 2013 were undertaken in Korean and Japanese populations only.*
(b) *One study (McVary 2007c) was funded by Pfizer, the actual data for the outcomes were not reported.*
(c) *Random effects analysis used due to different variables used in ANCOVA models in included studies. I^2= 71% indicating substantial heterogeneity. However the Tau^2 statistic is 0.74 (a Tau^2 value >1 indicates significant heterogeneity)*
(d) *Mean difference does not reach clinically significant 3 point change, but the confidence intervals are narrow and the estimate is precise*
(e) *The change reaches clinical significance, but there is some uncertainty around the result due to the 95%CI crossing the MID in one direction.*
(f) *Three studies were funded by Eli Lilly and no study reported randomisation or allocation concealment methods.*
(g) *Stief (2008) was the one study reporting the Urolife QoL, randomisation and allocation concealment were not reported.*
(h) *The point estimate does not reach clinical significance of 2mL/min change. The estimate is precise; the 95%CI do not cross the MID, but they do cross the line of no effect. Downgrade one level.*
(i) *The point estimate does not reach a clinically significant change of 2mL/min and the 95%CI cross the MID in both directions leading to significant uncertainty. Downgrade 2 levels.*
(j) *The point estimate reaches a clinically significant change of 2mL/min; the 95%CI cross the MID in one direction leading to some uncertainty in the result. Downgrade 1 level.*
(k) *Tamimi (2010) does not report randomisation or allocation concealment methods. For Qmax outcome only data from 100mg UK-369,003 MR was compared to placebo. No raw data, only mean difference and 90%CI reported for comparison.*
(l) *I^2 for subgroup differences was 67.3%, p= 0.05. Downgraded one level.*

(m) *All data came from one study, Giuliano (2010); this study did not report randomisation, allocation concealment or blinding, funded by Pfizer.*
(n) *I^2= 73% and p=<0.05, indicating substantial heterogeneity. Test for subgroup differences I^2= 75.6%, Tau^2=<1. Downgraded 2 levels.*

Table 9: PDE5Is vs placebo – dichotomous outcomes

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Outcome: Outcome: Postural hypotension- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 8)											
2	RCT	Very serious(j)	No serious	Serious(i)	Serious(b)	No serious	119/559 (21.3%)	84/372 (22.6%)	0.98 (0.76, 1.26)	5 fewer per 1000 (from 54 fewer to 59 more)	VERY LOW
Outcome: Flushing- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 9)											
1	RCT	Very serious(a)	No serious	No serious	Serious(b)	No serious	1/51 (2%)	1/51 (2%)	1.00 (0.06, 15.56)	0 fewer per 1000 (from 18 fewer to 285 more)	VERY LOW
Outcome: Flushing- Sildenafil (Evidence tables, appendix G1; Forest plots Figure 9)											
1	RCT	Very serious(a)	No serious	No serious	Serious(b)	No serious	9/189 (4.8%)	1/180 (0.56%)	8.57 (1.10, 66.97)	42 more per 1000 (from 1 more to 367 more)	VERY LOW
Outcome: Flushing- Vardenafil (Evidence tables, appendix G1; Forest plots Figure 9)											
1	RCT	Very serious(a)	No serious	No serious	Serious(b)	No serious	7/108 (6.5%)	1/113 (0.9%)	7.32 (0.92, 58.54)	56 more per 1000 (from 1 fewer to 509 more)	VERY LOW
Outcome: Flushing- UK-369,003 (Evidence tables, appendix G1; Forest plots Figure 9)											

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
1	RCT	Very serious[a]	No serious	No serious	Very serious[c]	No serious	12/782 (1.5%)	0/76 (0%)	1.29 (0.17, 9.76)	-	VERY LOW
Outcome: Flushing- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 9)											
4	RCT	Very serious[a]	No serious	No serious	No serious	No serious	29/1130	3/420	4.00 (1.47, 10.89)	21 more per 1000 (from 3 more to 71 more)	LOW
Outcome: Dizziness – Tadalafil (Evidence tables, appendix G1; Forest plots Figure 10)											
2	RCT	Very serious[d]	No serious	No serious	Very serious	No serious	7/477 (1.5%)	3/326 (0.9%)	1.74 (0.47, 6.46)	7 more per 1000 (from 5 fewer to 50 more)	LOW
Outcome: Headaches- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 11)											
10	RCT	Very serious[e]	No serious	No serious	No serious	No serious	100/2531 (4%)	28/1550 (1.8%)	2.00 (1.32, 3.04)	18 more per 1000 (from 6 more to 37 more)	LOW
Outcome: Headaches- Sildenafil (Evidence tables, appendix G1; Forest plots Figure 11)											
1	RCT	Very serious[f]	No serious	No serious	No serious	No serious	21/189 (11.1%)	6/180 (3.3%)	3.33 (1.38, 8.07)	78 more per 1000 (from 13 more to 236 more)	LOW
Outcome: Headaches- Vardenafil (Evidence tables, appendix G1; Forest plots Figure 11)											
1	RCT	Very serious[g]	No serious	No serious	No serious	No serious	14/108	2/113	7.32 (1.70,	112 more	LOW

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
		)[h]					(13%)	(1.8%)	31.47)	per 1000 (from 12 more to 539 more)	
Outcome: Headaches- UK-369,003 (Evidence tables, appendix G1; Forest plots Figure 11)											
1	RCT	Very serious[h]	No serious	No serious	Very serious[c]	No serious	21/234 (9%)	4/57 (7%)	1.28 (0.46, 3.58)	20 more per 1000 (from 38 fewer to 181 more)	VERY LOW
Outcome: Headaches- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 11)											
13	RCT	Very serious[e][f][g][h]	No serious	No serious	No serious	No serious	146/3062 (5.1%)	40/1900 (2.1%)	2.29 (1.63, 3.21)	27 more per 1000 (from 13 more to 47 more)	LOW
Outcome: Withdrawals due to adverse events- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 12)											
11	RCT	Very serious[e]	No serious	No serious	Very serious[c]	No serious	29/1547 (1.9%)	23/1565 (1.5%)	1.28 (0.75, 2.18)	4 more per 1000 (from 4 fewer to 17 more)	VERY LOW
Outcome: Withdrawals due to adverse events- Sildenafil (Evidence tables, appendix G1; Forest plots Figure 12)											
1	RCT	Very serious[f]	No serious	No serious	Serious[b]	No serious	20/189 (10.6%)	8/180 (4.4%)	2.38 (1.08, 5.27)	61 more per 1000 (from 4 more to 190 more)	VERY LOW
Outcome: Withdrawals due to adverse events- Vardenafil (Evidence tables, appendix G1; Forest plots Figure 12)											
1	RCT	Very serious[g]	No serious	No serious	Serious[b]	No serious	9/108 (8.3%)	2/113 (1.8%)	4.71 (1.04, 21.30)	66 more per 1000 (from 1	VERY LOW

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
										more to 359 more)	
Outcome: Withdrawals due to adverse events- UK-369,003 (Evidence tables, appendix G1; Forest plots Figure 12)											
1	RCT	Very serious[(h)]	No serious	No serious	Very serious[(c)]	No serious	3/59 (5.1%)	2/63 (3.2%)	1.60 (0.28, 9.25)	19 more per 1000 (from 23 fewer to 262 more)	VERY LOW
Outcome: Withdrawals due to adverse events- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 12)											
14	RCT	Very serious[(e)(f)(g)(h)]	No serious	No serious	Serious[(b)]	No serious	61/1903 (3.2%)	35/1921 (1.8%)	1.74 (1.16, 2.61)	13 more per 1000 (from 3 more to 29 more)	VERY LOW

(a) *Kim (2011), McVary (2007c), Stief (2008) and Tamimi (2010) were all funded by pharmaceutical companies; all studies did not adequately describe randomisation, allocation concealment or blinding.*
(b) *The 95%CI cross the MID in one direction, leading to uncertainty around the result. Downgraded 1 level.*
(c) *The 95%CI cross the MID in both directions, leading to significant uncertainty around the result. Downgraded 2 levels.*
(d) *Both Oelke (2012) and Yokoyama (2013) were funded by Eli Lilly. Neither study adequately reported randomisation or allocation concealment. Yokoyama (2013) population was composed of Japanese and Korean men only and they did not report baseline incidence of Erectile Dysfunction (ED). Downgraded 2 levels.*
(e) *All studies did not adequately describe randomisation, allocation concealment or blinding. At least 3 studies were sponsored by Eli Lilly. Takeda, 2008 & Yokoyama 2013 were undertaken in Korean and Japanese populations only.*
(f) *One study (McVary 2007c) was funded by Pfizer, the actual data for the outcomes were not reported.*
(g) *Stief (2008) did not adequately describe randomisation or allocation concealment. The study was funded by Baye).*
(h) *All data came from one study, Giuliano (2010); this study did not report randomisation, allocation concealment or blinding, funded by Pfizer.*
(i) *I^2=47%, p=NS indicating moderate heterogeneity. Downgraded 1 level.*
(j) *Both studies did not report method of randomisation, allocation concealment or blinding; both studies were funded by Eli Lilly. Additionally, Porst (2011) reported postural hypotension as 4 separate events; it could be possible that one person may have experienced one of the 4 events more than once, leading to overestimation of postural hypotension.*

H.21 PDE5Is vs alpha blockers

2 **Table 10: PDE5Is vs alpha blockers –continuous outcomes**

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference from baseline difference (95% CI)	
Outcome: Symptom score- (IPSS) – Tadalafil (Evidence tables, appendix G1; Forest plots Figure 13)										
5	RCT	Very serious [k]	No serious	No serious	No serious	No serious	373	366	0.09 (from 0.84 lower to 1.02 higher)	LOW
Outcome: Symptom score- (IPSS) –Sildenafil (Evidence tables, appendix G1; Forest plots Figure 13)										
3	RCT	Very serious [l]	No serious	Serious[a]	Serious[b]	No serious	71	70	1.65 (from 0.66 lower to 3.96 higher)	VERY LOW
Outcome: Symptom score- (IPSS) – UK369,003 (Evidence tables, appendix G1; Forest plots Figure 13)										
1	RCT		No serious				341	36	Not estimable	
Outcome: Symptom score- (IPSS) – PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 13)										
9	RCT	Very serious [k],[l]	No serious	Serious[a](c)	No serious	No serious	785	472	0.55 (from 0.55 lower to 1.65 higher)	VERY LOW
Outcome: Symptom score (BII) – Tadalafil (Evidence tables, appendix G1; Forest plots Figure 14)										
1	RCT	Very serious[m]	No serious	No serious	Serious[d]	No serious	51	49	-0.60 (from 1.43 lower to 0.23 higher)	VERY LOW
Outcome: Quality of Life (IPSS)- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 15)										
6	RCT	Very serious [k]	No serious	Very serious[f]	No serious	No serious	373	368	-0.00 (from 0.39 lower to 0.3 higher)	VERY LOW
Outcome: Quality of Life (IPSS)- Sildenafil (Evidence tables, appendix G1; Forest plots Figure 15)										
1	RCT	Very serious	No serious	No serious	Serious[e]	No serious	20	20	-0.61 (from 0.94 lower to 0.26	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference from baseline difference (95% CI)	
		(l),(n)							lower)	
Outcome: Quality of Life (IPSS)- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 15)										
7	RCT	Very serious (k),(l),(n)	No serious	Very serious[(g)]	Serious[(e)]	No serious	393	388	-0.16 (from 0.58 lower to 0.25 higher)	VERY LOW
Outcome: Qmax – Tadalafil (Evidence tables, appendix G1; Forest plots Figure 16)										
6	RCT	Very serious [(k)]	No serious	No serious	No serious	No serious	373	365	-0.18 (from 0.84 lower to 0.48 higher)	LOW
Outcome: Qmax – Sildenafil (Evidence tables, appendix G1; Forest plots Figure 16)										
2	RCT	Very serious (l),(n)	No serious	No serious	Serious[(h)]	No serious	41	40	-0.80 (from 2.47 lower to 0.87 higher)	VERY LOW
Outcome: Qmax – PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 16)										
8	RCT	Very serious (k),(l),(n)	No serious	No serious	No serious	No serious	414	405	-0.26 (from 0.88 lower to 0.35 higher)	LOW
Outcome: Voiding frequency- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 17)										
1	RCT	Very serious [(l)]	No serious	No serious	Serious[(e)]	No serious	21	20	1.40 (from 0.23 higher to 2.57 higher)	VERY LOW
Outcome: Nocturia- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 18)										
3	RCT	Very serious[(o)]	No serious	Serious[(i)]	Serious[(d)]	No serious	222	216	0.19 (from 0.29 lower to 0.66 higher)	VERY LOW
Outcome: Nocturia- Sildenafil (Evidence tables, appendix G1; Forest plots Figure 18)										
1	RCT	Very serious[(l)]	No serious	No serious	Serious[(d)]	No serious	21	20	0.50 (from 0.06 lower to 1.06 higher)	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference from baseline difference (95% CI)	
Outcome: Nocturia- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 18)										
4	RCT	Very serious[(o),(l)]	No serious	Serious[(j)]	Serious[(d)]	No serious	243	236	0.26 (from 0.11 lower to 0.64 higher)	VERY LOW

(a) *I2= 60%, indicating heterogeneity present, though p=>0.05/ Downgraded 1 level.*
(b) *The 95%CI crosses the MID of 3 in one direction, leading to uncertainty around the result. Downgraded 1 level.*
(c) *Tau^2 <1 indicating subgroup heterogeneity not significant.*
(d) *The 95%CI crosses the MID in one direction and also crosses the line of no effect. Downgraded 1level.*
(e) *The 95%CI crosses the MID of 0.5 in one direction leading to uncertainty around the result. Downgraded 1 level.*
(f) *I^2=75% and p=0.02, indicating considerable heterogeneity in results in the QoL of the tadalafil subgroup. Downgraded 2 levels.*
(g) *I^2= 85% and p=<0.05 for total heterogeneity; I^2 for subgroup differences was 80.7% and p=<0.05. Downgraded 2 levels.*
(h) *The 95%CI crosses the MID of 2mL/min in one direction, leading to uncertainty around the results. Downgraded 1 level.*
(i) *I^2=60% and p=>0.05 indicating moderate heterogeneity. Downgraded 1 level.*
(j) *I^2=52% and p=>0.05 indicating moderate heterogeneity. Downgraded 1 level.*
(k) *No study that reported this outcome reported the method of randomisation, allocation concealment and blinding. Studies were funded by Eli Lilly. One study had a population of Japanses and Korean men only. Kim (2011) and Yokoyama (2013) use dose of 0.2mg tamsulosin per day.*
(l) *No studies in this outcome reported methods for randomisation allocation concealment or blinding.*
(m) *Kim (2011) did not report method of randomisation, allocation concelament or blinding, study was funded by Eli Lilly, used suboptimal dose of tamsulsoin (0.2mg/ day).*
(n) *Tuncel (2010) did not report baseline demographics.*
(o) *No studies reporting this outcome reported method of randomisation, allocation concealment or blinding; all studies were funded by Eli Lilly.*

Table 11: PDE5Is vs alpha blockers – dichotomous outcomes

Quality assessment							No of patients		Effect estimate		Quali
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Outcome: Postural hypotension											
0	RCT		-	-	-	-	-	-	-	-	-
Outcome: Flushing-Tadalafil (Evidence tables, appendix G1; Forest plots Figure 19)											
1	RCT	Very serious [(d)]	No serious	No serious	Very serious[(a)]	No serious	1/51 (2%)	0/49 (0%)	2.88 (0.12, 69.16)	-	VERY LOW
Outcome: Flushing- Sildenafil (Evidence tables, appendix G1; Forest plots Figure 19)											

Quality assessment							No of patients		Effect estimate		Quali
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
1	RCT	Very serious [c]	No serious	No serious	Very serious[a]	No serious	1/21 (4.8%)	0/20 (0%)	2.86 (0.12, 66.44)	-	VERY LOW
Outcome: Flushing- UK-369,003 (Evidence tables, appendix G1; Forest plots Figure 19)											
1	RCT	Very serious[e]	No serious	No serious	Very serious[a]	No serious	13/341 (3.8%)	0/76 (0%)	4.23 (0.60, 29.61)	-	VERY LOW
Outcome: Flushing- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 19)											
3	RCT	Very serious [c],(d),(e)	No serious	No serious	Serious[b]	No serious	15/413 (3.6%)	0/145 (0%)	3.69 (0.84, 16.24)	-	VERY LOW
Outcome: Dizziness- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 20)											
2	RCT	Very serious[c],(f),(g)	No serious	No serious	Very serious[a]	No serious	7/477 (1.5%)	8/320 (2.5%)	0.68 (0.25, 1.89)	8 fewer per 1000 (from 19 fewer to 22 more)	VERY LOW
Outcome: Dizziness-Sildenafil (Evidence tables, appendix G1; Forest plots Figure 20)											
1	RCT	Very serious [c]	No serious	No serious	Very serious[a]	No serious	0/21 (0%)	2/20 (10%)	0.19 (0.01, 3.75)	81 fewer per 1000 (from 99 fewer to 275 more)	VERY LOW
Outcome: Dizziness- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 20)											
3	RCT	Very	No serious	No serious	Very	No serious	7/498	10/340	0.57	13	VERY

Quality assessment							No of patients		Effect estimate		Quali
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
		serious[(c),(f),(g)]			serious[(a)]		(1.4%)	(2.9%)	(0.22, 1.47)	fewer per 1000 (from 23 fewer to 14 more)	LOW
Outcome: Headaches- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 21)											
5	RCT	Very serious [(c),(f)]	No serious	No serious	Very serious[(a)]	No serious	16/597 (2.7%)	10/439 (2.3%)	1.31 (0.61, 2.84)	7 more per 1000 (from 9 fewer to 42 more)	VERY LOW
Outcome: Headaches- UK-369,003 (Evidence tables, appendix G1; Forest plots Figure 21)											
1	RCT	Very serious [(e)]	No serious	No serious	Very serious[(a)]	No serious	21/341 (6.2%)	4/72 (5.6%)	1.08 (0.37, 3.14)	4 more per 1000 (from 35 fewer to 119 more)	VERY LOW
Outcome: Headaches- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 21)											
7	RCT	Very serious [(c),(f),(e)]	No serious	No serious	Very serious [(a)]	No serious	37/938 (3.9%)	14/511 (2.7%)	1.23 (0.66, 2.30)	3 more per 1000 (from 9 fewer to 36	VERY LOW

Quality assessment							No of patients		Effect estimate		Quali
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
										more)	
Outcome: Withdrawals due to adverse events- Tadalafil (Evidence tables, appendix G1; Forest plots Figure 22)											
6	RCT	Very serious (c),(f),(g)	No serious	No serious	Serious(b)	No serious	20/593 (3.4%)	6/436 (1.4%)	2.23 (0.93, 5.35)	17 more per 1000 (from 1 fewer to 60 more)	VERY LOW
Outcome: Withdrawals due to adverse events- Sildenafil (Evidence tables, appendix G1; Forest plots Figure 22)											
1	RCT	Very serious (c)	No serious	No serious	Very serious(a)	No serious	2/21 (9.5%)	2/20 (10%)	0.95 (0.15, 6.13)	5 fewer per 1000 (from 85 fewer to 513 more)	VERY LOW
Outcome: Withdrawals due to adverse events- PDE5Is overall (Evidence tables, appendix G1; Forest plots Figure 22)											
7	RCT	Very serious (c),(f),(g)	No serious	No serious	Serious(b)	No serious	22/614 (3.6%)	8/456 (1.8%)	1.96 (0.89, 4.30)	17 more per 1000 (from 2 fewer to 58 more)	VERY LOW

**numbers in control group n=107 here as Tamimi control group counted twice in Forest plots, therefore 145-38=107 true number of alpha blocker group.*

(a) The 95%CI cross the MID of 0.75 and 1.25 in both directions, leading to substantial uncertainty around the result. Downgraded 2 levels.

(b) The 95%CI cross either the 0.75 or 1.25 MID in one direction, leading to some uncertainty around the result. Downgraded 1 level.

(c) No studies in this outcome reported methods for randomisation allocation concealment or blinding.

(d) Kim (2011) did not report method of randomisation, allocation concelament or blinding, study was funded by Eli Lilly, used suboptimal dose of tamsulsoin (0.2mg/ day).

(e) Tamimi (2010) did not report methods of randomisation, allocation concealment or blinding. There was unequal ratio of randomisation between intervention and tamsulosin groups.
(f) At least half of the studies reporting this outcome were funded by Eli Lilly.
(g) Yokoyama (2013) had a population solely of Japanese and Korean men

H.36 PDE5Is vs antimuscarinics

Table 12: PDE5I vs antimuscarinics- continuous outcomes

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment (T)	Comparator (C)	Mean difference (95% CI)	
Outcome: Symptom scores (IPSS) (Evidence tables, appendix G1; Forest plots Figure 23)										
1	RCT	Very serious[(c)]	No serious	No serious	Serious[(a)]	No serious	28	28	MD 0.3 higher (0.23 lower to 0.83 higher)	VERY LOW
Outcome: Quality of Life (IPSS) (Evidence tables, appendix G1; Forest plots Figure 24)										
1	RCT	Very serious[(c)]	No serious	No serious	Serious[(a)]	No serious	28	28	MD 0.00 (0.19 lower to 0.19 higher)	VERY LOW
Outcome: Qmax (Evidence tables, appendix G1; Forest plots Figure 25)										
1	RCT	Very serious[(c)]	No serious	No serious	Serious[(a)]	No serious	28	28	MD 5.00 lower (6.08 to 3.92 lower)	VERY LOW
Outcome: Voiding frequency (Evidence tables, appendix G1; Forest plots Figure 26)										
1	RCT	Very serious[(c)]	No serious	No serious	Serious[(a),(b)]	No serious	28	28	MD 0.20 (0.95 lower to 1.35 higher)	VERY LOW
Outcome: Nocturia (Evidence tables, appendix G1; Forest plots Figure 27)										
1	RCT	Very serious[(c)]	No serious	No serious	No serious	No serious	28	28	MD 0.1 higher (0.19 lower to 0.39 higher)	LOW

(a) Serious imprecision; the MIDs do not cross the MID of 2mL/min, however the study does not reach the OIS of n=45 per arm for IPSS, n=64 per arm for IPSS-QoL and n=63 per arm for Qmax.
(b) The 95%CI crosses the 0.5 MID in one direction. Downgrade 1 level.

(c) One study that reported the outcome (Maselli, 2010) did not report method of randomisation, allocation concealment or blinding. It was not clear whether the analysis was undertaken on a per protocol or ITT population. The study reported figures as mean value; they did not report whether results were mean (SD), however, baseline demographics were reported as mean (SD) therefore it has been assumed that the results are also reported as mean (SD) – therefore these reulsts should be interpreted with caution as they are only assumed to be mean (SD).

Table 13: PDE5I vs antimuscarinics- dichotomous outcomes

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Treatment	Comparator	Relative (95% CI)	Absolute	
Outcome: Headaches (Evidence tables, appendix G1; Forest plots Figure 28)											
1	RCT	Very serious[(a)]	No serious	No serious	Very serious[(b)]	No serious	5/28 (17.9%)	0/28 (0%)	11.00 (0.64, 89.96)	-	VERY LOW

(a) One study that reported the outcome (Maselli, 2010) did not report method of randomisation, allocation concealment or blinding. It was not clear whether the analysis was undertaken on a per protocol or ITT population.
(b) The 95%CI crosses the MID of 0.5 in both directions, leading to a lot of uncertainty around the result. Downgraded 2 levels.

Appendix I: Forest plots

I.1 PDE5Is versus placebo

Figure 1: Symptom scores -IPSS (Evidence table appendix G1; GRADE table 7)

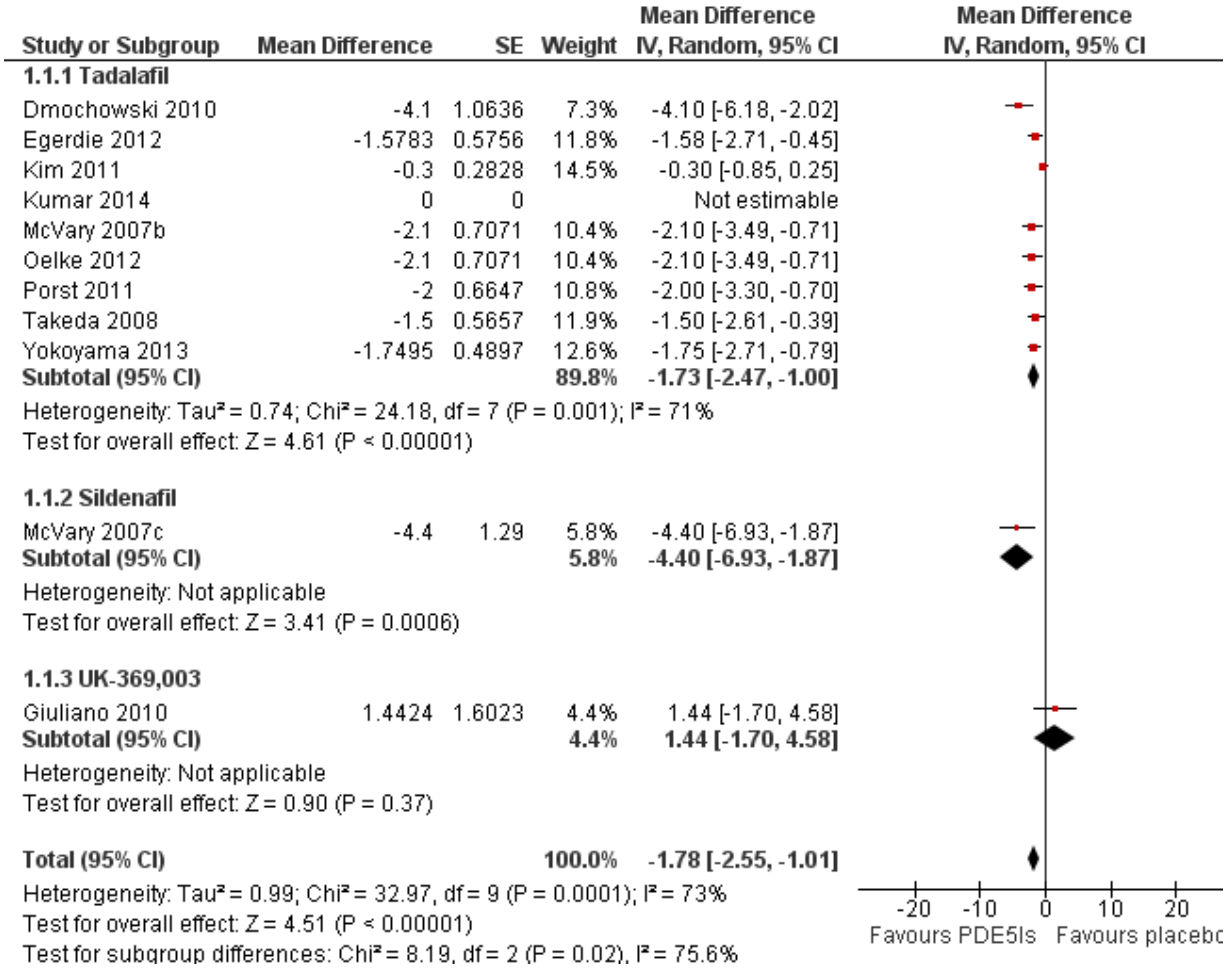


Figure 2: Symptom scores –BII (Evidence table appendix G1; GRADE table 7)

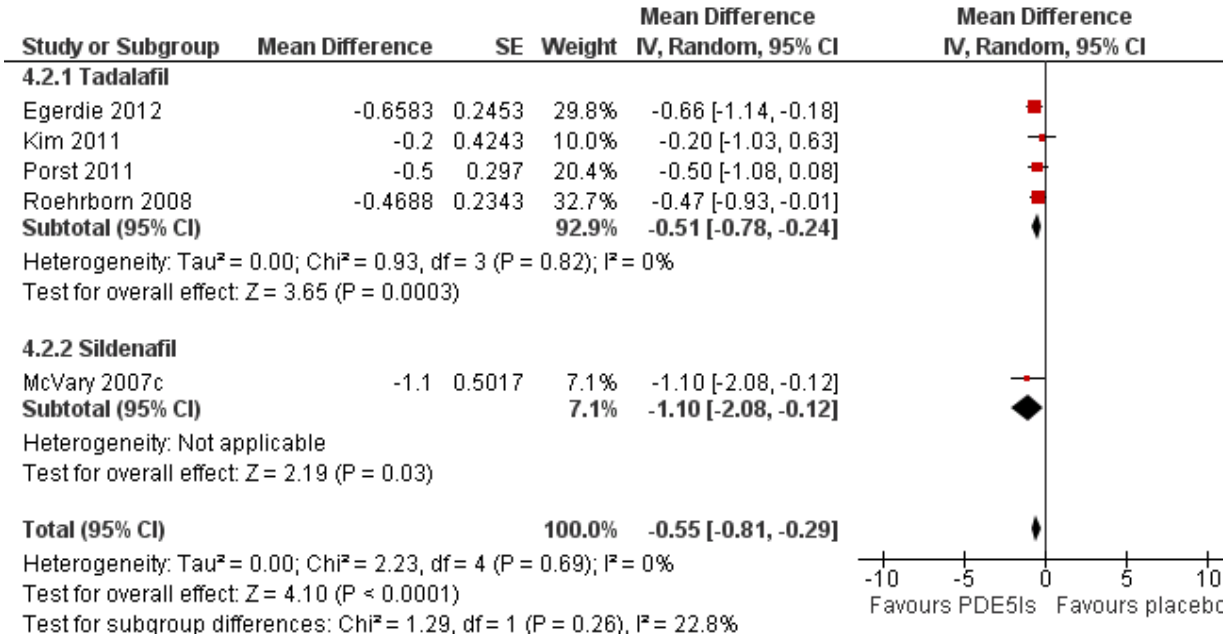


Figure 3: Quality of Life (IPSS) (Evidence table appendix G1; GRADE table 7)

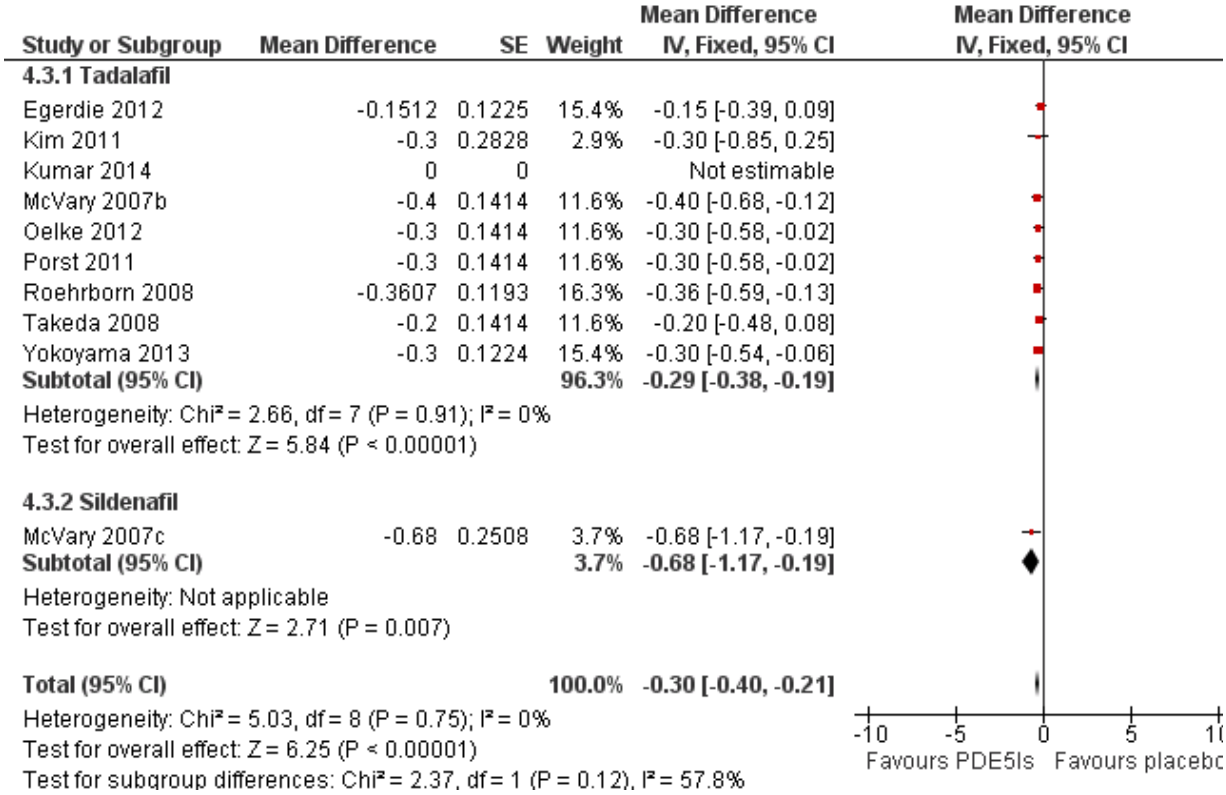


Figure 4: Quality of Life (Urolife) (Evidence table appendix G1; GRADE table 7)

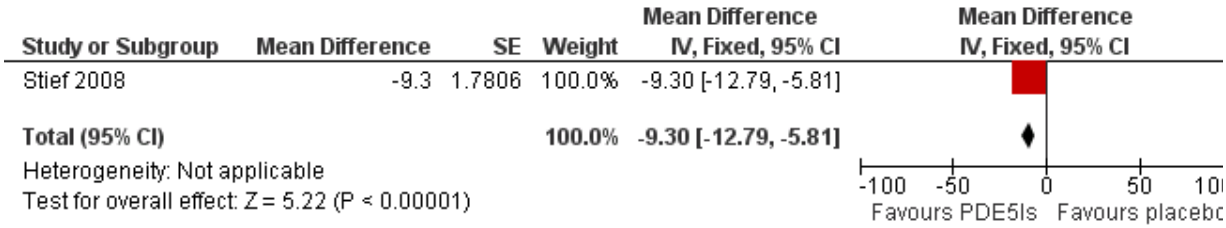


Figure 5: Maximal Urinary Flow rate (Qmax) (Evidence table appendix G1; GRADE table 7)

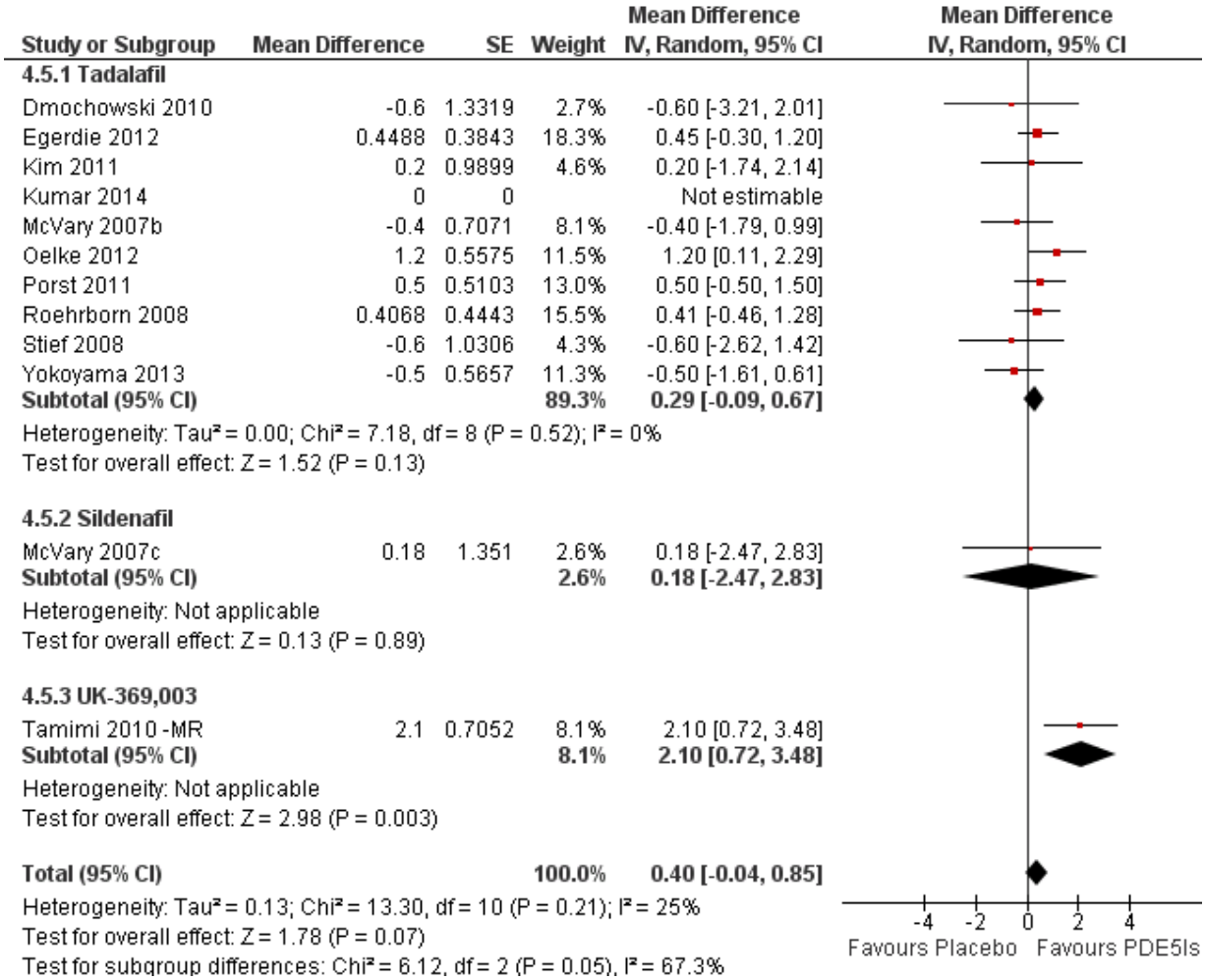


Figure 6: Voiding frequency (Evidence table appendix G1; GRADE table 7)

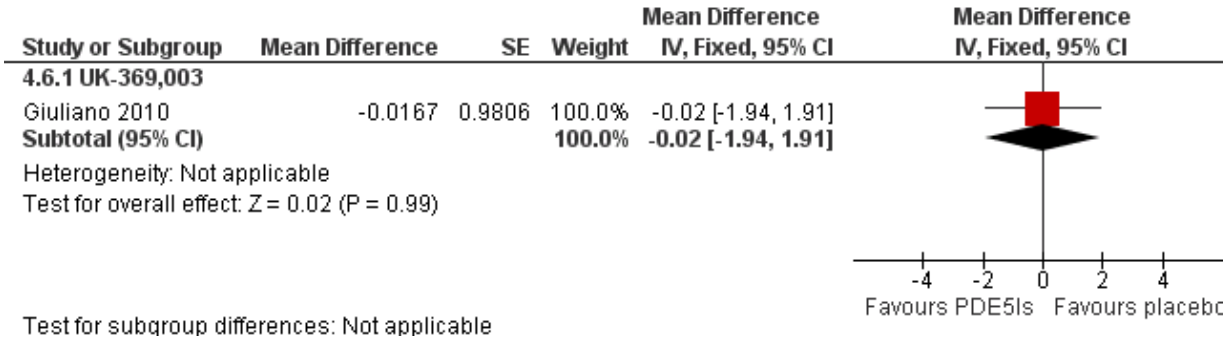


Figure 7: Nocturia (Evidence table appendix G1; GRADE table 7)

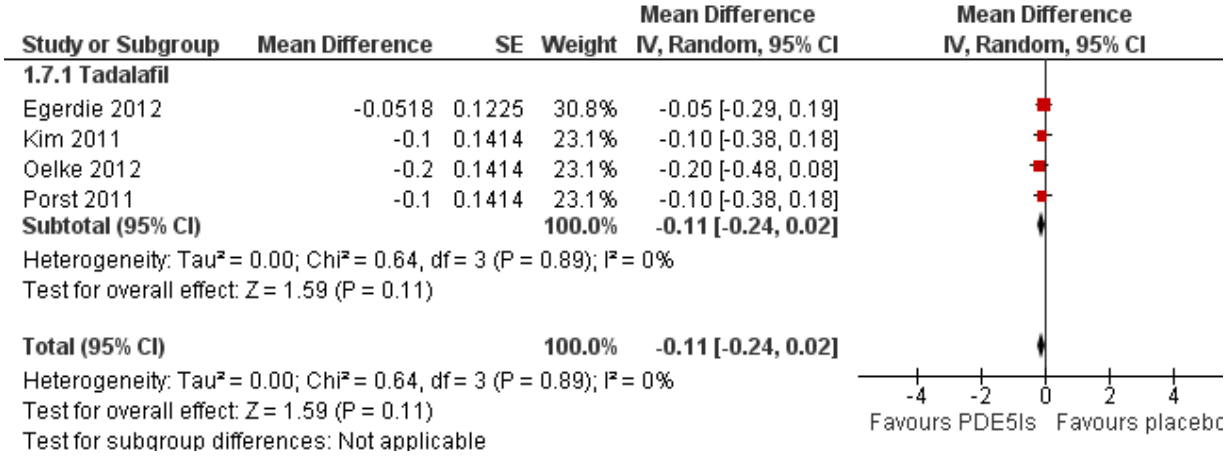


Figure 8: Postural hypotension (Evidence table appendix G1; GRADE table 8)

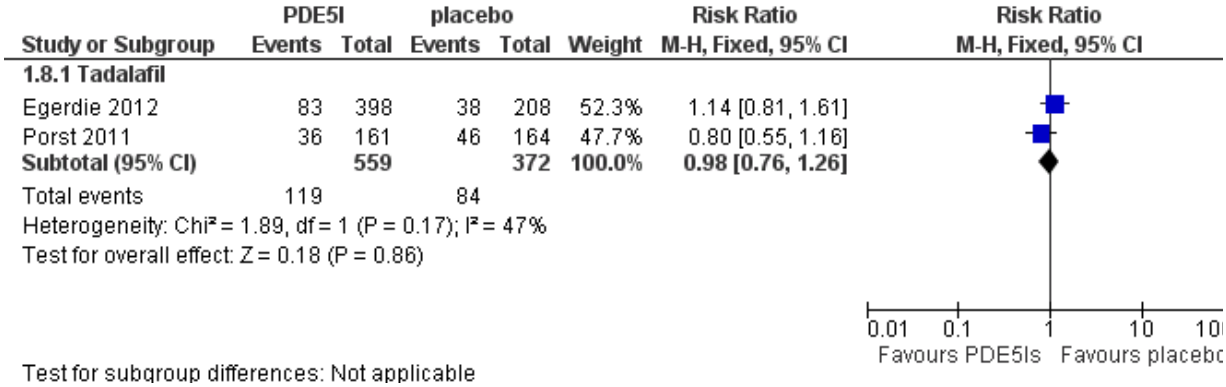


Figure 9: Flushing (Evidence table appendix G1; GRADE table 8)

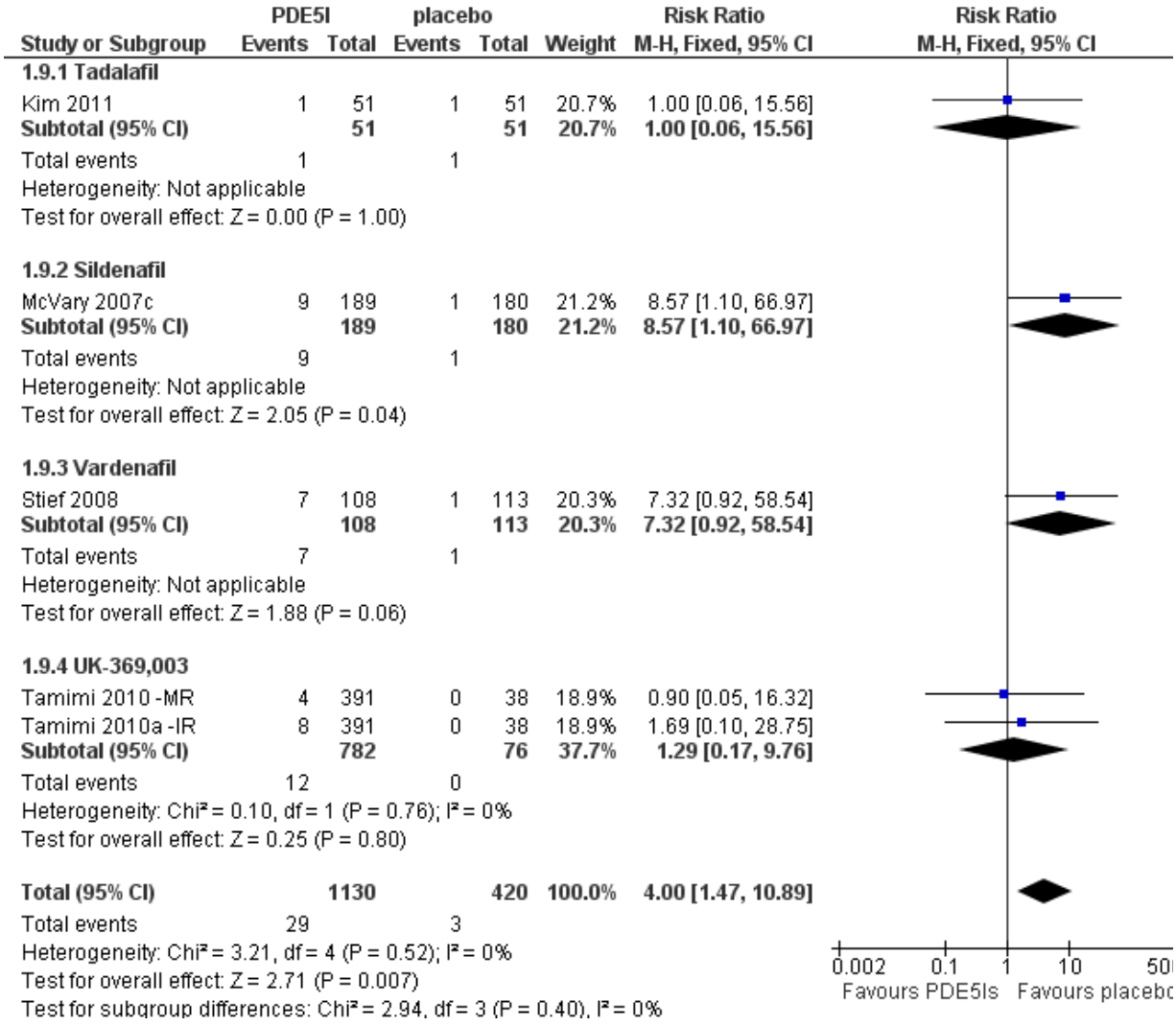


Figure 10: Dizziness (Evidence table appendix G1; GRADE table 8)

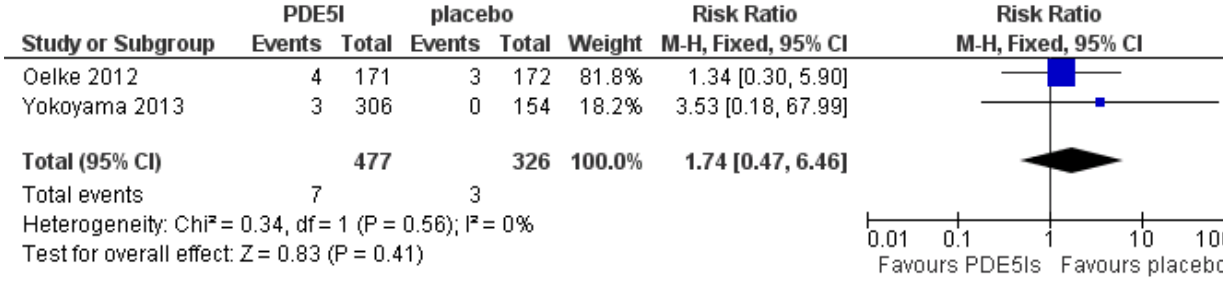


Figure 11: Headaches (Evidence table appendix G1; GRADE table 8)

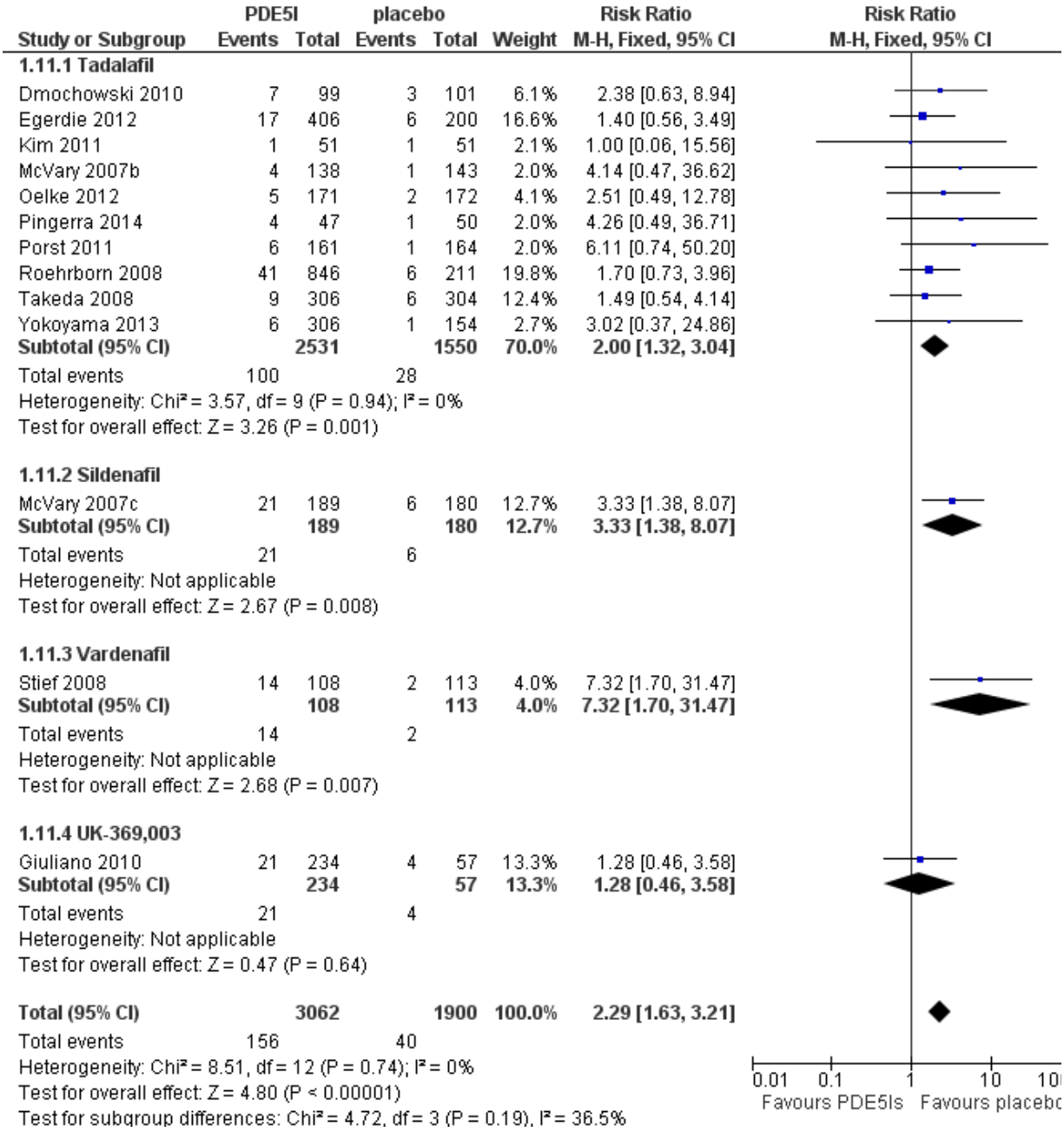
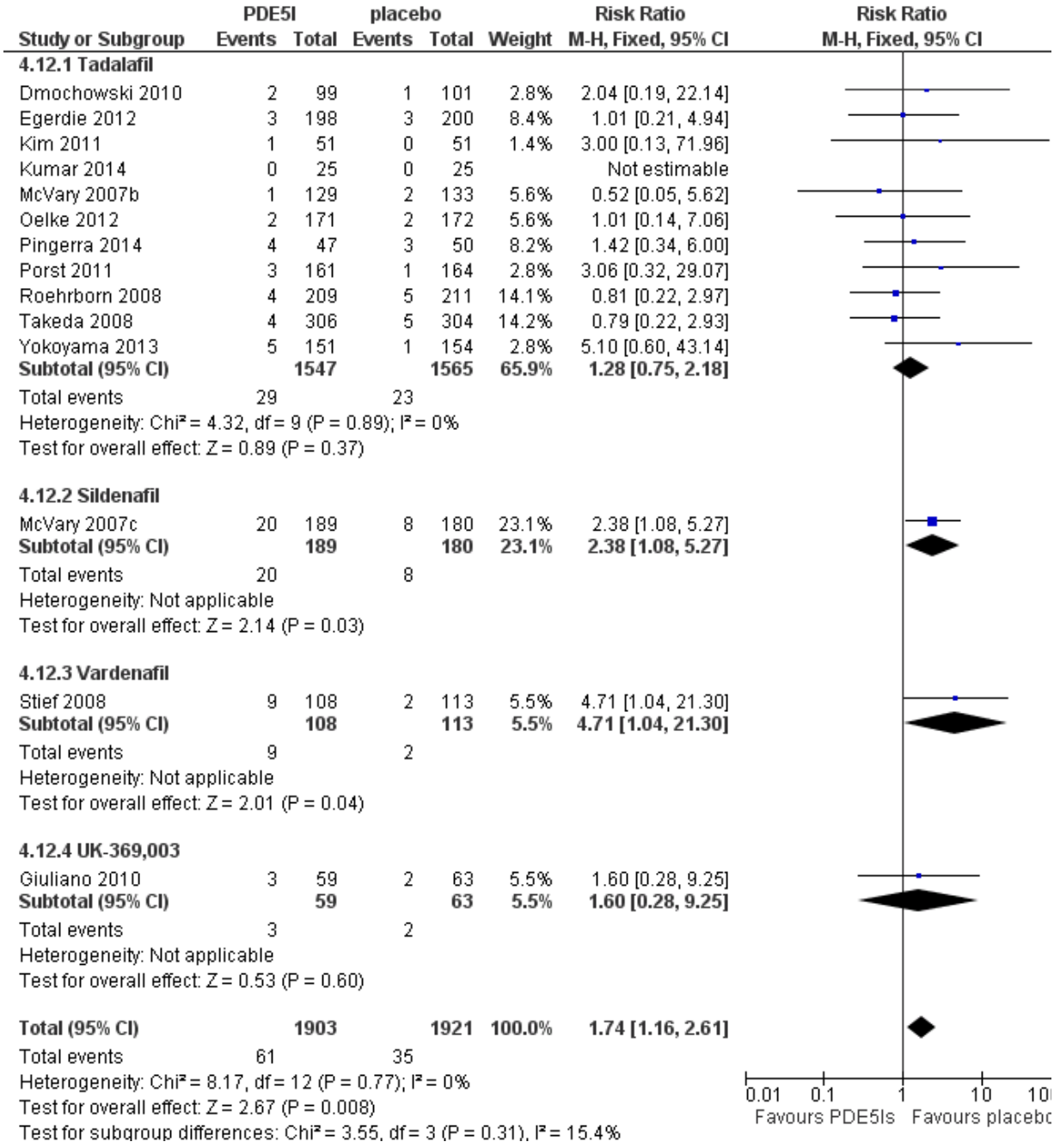


Figure 12: Withdrawals due to Adverse events (Evidence table appendix G1; GRADE table 8)



I.2 PDE5Is versus alpha blockers

Figure 13: Symptom scores –IPSS (Evidence table appendix G1; GRADE table 9)

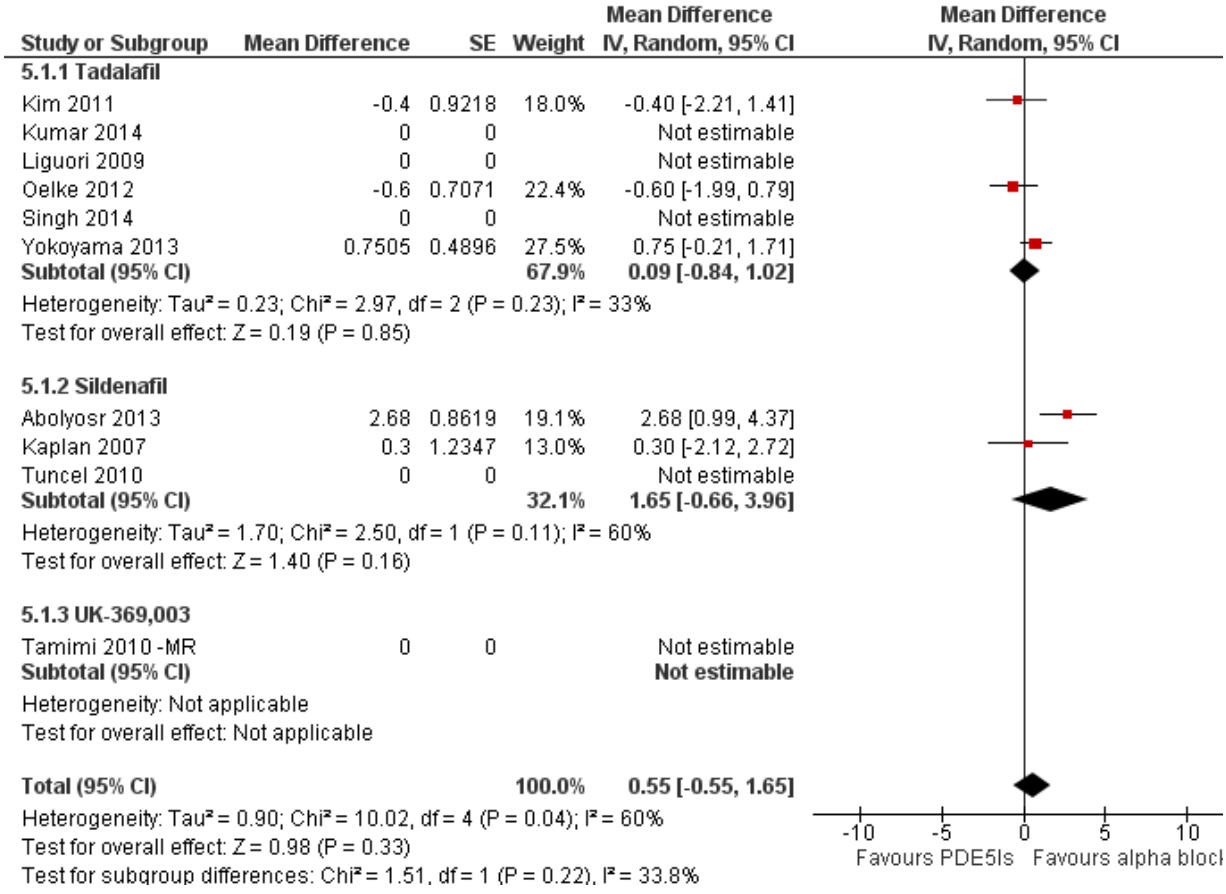


Figure 14: Symptom scores –BII (Evidence table appendix G1; GRADE table 9)

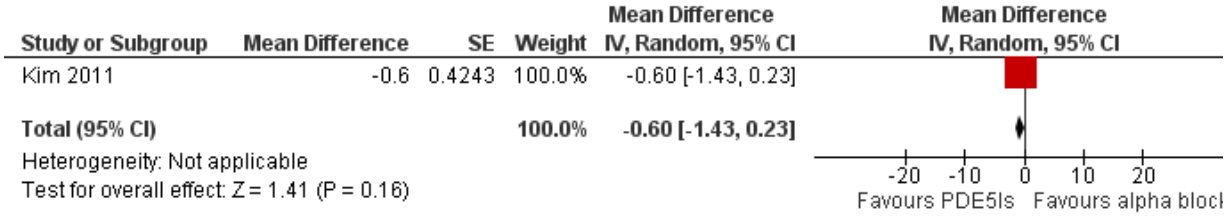


Figure 15: Quality of Life (IPSS) (Evidence table appendix G1; GRADE table 9)

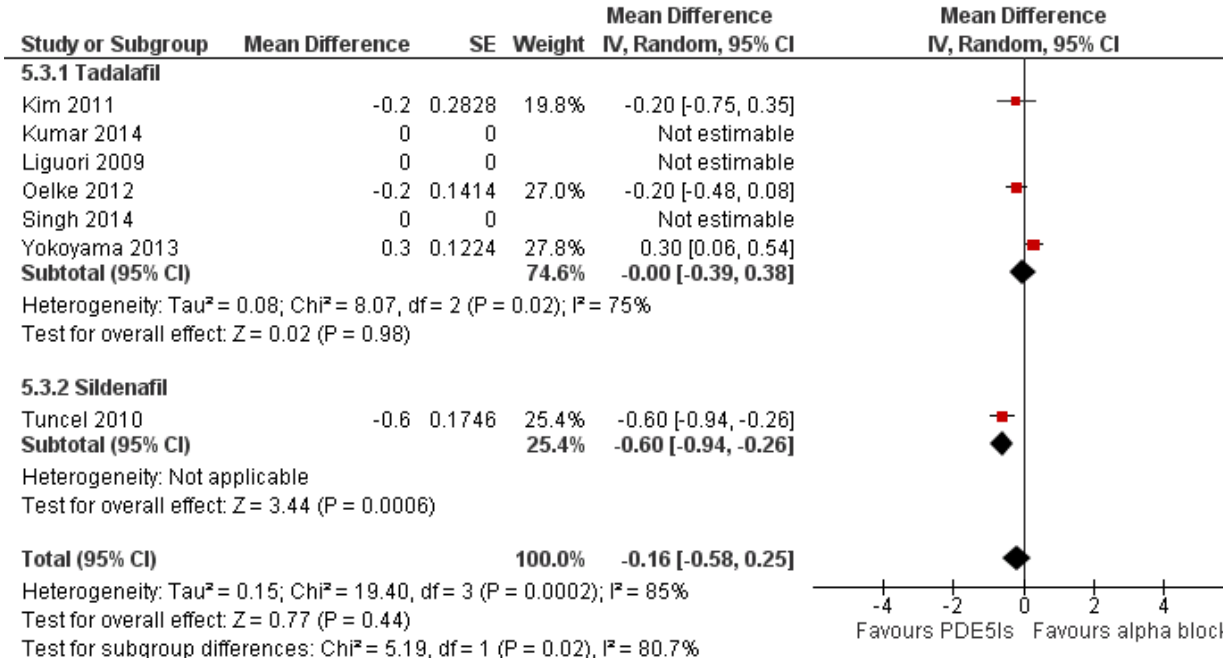


Figure 16: Maximal urinary flow rate (Qmax) (Evidence table appendix G1; GRADE table 9)

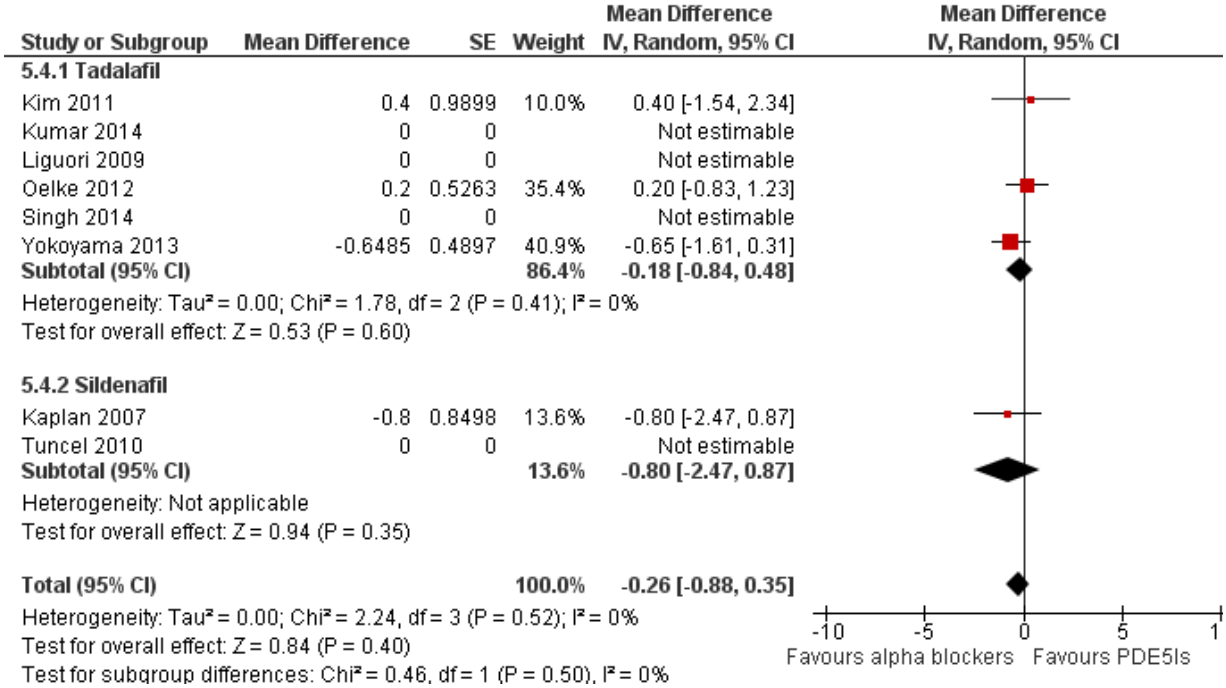


Figure 17: Voiding frequency (Evidence table appendix G1; GRADE table 9)

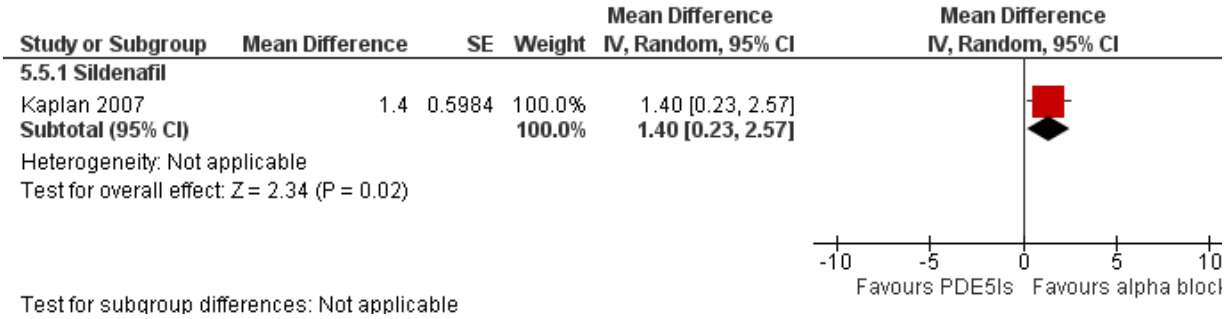


Figure 18: Nocturia (Evidence table appendix G1; GRADE table 9)

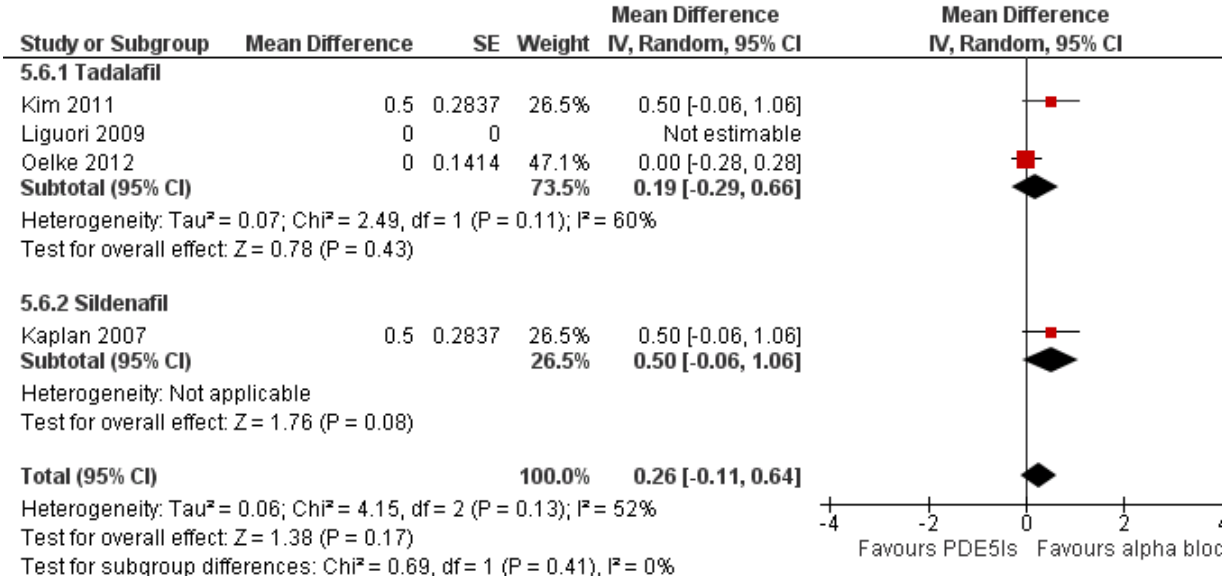


Figure 19: Flushing (Evidence table appendix G1; GRADE table 10)

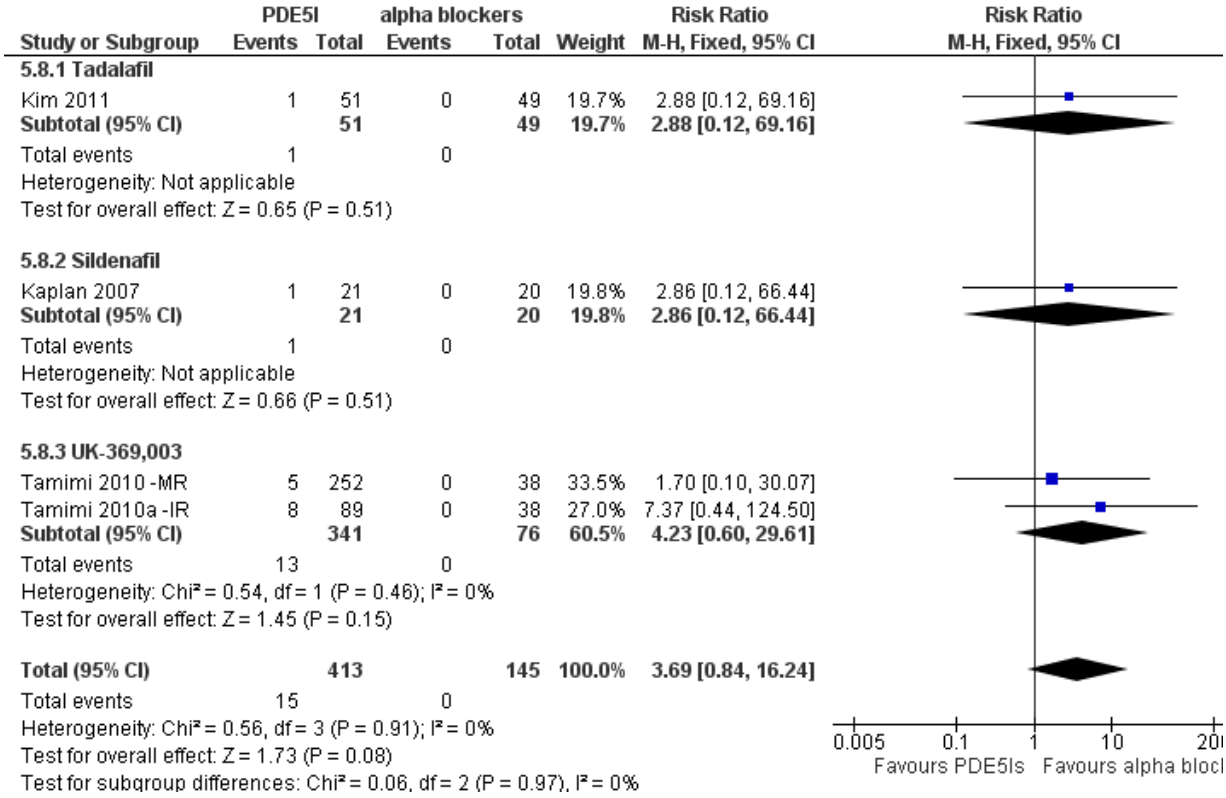


Figure 20: Dizziness (Evidence table appendix G1; GRADE table 10)

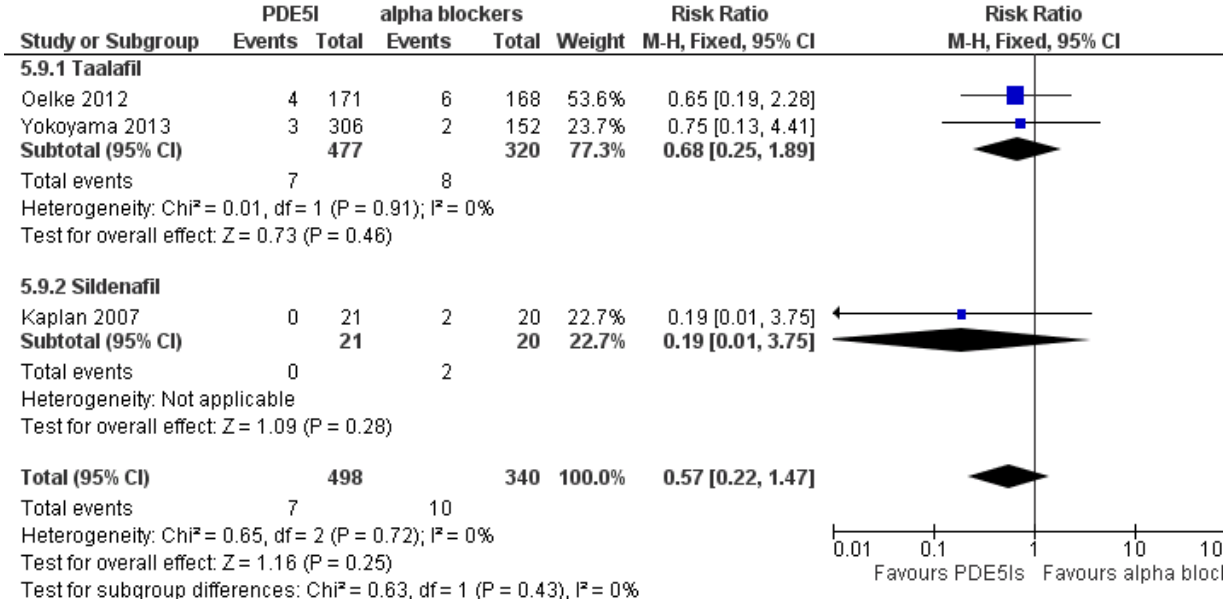


Figure 21: Headaches (Evidence table appendix G1; GRADE table 10)

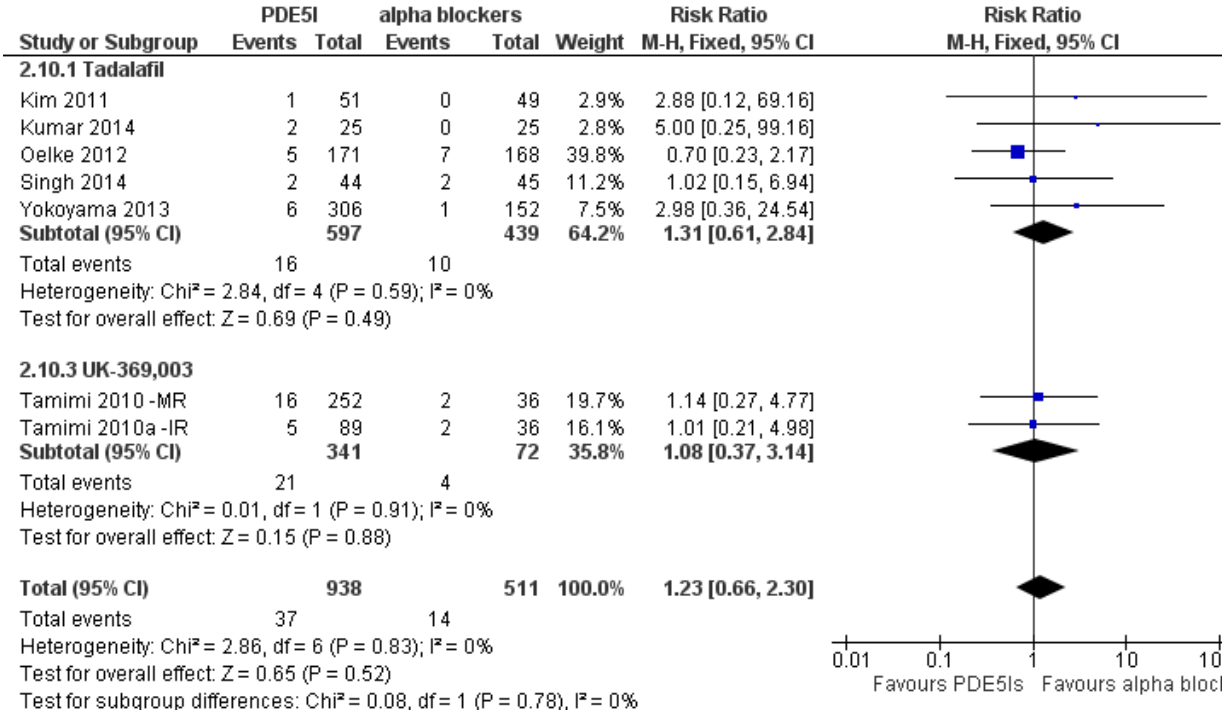
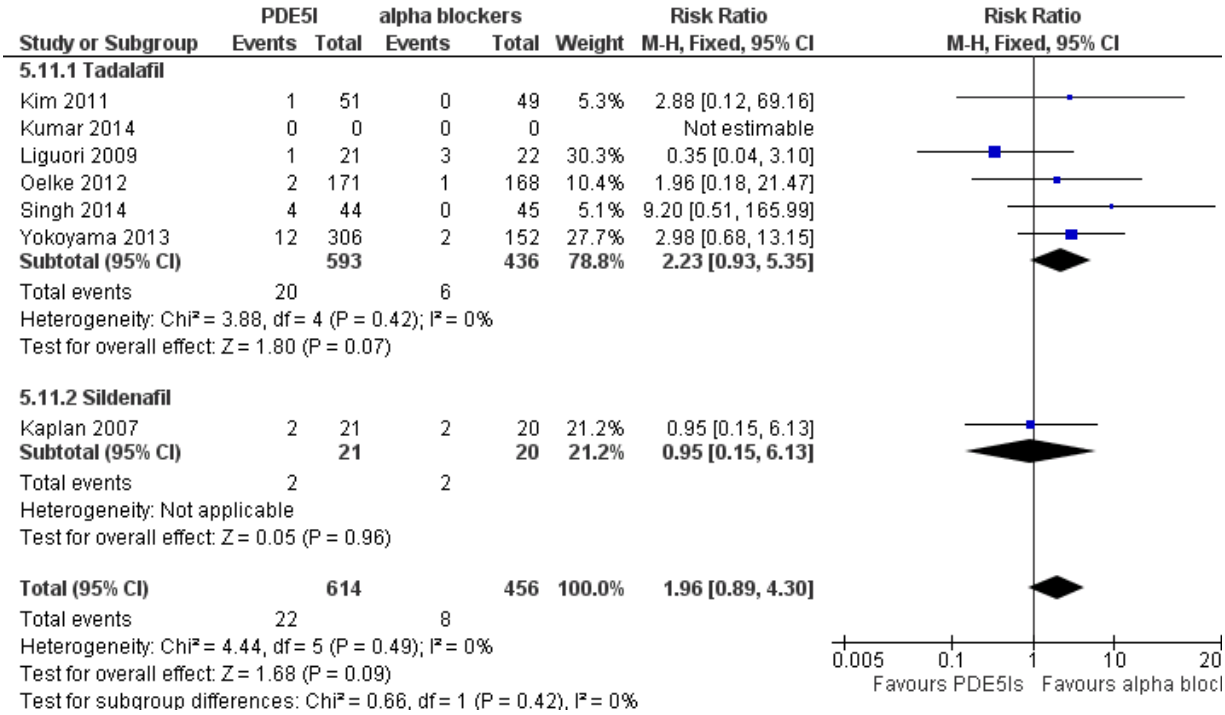


Figure 22: Withdrawals due to Adverse Events (Evidence table appendix G1; GRADE table 10)



I.3 PDE5Is versus antimuscarinics

Figure 23: Symptom scores- IPSS (Evidence table appendix G1; GRADE table 11)

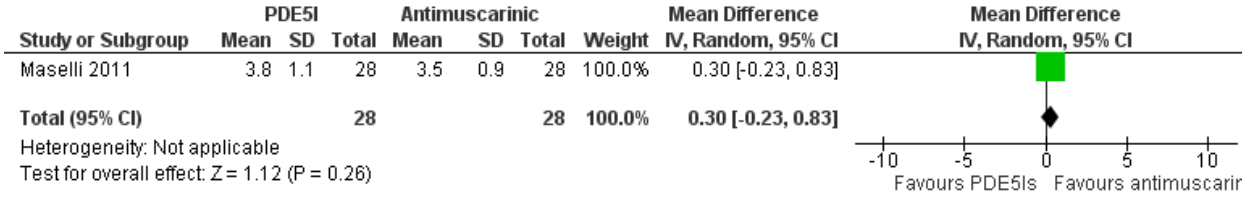


Figure 24: Quality of Life (IPSS) (Evidence table appendix G1; GRADE table 11)

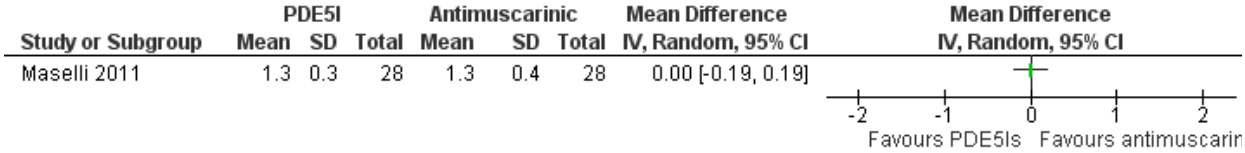


Figure 25: Maximal urinary flow rate (Qmax)

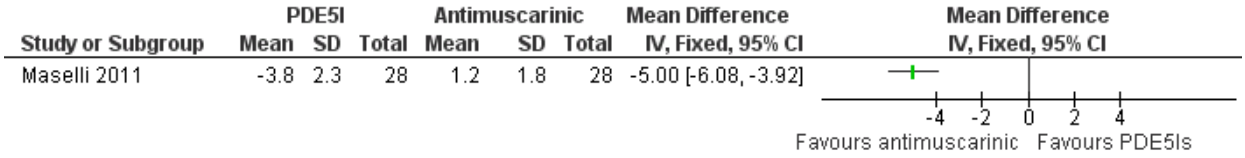


Figure 26: Voiding frequency (Evidence table appendix G1; GRADE table 11)

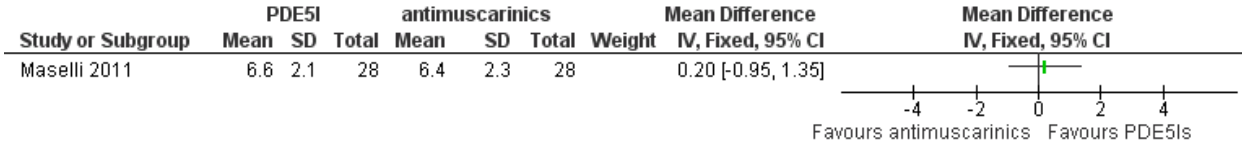


Figure 27: Nocturia (Evidence table appendix G1; GRADE table 11)

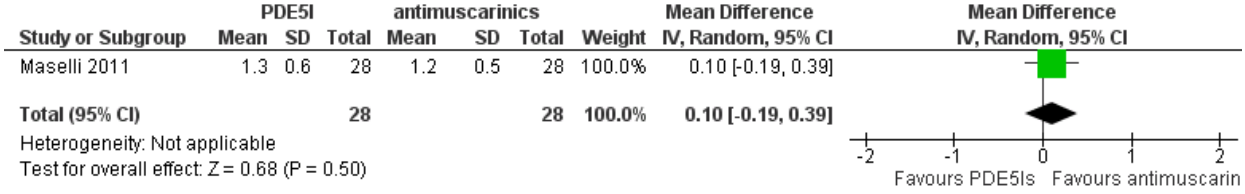
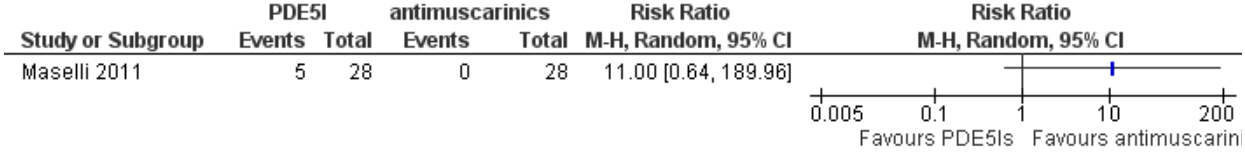


Figure 28: Headaches (Evidence table appendix G1; GRADE table 12)



Appendix J: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 14. The economic search strategy is shown in Table 15. The same strategy was translated for the other databases listed.

Table 14: Economic search summary

Databases	Date searched	No. retrieved
MEDLINE (Ovid)	27/08/2014	103
MEDLINE In-Process (Ovid)	27/08/2014	14
EMBASE (Ovid)	27/08/2014	203
PubMed	27/08/2014	13
NHS Economic Evaluation Database - NHS EED (Wiley)	27/08/2014	0
Health Economic Evaluations Database – HEED (Wiley)	27/08/2014	23
Health Technology Asessment Database	14/01/2015	0

Table 15: Economic search strategy

Database: Cochrane – NHS EED
Strategy used: Search Name: GU LUTS - phosphodiesterase 5 inhibitors_27 08 2014 Date Run: 27/08/14 12:38:05.962 Description: ID Search Hits #1 MeSH descriptor: [Lower Urinary Tract Symptoms] explode all trees 1926 #2 (LUTS or LUTD):ti,ab,kw (Word variations have been searched) 282 #3 (Lower urinary tract near/4 (symptom* or disease* or disorder* or dysfunction*)):ti,ab,kw (Word variations have been searched) 814 #4 MeSH descriptor: [Prostatic Hyperplasia] this term only 1366 #5 (prostat* near/4 (benign or hyperplas* or enlarg* or hypertroph* or obstruct* or adenoma*)):ti,ab,kw (Word variations have been searched) 2061 #6 hyperplasia:ti,ab,kw 3030 #7 (BPH or BPH-LUTS):ti,ab,kw (Word variations have been searched) 857 #8 prostatism:ti,ab,kw (Word variations have been searched) 102 #9 MeSH descriptor: [Urinary Retention] this term only 282 #10 (retent* near/4 (chronic* or urin* or acute*)):ti,ab,kw (Word variations have been searched) 1381 #11 MeSH descriptor: [Urinary Bladder, Overactive] this term only 315 #12 MeSH descriptor: [Urinary Incontinence] this term only 870 #13 (urin* adj4 incontinen*):ti,ab,kw 0 #14 (residual* near/4 urin*):ti,ab,kw (Word variations have been searched) 577 #15 (storage near/4 symptom*):ti,ab,kw (Word variations have been searched) 76 #16 MeSH descriptor: [Enuresis] explode all trees 257 #17 enuresis:ti,ab,kw (Word variations have been searched) 596 #18 ((micturition or urin* or bladder or voiding) near/4 (disorder* or dysfunct* or symptom* or urgen* or incontinen*)):ti,ab,kw (Word variations have been searched) 5449 #19 (nocturia or pollakisuria or bedwett*):ti,ab,kw (Word variations have been searched)

Database: Cochrane – NHS EED

433
#20 ((weak* or overactiv* or over-activ* or obstruct* or incomplet* or impair* or irritabl*) near/4 (bladder* or detrusor*)):ti,ab,kw (Word variations have been searched) 1492
#21 (post near/4 micturition near/4 dribbl*):ti,ab,kw (Word variations have been searched) 5
#22 (haematuria or hematuria):ti,ab,kw (Word variations have been searched) 674
#23 (male or man or men):ti,ab,kw (Word variations have been searched) 389847
#24 #1 or #2 or #3 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 8536
#25 #23 and #24 4333
#26 #4 or #5 or #6 or #7 or #8 or #25 6579
#27 MeSH descriptor: [Phosphodiesterase 5 Inhibitors] this term only 188
#28 phosphodiesterase 5 inhibitor*:ti,ab,kw (Word variations have been searched) 888
#29 (pde 5 or pde5 or pde-5):ti,ab,kw (Word variations have been searched) 257
#30 (pde v or pdev or pde-v):ti,ab,kw 29
#31 MeSH descriptor: [Phosphodiesterase Inhibitors] this term only 777
#32 (Phosphodiesteras* near/4 Inhibitor*):ti,ab,kw 1324
#33 MeSH descriptor: [Piperazines] this term only 2771
#34 MeSH descriptor: [Carbolines] this term only 239
#35 (piperazine* or carboline*):ti,ab,kw (Word variations have been searched) 3185
#36 (tadalafil* or sildenafil* or vardenafil* or avanafil*):ti,ab,kw (Word variations have been searched) 1186
#37 (cialis or nipatra or viagra or revatio or spedra or levitra):ti,ab,kw (Word variations have been searched) 155
#38 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 4307
#39 #26 and #38 130

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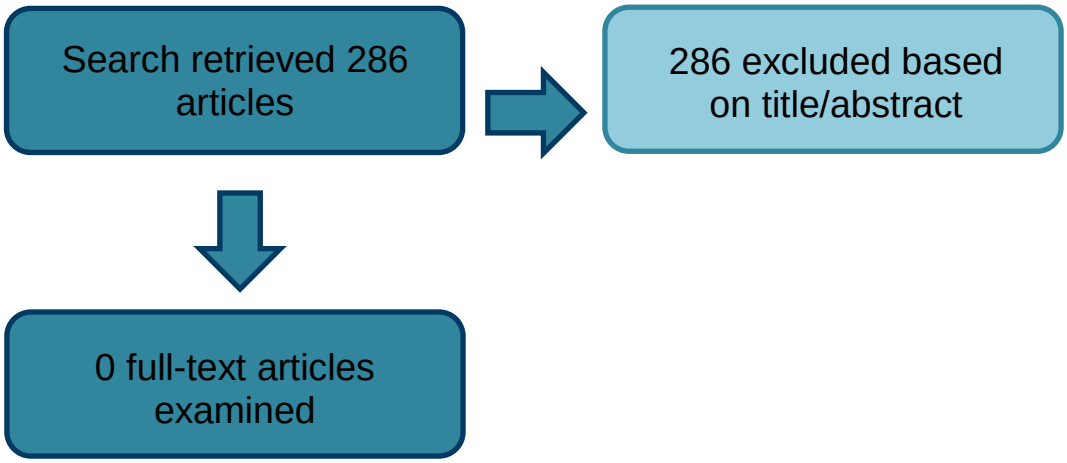
Appendix K: Economic review flowchart



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