INTRODUCTION

- Benign prostatic hyperplasia (BPH), characterized by an increase in the size of prostate, involves the proliferation of epithelial and stromal cells of the prostate gland.
- Symptoms of BPH begin to appear as early as age 40 years. An estimated 50% men have BPH by the age of 60 years and 90% men by age 85 years.
- Tadalafil, an oral, potent selective phosphodiesterase type 5 inhibitor, is approved for the treatment of BPH in men with/without erectile dysfunction (ED).3 4
- To the best of our knowledge, no systematic review has evaluated the adverse events (AEs) associated with use of tadalafil in clinical trials.

OBJECTIVE

- The aim of this systematic review was to identify AEs occurring in the randomized controlled trials (RCTs) of tadalafil in patients with BPH.

METHODS

- PubMed, EMBASE, Cochrane Library, and Google Scholar databases were searched, from inception to August 2014, for RCTs comparing tadalafil with placebo or active comparators for the treatment of BPH with/without ED.
- Search terms included “Benign prostatic hyperplasia,” “benign enlargement of prostate,” “adenofibromyomatous hyperplasia,” benign prostatic hypertrophy,” “lower urinary tract symptom,” and “tadalafil.”
- The selection of study for inclusion was based on a pre-specified protocol with the following inclusion criteria:
  - Population: Adults (aged ≥40) with BPH as defined by international prostate symptom score or maximum urinary flow rate
  - Exclusion criteria were suspected or confirmed prostate cancer, surgery of the prostate, urethra and bladder.
  - Intervention: Tadalafil (5 mg/day) as a single therapy
  - Comparators: Placebo or any approved intervention for BPH
  - Outcomes: Any AE
  - All retrieved articles were assessed for the inclusion or exclusion by two independent reviewer, and disagreements between them were resolved through discussion.
  - Two independent reviewer extracted the data (including study sample size, AEs, withdrawals due to AEs etc.) in a customized spreadsheet; any disagreement was resolved by a third independent reviewer.
  - Cochrane risk bias assessment tool was used to assess bias.
  - Data analysis: descriptive and quantitative data synthesis was performed for AEs when appropriate. Meta-analysis was performed using STATA® SE11.2 and results were presented as risk ratios (RR) and associated 95% confidence interval (CI).

RESULTS

- A total of 157 articles were screened, of which 10 RCTs (12 publications; 4,356 patients) met the inclusion criteria. Figure 1 presents the flow of studies according to PRISMA guidelines.
- The risk of bias was low across the included studies.
- In 7 studies, tadalafil was compared with placebo. In 3 studies, it was compared with tamsulosin along with placebo (Table 1).

Table 1. List of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Comparator</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brock G, et al. 2013</td>
<td>1599</td>
<td>Placebo</td>
<td>BJU Int. 112: 920-7</td>
</tr>
<tr>
<td>Giannouli F, et al. 2013</td>
<td>511</td>
<td>Placebo</td>
<td>Eur Urol. 64: 917-20</td>
</tr>
<tr>
<td>Onkela M, et al. 2014</td>
<td>301</td>
<td>Placebo</td>
<td>Urology. 88: 917-20</td>
</tr>
</tbody>
</table>

- Among the included RCTs, headache, backache, dyspepsia, myalgia, nasopharyngitis, and pain in extremity were the most common AEs, and were selected for a direct comparison assessing the comparative safety of tadalafil.

DISCUSSION

- As compared to placebo, tadalafil was associated with a significantly higher incidence of all analyzed AEs except nasopharyngitis (Fig. 2).
- Significant differences were not observed for incidence of any AEs between monotherapy of tadalafil and tamsulosin (0.2-0.4 mg/day) (Fig. 3).
- This systematic review and meta-analysis of RCTs suggested that tadalafil is a safe option when used in BPH patients at the approved dose without any concerning AE.
- Direct meta-analysis comparing tadalafil to other approved BPH interventions, except tamsulosin, was not possible due to lack of head-to-head RCTs. Further analysis using indirect or mixed treatment studies is warranted.

REFERENCES