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Comparative Effectivenes of Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: A Systematic Review and Meta-analysis

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Abstract

Context: Alpha-blockers (ABs) and 5-alpha reductase inhibitors have an established role in treating male lower urinary tract symptoms (LUTS) attributed to benign prostatic hyperplasia (BPH). Recently, newer drugs have shown promise for this indication.
Objective: To assess the comparative effectiveness and adverse effects (AEs) of newer drugs to treat LUTS attributed to BPH through a systematic review and meta-analysis.
Evidence acquisition: Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and Ovid Embase bibliographic databases (through June 2016) were hand searches for references of relevant studies. Eligible studies included randomized controlled trials published in English of newer ABs, antimuscarinics, a beta-3 adrenoceptor agonist, phosphodiesterase type-5 inhibitors, or combination therapy with one of these medications as an active comparator. Observational studies of the same agents with a duration $\geq$1 yr that reported AEs were also included.
Evidence synthesis: We synthesized evidence from 43 randomized controlled trials as well as five observational studies. Based on improvement of mean International Prostate Symptom Score and quality of life scores, the effectiveness of the newer ABs was not different from the older ABs (moderate strength of evidence [SOE]), but had more AEs (low SOE). Antimuscarinics/AB combination therapy had similar outcomes as AB monotherapy (all moderate SOE), but often had more AEs. Phosphodiesterase type-5 inhibitors alone or in combination with ABs had similar or inferior outcomes than ABs alone. Evidence was insufficient for the beta-3 adrenoceptor agonist. For all newer agents, the evidence was generally insufficient to assess long-term efficacy, prevention of symptom progression, or AEs.
Conclusions: None of the drugs or drug combinations newly used to treat LUTS attributed to BPH showed outcomes superior to traditional AB treatment. Given the lack of superior outcomes, the studies' short time-horizon, and less assurance of their safety, their current value in treating LUTS attributable to BPH appears low.
Patient summary: In this paper, we reviewed the evidence of newer drugs to treat men with urinary problems attributable to an enlarged prostate. We found none of the new drugs to be better but there was more concern about side effects.

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1. Introduction

Alpha-blockers (ABs) and 5-alpha reductase inhibitors (5-ARIs) have an established role in treating lower urinary tract syptoms (LUTS) attributed to benign prostatic hyperplasia (BPH) [1–6]. Recently, a new AB and drugs in other classes approved for different indications have shown promise in this setting. The purpose of our review was to determine the comparative effectiveness and safety of medications newly used in the last 10 yr for LUTS attributed to BPH, both as single agents and in combination.

2. Evidence acquisition

2.1. Protocol

We developed an a priori written protocol, together with a technical report that incorporated input from key stakeholders, a multidisciplinary Technical Expert Panel, and public comment (available at the Agency for Healthcare Research and Quality [AHRQ] website http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=2067&pageaction=displayproduct).

2.2. Eligibility criteria

Based on our Population, Interventions, Comparisons, Outcomes, Timing, and Setting criteria (Supplementary data) we included randomized controlled trials (RCTs) that tested comparative effectiveness of treatments involving newer drugs in men aged ≥45 yr with LUTS attributed to BPH. We defined these newer drugs as those that were Food and Drug Administration (FDA) approved for BPH since 2008 or which, though not FDA approved for BPH, have been studied for the treatment of BPH since 2008 and were selected through a formal process of stakeholder involvement (Supplementary data). Comparators included medications FDA approved for BPH before 2008. Included RCTs were at least 1 mo in duration with no minimum sample size. We additionally searched for large ($n \geq 100$ patients), longer-term (≥ 1 yr duration) observational studies to assess long-term or rare treatment associated harms only. We limited inclusion to English language articles.

The primary predefined outcomes of interest were changes reflecting clinically important differences (Supplementary data) in validated measures to assess LUTS (International Prostate Symptom Score [I-PSS]: score ranges 0–35 with higher scores indicating more severe symptoms; or American Urological Association Symptom Index scores), prostate-related bother or quality of life (QoL; I-PSS QoL question; BPH/LUTS impact scale), as well as rates of disease progression and/or treatment failure (prevention/delay of need for surgical intervention; acute urinary retention [AUR]). We also assessed common and serious medication adverse effects (AEs).

2.3. Information sources and literature search

We searched Ovid Medline, Ovid Embase, and the Cochrane Central Register of Controlled Trials with filters for study design (Supplementary data), to identify relevant RCTs published through June 20, 2016. We also searched for relevant systematic reviews and other key references. Lastly, we searched the Clinical Trials (www.clinicaltrials.gov) and the FDA (www.fda.gov/Drugs) websites to identify additional completed and ongoing studies.

2.4. Study selection process, data extraction, and risk of bias in studies

Two independent investigators screened titles and abstracts to identify studies meeting the eligibility criteria. Data were extracted by one investigator and reviewed and verified for accuracy by a second investigator. Risk of bias (RoB) of eligible studies was assessed using AHRQ guidance by one investigator and reviewed by a second [7].

2.5. Synthesis of results

We assessed clinical and methodological heterogeneity and variation in effect size to determine the appropriateness of pooling data [8]. When three or more trials reported similar comparisons and outcomes, data were pooled using a Hartung, Knapp, Sidik, and Jonkman method [9] random effects model for proportion of I-PSS responders or mean changes in I-PSS scores in Stata (StataCorp., College Station, TX, USA). We pooled other outcomes in RevMan (RevMan, Spartanburg, SC, USA) [10] and converted DerSimonian-Laird random effects confidence intervals to Hartung, Knapp, Sidik, and Jonkman confidence intervals using an excel spreadsheet provided in Inthout et al [9]. We assessed between study variance with Tau^2 and measured the magnitude of heterogeneity with the I^2 statistic. If substantial heterogeneity was present (ie, $I^2 \geq 70\%$), we stratified the results to assess treatment effects based on patient or study characteristics and/or explored sensitivity analyses [8,11]. We pooled across different ABs unless there were at least three trials for a given agent. We interpreted efficacy and comparative effectiveness using established thresholds indicating clinical significance (Supplementary data).

For the body of evidence from RCTs, we rated our confidence in the estimates of effect for the primary outcomes as overall strength of evidence (SOE) as high, moderate, low, or insufficient (Supplementary data) [12]. For observational studies, we did not formally assess SOE, but provided descriptive information in narrative form.

3. Evidence synthesis

3.1. Search results

Our literature search identified 1139 references, of which 124 were selected for full-text review (Fig. 1). This process mapped to 43 unique RCTs. In addition, we

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