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Platinum Priority – Review – Voiding Dysfunction

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Medical Treatment of Nocturia in Men with Lower Urinary Tract Symptoms: Systematic Review by the European Association of Urology Guidelines Panel for Male Lower Urinary Tract Symptoms

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Abstract

Context: The treatment of nocturia is a key challenge due to the multi-factorial pathophysiology of the symptom and the disparate outcome measures used in research.
Objective: To assess and compare available therapy options for nocturia, in terms of symptom severity and quality of life.
Evidence acquisition: Medical databases (Embase, Medline, Cochrane Systematic Reviews, Cochrane Central) were searched with no date restriction. Comparative studies were included which studied adult men with nocturia as the primary presentation and lower urinary tract symptoms including nocturia or nocturnal polyuria. Outcomes were symptom severity, quality of life, and harms.
Evidence synthesis: We identified 44 articles. Antidiuretic therapy using dose titration was more effective than placebo in relation to nocturnal voiding frequency and duration of undisturbed sleep; baseline serum sodium is a key selection criterion. Screening for hyponatremia (< 130 mmol/l) must be undertaken at baseline, after initiation or dose titration, and during treatment. Medications to treat lower urinary tract dysfunction (α-1 adrenergic antagonists, 5-α reductase inhibitors, phosphodiesterase type 5inhibitor, antimuscarinics, beta-3 agonist, and phytotherapy) were generally not significantly better than placebo in short-term use. Benefits with combination therapies were not consistently observed. Other medications (diuretics, agents to promote sleep, nonsteroidal anti-inflammatories) were sometimes associated with response or quality of life improvement. The recommendations of the Guideline Panel are presented.

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Conclusions: Issues of trial design make therapy of nocturia a challenging topic. The range of contributory factors relevant in nocturia makes it desirable to identify predictors of response to guide therapy. Consistent responses were reported for titrated antidiuretic therapy. For other therapies, responses were less certain, and potentially of limited clinical benefit.
Patient summary: This review provides an overview of the current drug treatments of nocturia, which is the need to wake at night to pass urine. The symptom can be caused by several different medical conditions, and measuring its severity and impact varies in separate research studies. No single treatment deals with the symptom in all contexts, and careful assessment is essential to make suitable treatment selection.

1. Introduction

Nocturia is defined by the International Continence Society (ICS) as the complaint that an individual has to wake at night one or more times to void [1]. It reflects the relationship between the amount of urine produced while asleep, and the storage by the bladder of urine received. Nocturia can occur as part of lower urinary tract dysfunction (LUTD), notably in overactive bladder syndrome (OAB). Nocturia can also occur in association with other forms of LUTD, such as bladder outlet obstruction or chronic pelvic pain syndrome. Nocturia is a feature of systemic conditions affecting water and salt balance [2], leading to excessive production of urine at all times (global polyuria) or primarily at night (nocturnal polyuria), so that nocturia can be a systemic symptom [3,4]. For example, cardiovascular, endocrine, and renal disease can affect water and salt homeostasis [5], leading to increased rate of urine production.

Summarizing the causative categories for nocturia, the International Consultation on Male Lower Urinary Tract symptoms (LUTS) [6] listed:

1. Bladder storage problems;
2. 24-h (global) polyuria (> 40 ml/kg urine output over a 24-h period);
3. Nocturnal polyuria (nocturnal output exceeding 20% of 24-h urine output in younger patients, or 33% of urine output in people aged over 65 yr [1]);
4. Sleep disorders;
5. Mixed etiology.

Thus, the treatment of nocturia is potentially complex, and was identified by the European Association of Urology Guidelines Panel for Male non-neurogenic LUTS as a key challenge. The aim of the current systematic review of treatment was to assess and compare available therapy options for nocturia, in terms of symptom severity and quality of life. The review focusses on men, in view of the differing lower urinary tract anatomy and medication options available compared with women.

2. Evidence acquisition

The objectives were to determine the relative benefits and harms of treatment options for nocturia, and to perform subgroup and/or sensitivity analysis.

The Embase, Medline, Cochrane Systematic Reviews, and Cochrane Central (Cochrane Health Technology Assessment, Database of Abstracts of Reviews of Effects, Health Economics Evaluations Database) were searched with no restriction on date of publication (date of final search September 2016). The search strategy was registered on PROSPERO on October 21, 2015 (http://dx.doi.org/10.15124/CRD42015027092). Comparative studies were included (randomized controlled trials [RCTs], and nonrandomized comparative studies [both prospective and retrospective, interventional, or observational]), studying adult men (male-only or mixed sex populations), with nocturia or nocturnal polyuria as a primary outcome, categorized within the following symptom groups:

1. Nocturia (ICS definition [7], or as defined by trialist) as the primary presentation (ie, nocturia as the predominant bothersome symptom);
2. Nocturia as a secondary component of LUTS (ie, LUTS including nocturia);
3. Nocturnal polyuria (ICS definition [7], or alternative definition if stated by the investigating group).

Interventions included: anticholinergics, mirabegron, α-blockers, 5-α reductase inhibitors, oral phosphodiesterase-5 inhibitors, desmopressin, diuretics, sleep-promoting agents, and phytotherapy. Comparator controls were: no treatment, placebo, and alternative experimental treatment.

The primary outcomes were:

- Symptom severity for nocturia (outcome measure defined as < 2 episodes, or cure [ie, no episodes of nocturia] or reduction in nocturia episodes, or as defined by trialist);
- Quality of life for nocturia.

The secondary outcomes were:

- Harms: adverse events of treatment and events leading to potential harm (eg, hyponatremia, voiding difficulties), withdrawal, or drop-out rates;
- Any other outcomes judged relevant by reviewer.

Two review authors independently screened the titles and abstracts of identified records, and the full text of potentially eligible records was evaluated using a standardized form. Risk of bias was assessed, including: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. A list of potential confounders was

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