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Anticholinergic Drugs for Adult Neurogenic Detrusor Overactivity: A Systematic Review and Meta-analysis

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Abstract

Context: There is a lack of evidence about the efficacy and safety of anticholinergic drugs and about the optimal anticholinergic drug, if any, for the treatment of adult neurogenic detrusor overactivity (NDO).
Objective: Review the current evidence on the efficacy, safety, and tolerability of anticholinergic drugs in the treatment of adult NDO.
Evidence acquisition: A literature search was conducted from 1966 to May 2011. Meta-analysis of all published randomised controlled trials (RCTs) comparing anticholinergic drugs with placebo and comparing different types, doses, and routes of administration of anticholinergic drugs, in adults with NDO, was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. The primary outcome was patient-reported cure/improvement of overactive bladder symptoms. Secondary outcomes were quality of life (QoL) changes, bladder diary events, urodynamic outcomes, adverse events, and costs to health services.
Evidence synthesis: A total of 960 patients from 16 RCTs with mean follow-up of 3.8 wk were included. Anticholinergic drugs were associated with statistically significantly better patient-reported cure/improvement (risk ratio: 2.80; 95% confidence interval [CI], 1.64 to 4.77), higher maximum cystometric capacity (weighted mean difference [WMD]: 49.49; 95% CI, 15.38 to 84.20), higher volume at first contraction (WMD: 49.92; 95% CI, 20.06 to 79.78), and lower maximum detrusor pressure (WMD: −38.30; 95% CI, −53.17 to −23.43) when compared with placebo. The dry-mouth rates were statistically significantly higher with anticholinergics, with no difference in withdrawals because of adverse events. There was no statistically significant difference in any of the outcomes between oxybutynin and other anticholinergics or among different doses and preparations of anticholinergic drugs. No study reported QoL changes or costs to health services.
Conclusions: Compared with placebo, anticholinergic treatment in patients with NDO is associated with better patient-reported cure/improvement and significant reduction of maximum detrusor pressure; however, there is a higher incidence of adverse events. None of the anticholinergic drugs or different dosages assessed in this review was superior to another.

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1. Introduction

Neurogenic detrusor overactivity (NDO) is defined as urodynamic observation of involuntary detrusor contraction(s) during the bladder-filling phase, which may be spontaneous or provoked, due to an underlying relevant neurologic condition. The term *NDO* replaced the previous term *detrusor hyperreflexia* [1]. Patients with NDO are a heterogeneous

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group with different underlying neurologic conditions, such as Parkinson disease, cerebral palsy, multiple sclerosis, spinal cord injury, and meningomyelocele [2]. Symptoms of NDO include urinary frequency, urgency, and urgency urinary incontinence or urinary incontinence episodes that are not associated with urgency or any other sensation related to bladder filling. NDO can lead to elevation of the intravesical pressure at the filling phase and/or vesicoureteric reflux, both of which, in the long term, can lead to serious deterioration in a patient's renal function. Hence, the main objectives for current strategies in the treatment of NDO are (1) protection of the upper urinary tract, (2) improvement of urinary continence, (3) restoration of the lower urinary tract function (or parts of it), and (4) improvement in the patient's quality of life (QoL) [3].

Conservative treatment options currently available for patients with NDO include (1) assisted bladder emptying and/or intermittent self-catheterisation and (2) drug treatment, including anticholinergic drugs, phosphodiesterase inhibitors, and intravesical drug treatment with anticholinergic preparations, vanilloids, capsaicin, or resiniferatoxin [3]. Surgical treatment options in unresponsive cases include detrusor myectomy, sacral rhizotomy, bladder augmentation, and urinary diversion as a last surgical resort [3]. Recently, sacral nerve stimulation and intradetrusor botulinum toxin injections have provided an effective alternative to surgery for patients with NDO refractory to conservative and medical treatment. Unfortunately, some patients do not respond to, or are medically unfit for, a number of or all the treatment options discussed and use containment methods such as permanent catheters, condoms, or incontinence pads.

Anticholinergic treatment is currently the mainstay conservative treatment of NDO [2,3]. The mode of action of anticholinergic drugs is unclear; however, it is believed that the drugs reduce detrusor overactivity and make it moderately refractory to parasympathetic stimulation by blocking the muscarinic receptors. This action results in improved bladder compliance and reduced symptoms of overactive bladder (OAB) [3–5], which in turn helps to prevent renal and bladder damage and improve the patient's QoL [3]. There are different types and brands of anticholinergic drugs: flavoxate, oxybutynin, propantheline, propiverine, tolterodine, trospium, solifenacin, darifenacin, and fesoterodine. Currently, there is a clear lack of evidence in the medical literature about the efficacy and safety of anticholinergic drugs in treating urologic symptoms and enhancing QoL in patients with NDO. To our knowledge, this study is the first meta-analysis of randomised controlled trials (RCTs) to assess the efficacy, safety, and tolerability of (1) anticholinergic drugs compared with placebo, (2) one type of anticholinergic drug compared with another type of anticholinergic drug, (3) different doses and preparation of the same anticholinergic drug, and (4) different routes of administration of anticholinergic drugs in patients with NDO.

2. Evidence acquisition

A prospective peer-reviewed protocol was prepared a priori. Meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [6]. Eligible for inclusion were all published randomised or quasi-randomised controlled trials comparing (1) an anticholinergic drug with placebo, (2) one anticholinergic drug with another anticholinergic drug, (3) different doses and preparation of the same anticholinergic drug, and (4) different routes of anticholinergic drug administration in adults with NDO. Trials involving children and patients with idiopathic detrusor overactivity were excluded. There were no exclusion criteria based on language or publication status. Studies were identified through Medline, Embase, the Cochrane incontinence specialised trials register, ClinicalTrials.gov, and the International Urogynaecological Association/International Continence Society conference abstract databases from 1966 to May 2011. A literature search was performed independently in May 2011 by two authors (M.S. and H.Z.) using the search terms *urinary incontinence/neurogenic detrusor overactivity/neurogenic bladder/overactive bladder/detrusor hyperreflexia/multiple sclerosis/spinal cord injury/anticholinergic/antimuscarinics/muscarinic antagonists*. All titles were screened, and studies were excluded if obviously irrelevant. If there was any doubt concerning the eligibility of a study, abstracts—and if necessary, the full text—were examined. Data were extracted independently by two authors (M.S. and H.Z.). Any difference in study inclusion or data extraction was resolved by opinion from senior authors (P.M. and M.A.F.). Authors were contacted if supplementary data were required, and articles were translated into English if indicated.

Primary outcome measures were clinical cure or improvement of OAB symptoms with anticholinergic drugs compared with placebo, between different anticholinergic drugs, or between different doses/routes of administration of the same anticholinergic drug. Clinical cure/improvement was assessed for both patient-reported cure and objective cure. For the purpose of this review, we defined *objective cure* as absence of detrusor overactivity, increase in compliance to $\geq$20 ml/cm H_20, increase in maximum cystometric capacity to >250 ml, and decrease in maximum detrusor pressure $\leq$40 cm H_20 at the end of treatment. Secondary outcomes included (1) bladder diary (urinary frequency episodes per 24 h, urgency episodes per 24 h, incontinence episodes per 24 h), (2) urodynamic outcomes (maximum cystometric capacity, volume at first detrusor contraction, maximum detrusor pressure, compliance, number of detrusor contractions, residual volume), (3) impact on the patient's QoL, (4) adverse events, and (5) health economic measures.

Data were analysed using Review Manager 5 (Cochrane Collaboration, Oxford, UK); risk ratio (RR) and weighted mean difference (WMD) were used as summary measures. Methodological heterogeneity was assessed during the selection, and statistical heterogeneity was measured using the chi-square test and I^2 scores. A random effect model [7] was used throughout to reduce the effect of statistical heterogeneity. Risk of bias across studies was assessed using risk of bias tables generated through Review Manager. Sensitivity analysis was performed by excluding studies