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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

with unclear quality. Funnel plots were not used to measure publication bias because of the small number of studies and their similar sizes.

3. Evidence synthesis

Figure 1 describes the literature search outcome. Sixteen RCTs were included, with a total of 960 patients (485 men and 372 women; one study did not mention sex distribution) (Table 1), comparing anticholinergic drugs and placebo (eight RCTs; $n = 390$), one anticholinergic drug compared with another (five RCTs; $n = 358$), different doses and formulation of the same anticholinergic drug (five RCTs; $n = 384$), and different routes of administration of the same anticholinergic drug (three RCTs; $n = 84$). Ten studies were excluded [24–33]; reasons for exclusion are listed in Table 2. A total of 98 patients were lost to follow-up. The mean age was 38.5 yr, and the mean follow-up was 3.8 wk. One study was translated from German [17].

3.1. Comparison of anticholinergic drugs and placebo

Eight studies compared different anticholinergic drugs with placebo [8–12,19,20,23]. A total of 390 patients were included; 21 patients were lost to follow-up. Mean age was comparable in both groups (33.1 and 39.7 yr). Mean follow-up was 3 wk in both groups.

3.1.1. Cure or improvement

Only one study reported patient-reported cure/improvement [20]; a statistically significantly better cure/improvement was seen in the anticholinergic drug group compared with placebo at 2 wk (RR: 2.80; 95% confidence interval [CI], 1.64 to 4.77; anticholinergic 63% vs placebo 22%) (Fig. 2a). None of the studies assessed objective cure or the impact on patients' QoL.

3.1.2. Bladder diary

One study [23] reported no statistically significant difference in frequency of micturition (WMD: 0.00; 95% CI, −0.99 to 0.99) (Fig. 2b) and mean change in incontinence episodes per 24 h (WMD: −0.50; 95% CI, −2.48 to 1.48) (Fig. 2c) from baseline between the groups.

3.1.3. Urodynamic outcomes

Meta-analysis of three studies [8,20,23] showed a statistically significantly higher maximum cystometric capacity (WMD: 49.79; 95% CI, 15.38 to 84.20) (Fig. 2d), higher mean volume at first contraction (WMD: 49.92; 95% CI, 20.06 to 79.78) (Fig. 2e), and lower detrusor pressure at highest contraction

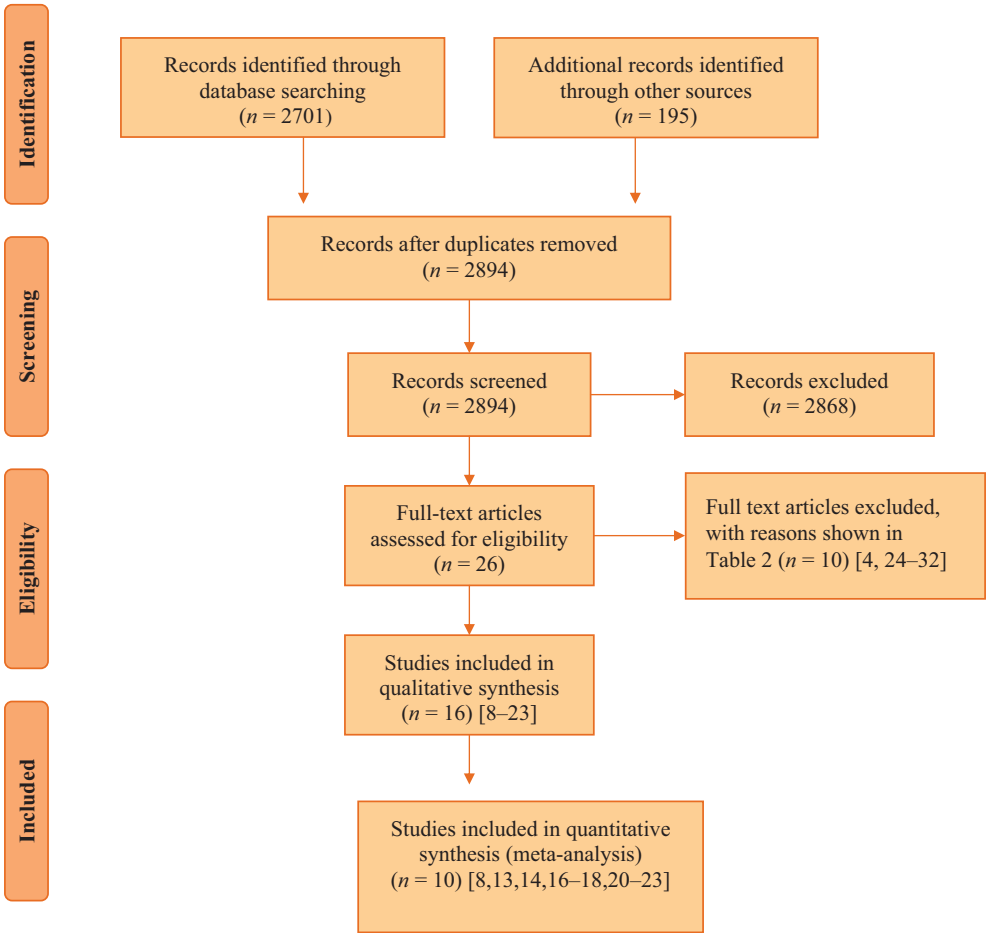


Fig. 1 – PRISMA flow diagram.

(one study only [20]; WMD: −38.30; 95% CI, −53.17 to −23.43) (Fig. 2f) in the anticholinergic drugs group compared with placebo, while there was no evidence of a statistically significant difference in bladder compliance (WMD: 9.46; 95% CI, −5.22 to 24.13) (Fig. 2g) or postvoiding residual volume (WMD: 26.75; 95% CI, −1.00 to 54.49) (Fig. 2h).

3.1.4. Adverse events

Meta-analysis of three studies [8,20,23] showed statistically significantly higher dry mouth with anticholinergic drugs compared with placebo (RR: 4.23; 95% CI, 1.85 to 9.67; anticholinergic 32% vs placebo 7%) (Fig. 2i). There was no statistically significant difference in any other reported adverse events (Fig. 2i). One study [20] reported withdrawals because of adverse events; there was no statistically significant difference in withdrawals because of adverse events between the groups (RR: 4.42; 95% CI, 0.53 to 36.61; anticholinergic 8% vs placebo 2%) (Fig. 2j).

3.2. Comparison of one type of anticholinergic with another

Four studies [13,14,16,21] compared different anticholinergic drugs with immediate-release (IR) oxybutynin. One study [15] compared methantheline bromide, flavoxate, and meladrazine but reported no useable data for this analysis. A total of 358 patients were included; 66 patients were lost to follow-up. The mean ages of both the groups were comparable (34.5 and 35.8 yr). Mean follow-up was 4 wk.

3.2.1. Cure or improvement

One study reported patient-reported cure/improvement [14] and showed no statistically significant difference between the two groups at 8 wk (RR: 0.57; 95% CI, 0.28 to 1.14; other 45% vs oxybutynin 80%) (Fig. 3a). No study assessed objective cure. One study [13] assessed QoL but reported no data for analysis.

3.2.2. Bladder diary

Meta-analysis of two studies [13,21] showed no evidence of statistically significant difference in frequency of micturition (RR: −0.40; 95% CI, −1.00 to 0.20) (Fig. 3b) or incontinence episodes per 24 h (RR: −0.11; 95% CI, −0.59 to 0.38) (Fig. 3c) between the two groups.

3.2.3. Urodynamic outcomes

Meta-analysis of three studies [14,16,21] showed no evidence of statistically significant differences in maximum cystometric capacity (WMD: −23.22; 95% CI, −69.00 to 22.57) (Fig. 3d), maximum detrusor pressure (WMD: 2.97; 95% CI, −7.17 to 13.11) (Fig. 3e), or postvoiding residual volume (WMD: −15.07; 95% CI, −63.49 to −33.36) (Fig. 3f) between oxybutynin and other anticholinergic drugs.

3.2.4. Adverse events

Meta-analysis of three studies [13,16,21] showed no statistically significant difference in dry mouth (RR: 0.60; 95% CI, 0.32 to 1.10; other drug 39% vs oxybutynin 63%), other adverse events (Fig. 3g), or withdrawals because of adverse events (RR: 1.08; 95% CI, 0.30 to 3.91; other drug 9% vs oxybutynin 8%) (Fig. 3h).

3.3. Comparison of different doses of same anticholinergic preparation: different doses of tolterodine

Two studies [8,23] compared different doses of IR tolterodine (n = 172); there was no loss to follow-up (mean follow-up: 2 wk). For the purpose of this review, we compared the standard 4-mg dose (2 mg twice daily) to 1 mg, 2 mg, and 8 mg of IR tolterodine. None of the studies reported patient-reported cure/improvement, objective cure, or impact on patients' QoL.

3.3.1. Bladder diary

One study [23] reported change in frequency of micturition and change in incontinence episodes per 24 h from baseline. There was no statistically significant difference when 4 mg was compared with 1 mg (WMD: 0.3; 95% CI, −0.74 to 1.34), 2 mg (WMD: −0.30; 95% CI, −1.66 to 1.06), or 8 mg (WMD: −0.20; 95% CI, −1.60 to 1.20).

3.3.2. Urodynamic outcomes

Meta-analysis [8,23] showed no statistically significant difference in maximum cystometric capacity and residual urine volume when 4 mg was compared with 1 and 2 mg tolterodine; however, both parameters were significantly increased with the 8-mg preparation compared with the 4-mg preparation (WMD: 73.7; 95% CI, 3.23 to 144.22 and WMD: 83.35; 95% CI, 2.52 to 164.19, respectively). There was no statistically significant difference in volume at first contraction or number of detrusor contractions between the doses.

3.3.3. Adverse events

Meta-analysis of two studies [8,23] showed no significant difference in dry mouth when 4 mg was compared with 1 mg (RR: 0.49; 95% CI, 0.17 to 1.45; 1 mg 9% vs 4 mg 23%), 2 mg (RR: 0.47; 95% CI, 0.15 to 1.44; 2 mg 10% vs 4 mg 23%), and 8 mg (RR: 1.1; 95% CI, 0.40 to 2.53; 8 mg 22% vs 4 mg 23%). Withdrawals because of adverse events were not reported.

3.4. Comparison of different doses of same anticholinergic preparation: different doses of trospium

One study [18] compared a standard dose of 45 mg of oral IR trospium with an adjustable dose (90–135 mg). A total of 80 men and women were included; 7 patients were lost to follow-up. Mean ages of both the groups were comparable (36 yr for both standard dose and adjustable dose). The follow-up was 3–5 wk. Patient-reported cure or improvement, objective cure, QoL, and symptoms were not reported.

3.4.1. Urodynamic outcomes

There was no statistically significant difference in the mean change in maximum cystometric capacity (mean difference [MD]: −45.00; 95% CI, −110 to 20.58), maximum detrusor pressure (MD: 13; 95% CI, −0.58 to 26.58), or

Table 1 – Summary of characteristics of included studies

Study	Design	Participants	Intervention	Duration of treatment	Outcome
Abrams et al. [8]	Randomised, multicentre, UK, abstract	82 patients with objective signs of neurologic disease and with urinary frequency or incontinence and urodynamically proven detrusor hyperreflexia (no loss to follow-up)	Gr 1: tolterodine 0.5 mg bid, po (n = 12) Gr 2: tolterodine 1 mg bid, po (n = 14) Gr 3: tolterodine 2 mg bid, po (n = 16) Gr 4: tolterodine 4 mg bid, po (n = 10) Gr 5: placebo po (n = 15)	2 wk	Micturition frequency and volume, number of incontinence episodes, urodynamic parameters, number and height of unstable waves, volume at first contraction, cystometric capacity, compliance, bladder sensation, maximum urinary flow with associated detrusor pressure and residual volume, side effects
Bycroft et al. [9]	Randomised, Germany, abstract	8 men following spinal injury (thoracic- and cervical-level injury) (no loss to follow-up)	Gr 1: darifenacin 6 mg intravesical in 5% mannitol (n = 8) Gr 2: placebo in 5% mannitol intravesical (n = 8)	Single dose	Volume at first unstable contraction, unstable provoked bladder contraction
Di Stasi et al. [10]	Randomised, single centre, Italy	10 men and women with spinal cord injury of American Spinal Injury Association Impairment Scale A and with CISC and detrusor hyperreflexia (no loss to follow-up)	Gr 1: oxybutynin 5 mg od, po (n = 10) Gr 2: oxybutynin 5 mg intravesical with passive diffusion for 60 min (n = 10) Gr 3: oxybutynin 5 mg intravesical with electromotive diffusion for 30 min (n = 10) Gr 4: 0.9% saline intravesical with passive diffusion (n = 10) Gr 5: 0.9% saline intravesical with electromotive diffusion (n = 10) Gr 6: placebo po (n = 10)	Single dose	8-h urodynamic monitoring of change in uninhibited detrusor contraction, maximum amplitude of detrusor contraction, change in residual volume, number of urinary leakage episodes during 8-h monitoring period, peak plasma concentration of oxybutynin between different methods of administration, adverse outcome
Di Stasi et al. [11]	Randomised, single centre, Italy	12 men and women with spinal cord injury of American Spinal Injury Association Impairment Scale A and with CISC and detrusor hyperreflexia (no loss to follow-up)	Gr 1: oxybutynin 5 mg od, po (n = 12) Gr 2: oxybutynin 15 mg intravesical with passive diffusion (n = 12) Gr 3: oxybutynin 15 mg intravesical electromotive diffusion (n = 12) Gr 4: 0.9% saline intravesical with passive diffusion (n = 12) Gr 5: 0.9% saline with electromotive administration (n = 12) Gr 6: placebo po (n = 12)	Single dose	Uninhibited detrusor contraction, bladder compliance, following void residual volume, number of urinary leakage episodes, measurement of oxybutynin and N-desethyl-oxybutynin plasma level, measurement of intravesical oxybutynin uptake, side effects
Ethans et al. [12]	Randomised, single centre, Canada	14 men and women with NDO and urinary incontinence due to SCI or MS using CISC (4 lost to follow-up)	Gr 1: tolterodine 2 mg bid, po (n = 14) Gr 2: placebo po (n = 14)	4 wk	Bladder volume at first contraction, mean bladder catheterisation volumes, mean daily incontinence episodes, mouth dryness (VAS score)
Fader et al. [13]	Randomised, multicentre, UK, Australia	64 men and women with MS if they had benefit from using oral antimuscarinics for overactive bladder performing CISC (7 lost to follow-up)	Gr 1: atropine variable dose of 2 mg od to maximum of 6 mg qid intravesical (n = 57) Gr 2: oxybutynin 5 mg bid, po (n = 57)	5 wk	Bladder capacity, change in number of micturitions per unit time, change in incontinence events per unit time, health status measure: King's QoL measure, number of adverse events
Gajewski et al. [14]	Randomised, single centre, Canada	34 men and women with MS and symptoms of detrusor hyperreflexia and on urodynamics DO (8 lost to follow-up)	Gr 1: oxybutynin 5 mg tid, po (n = 19) Gr 2: propantheline 15 mg tid, po (n = 15)	6–8 wk	Subjective improvement in symptoms (frequency, urgency, nocturia, and urge incontinence), change in maximum cystometric capacity and height of contraction on the cystometrogram
Hebjorn et al. [15]	Randomised, single centre, Hellurp	34 men and women with MS and urologic symptoms due to detrusor hyperreflexia (2 lost to follow-up)	Gr 1: methantheline 50 mg po (n = 32) Gr 2: flavoxate 200 mg qid, po (n = 31) Gr 3: meladrazine 150 mg qid, po (n = 20)	6 wk	Residual urine, volume at first contraction, amplitude of first bladder contraction, urgency and urge incontinence

Madersbacher et al. [16]	Randomised, multicentre, Austria, Germany, Switzerland	95 men and women with spinal cord injuries and detrusor hyperreflexia (10 lost to follow-up)	Gr 1: trospium 20 mg bid, po (n = 52) Gr 2: oxybutynin 5 mg tid, po (n = 43)	2 wk	Urodynamic investigation before and after treatment on maximum cystometric bladder capacity, maximum voiding detrussor pressure, bladder compliance, residual urine, adverse effects
Mazur et al. [17]	Randomised, multicentre, Germany	66 men and women with reflex incontinence of neurogenic origin (posttraumatic, postoperative, with myelitis, myelodegenerative) (2 dropouts)	Gr 1: propiverine 15 mg/d, po (n = 14) Gr 2: propiverine 30 mg/d, po (n = 21) Gr 3: propiverine 45 mg/d, po (n = 17) Gr 4: propiverine 60 mg/d, po (n = 14)	3 wk	Bladder capacity at first desire to void, maximum bladder capacity, maximum detrusor pressure, bladder compliance, number of detrusor contractions, urinary diary frequency and voiding volume, side effects
Menarini et al. [18]	Randomised, multicentre, Argentina, Austria, Chile, Germany, Italy, Switzerland	80 men and women with traumatic spinal cord lesion between C2 and T12 (both complete and incomplete) with at least two of the following criteria: bladder compliance $\leq$20 cm H_2O, maximum cystometric capacity $\leq$250 ml, maximum detrusor pressure $\geq$40 cm H_2O (7 lost to follow-up)	Gr 1: trospium standard dose, 15 mg tid, po (n = 40) Gr 2: trospium adjustable dose, 90–135 mg, po (n = 36)	3–5 wk	Bladder compliance, maximum cystometric capacity, maximum detrusor pressure, safety and tolerability data, plasma level of trospium chloride tested on each day of urodynamic testing, patient's subjective rating of OAB symptoms and number of incontinence episodes
Stöhrer et al. [19]	Randomised, multicentre, Germany	61 men and women with spinal cord injury with detrusor hyperreflexia (6 lost to follow-up)	Gr 1: trospium 20 mg bid, po (n = 29) Gr 2: placebo bid, po (n = 32)	3 wk	Maximum cystometric capacity, maximum detrusor pressure, bladder compliance, maximum flow rate, residual urine, haematologic and biochemical parameters
Stöhrer et al. [20]	Randomised, multicentre, Germany	113 men and women with detrusor hyperreflexia and suprasacral spinal cord injury (11 lost to follow-up)	Gr 1: propiverine 15 mg tid, po (n = 60) Gr 2: placebo tid, po (n = 53)	2 wk	Maximum cystometric capacity, duration and amplitude of maximum detrusor contraction, bladder compliance, residual urine, subjective assessment of patient's clinical symptoms, physician's assessment of efficacy, adverse events, laboratory parameters
Stöhrer et al. [21]	Randomised, multicentre, Germany	131 men and women with traumatic spinal cord injury with complete and incomplete lesion, myelitis, MS, myelodysplasia, and spinal tumour with neurogenic detrusor overactivity confirmed urodynamically (40 lost to follow-up)	Gr 1: propiverine 15 mg tid, po (n = 70) Gr 2: oxybutynin 5 mg tid, po (n = 61)	3 wk	Maximum cystometric capacity, maximum detrusor pressure during filling phase, detrusor compliance, following void residual, frequency per 24 h, incontinence episodes per 24 h, mean volume voided per micturition, adverse effects
Stöhrer et al. [22]	Randomised, multicentre, Holland, Germany, Austria, abstract	66 men and women with spinal cord trauma, stroke, inflammation, and degenerative neurologic disease and proven neurogenic detrusor overactivity (no loss to follow-up)	Gr 1: propiverine extended release, 45 mg od, po (n = 33) Gr 2: propiverine immediate release 15 mg tid, po (n = 33)	3 wk	Change in reflex volume defined as urodynamically assessed volume at first uninhibited detrusor contraction, maximum detrusor pressure, bladder compliance, tolerability outcomes, adverse outcomes
Van Kerrebroeck et al. [23]	Randomised, multicentre, Netherlands, Germany, Austria, France	90 men and women randomised (no loss to follow-up) with objective evidence of neurologic disease (MS, paraplegia, quadriplegia, hemiplegia, spinal cord injury) with overactive bladder symptoms and urodynamically proven detrusor hyperreflexia (no loss to follow-up)	Gr 1: tolterodine 0.5 mg bid, po (n = 20) Gr 2: tolterodine 1 mg bid, po (n = 16) Gr 3: tolterodine 2 mg bid, po (n = 18) Gr 4: tolterodine 4 mg bid, po (n = 17) Gr 5: placebo (n = 19)	2 wk	Urodynamic variables, micturition diary variables, subjective assessment of symptoms, serum drug concentration, ECG, BP, incidence of adverse events

Gr = group; bid = twice daily; po = orally; CISC = clean intermittent self-catheterisation; od = once daily; NDO = neurogenic detrusor overactivity; SCI = spinal cord injury; qid = four times daily; QoL = quality of life; MS = multiple sclerosis; tid = three times daily; ECG = electrocardiogram; BP = blood pressure; DO = detrusor overactivity; VAS = visual analogue scale; OAB = overactive bladder.

Table 2 – Excluded studies

No.	Study	Reason for exclusion
1	Lehtoranta et al. [24]	Includes both NDO and IDO; results for NDO not reported separately
2	Ulshofer et al. [25]	Includes both IDO and NDO; results for NDO not reported separately
3	Amend et al. [4]	Not RCT
4	Birns et al. [26]	Includes both IDO and NDO; results for NDO not reported separately
5	Osca et al. [27]	Includes both IDO and NDO; results for NDO not reported separately
6	Kennelly et al. [28]	Not RCT
7	O'Leary et al. [29]	Not RCT
8	Horstmann et al. [30]	Not RCT
9	SONIC NCT00629642 [31]	Ongoing RCT
10	Hassouna [32]	Ongoing RCT

NDO = neurogenic detrusor overactivity; IDO = idiopathic detrusor overactivity; RCT = randomised controlled trial.

compliance (MD: 8; 95% CI, −34.41 to 50.41) between the two groups.

3.4.2. Adverse events

There was no statistically significant difference in dry-mouth rates (RR: 0.81; 95% CI, 0.45 to 1.46; adjustable 32% compared with standard 40%) or withdrawals because of adverse events (RR: 1.11; 95% CI, 0.07 to 18.49; adjustable 3% compared with standard 2.5%) between the two doses of trospium.

3.5. Comparison of different doses of same anticholinergic preparation: different doses of oral propiverine

One study [17] compared the standard 30-mg dose with 15-, 45-, and 60-mg doses in a total of 66 patients with a 3-wk follow-up; 2 patients were lost to follow-up. Patient-reported cure or improvement, objective cure, and QoL were not reported.

3.5.1. Bladder diary

There was no statistically significant difference in frequency of micturition per 24 h when 30 mg was compared with 15 mg (MD: 0.40; 95% CI, −0.71 to 1.51), 45 mg (MD: 0.40; 95% CI, −0.54 to 1.34), and 60 mg (MD: 0.70; 95% CI, −0.39 to 1.79).

3.5.2. Urodynamic outcomes

Bladder compliance was significantly reduced with 60 mg compared with 30 mg of propiverine (MD: −8.10; 95% CI, −15.7 to −0.5). There was no significant difference reported in any of the other urodynamic parameters.

3.5.3. Adverse events

There was no significant difference in dry mouth when 30 mg was compared with 15 mg (RR: 0.13; 95% CI, 0.01 to 2.70; 0% vs 19%), 45 mg (RR: 0.57; 95% CI, 0.09 to 3.55; 11% vs 19%), and 60 mg (RR: 1.16; 99% CI, 0.22 to 6.21; 21% vs 19%). Withdrawals because of adverse events were not reported.

3.6. Comparison of different doses of same anticholinergic preparation: extended- versus immediate-release propiverine

One study with a total of 66 patients was found [22]. Follow-up was for 3 wk, and loss to follow-up was not reported. Mean ages of both the groups were comparable (40.9 yr for extended-release [ER] propiverine and 41.4 yr for IR propiverine). Patient-reported cure/improvement, objective cure, and QoL were not reported. There was no statistically significant difference in incontinence episodes per 24 h (MD: 3.21; 95% CI, −0.40 to 6.82) or maximum cystometric capacity (MD: −22.6; 95% CI, −77.58 to 32.38).

3.7. Comparison of different routes of administration of anticholinergic drugs

Three studies [10,11,13] compared different routes of administration of anticholinergic drugs. Two studies [10,11] compared oral oxybutynin with intravesical oxybutynin using passive diffusion and intravesical oxybutynin using electromotive diffusion. One study compared oral oxybutynin with intravesical atropine [13]. No useable data were reported for analysis by two studies [10,11].

There was no statistically significant difference in the frequency episodes (MD: −0.40; 95% CI, −1.10 to 0.30), incontinence episodes per 24 h (MD: 0.00; 95% CI, −0.61 to 0.61), or average bladder capacity (MD: 24.1; 95% CI, −4.98 to 53.18) between intravesical atropine and oral oxybutynin [13]. The dry mouth was statistically significantly lower (RR: 0.28; 95% CI, 0.16 to 0.49) with intravesical atropine compared with oral oxybutynin [13], but there was no significant difference in the withdrawals because of adverse events between the groups.

3.8. Health economic evaluation

None of the studies assessed the costs to health services.

3.9. Heterogeneity

Methodological heterogeneity was assessed before analysis. No studies were excluded on the basis of methodological heterogeneity. There was a low estimate of statistical heterogeneity ($I^2 \leq 25\%$) in the maximum cystometric capacity (comparison 2: one anticholinergic vs another). There was moderate heterogeneity ($I^2 = 25–75\%$) in compliance (comparison 1: anticholinergic vs placebo), highest contraction, and withdrawals (comparison 2). There was a high degree of statistical heterogeneity (≥75%) in dry-mouth rate (comparison 2); however, the heterogeneity disappeared in sensitivity analysis after excluding Fader et al. [13] (comparing intravesical atropine with oral oxybutynin); dry-mouth rates were not significantly different between the groups (RR: 0.81; 95% CI, 0.58 to 1.1).

3.10. Risk of bias

The risk of bias was assessed using a risk of bias graph (Fig. 4). Sequence generation and allocation concealment

were poorly reported. There was good reporting of blinding. One study was an open randomised study [17]

3.11. Discussion

Anticholinergic drugs are currently the first choice for treatment of NDO. There is still uncertainty about which anticholinergic drugs are most effective, at which dose, and by which route of administration. The number of anticholinergic drugs available on the market is increasing, and various studies, both observational and randomised controlled trials, have evaluated their effectiveness. A Cochrane systematic review [33] has evaluated the efficacy and tolerability of anticholinergic drugs in heterogeneous populations with

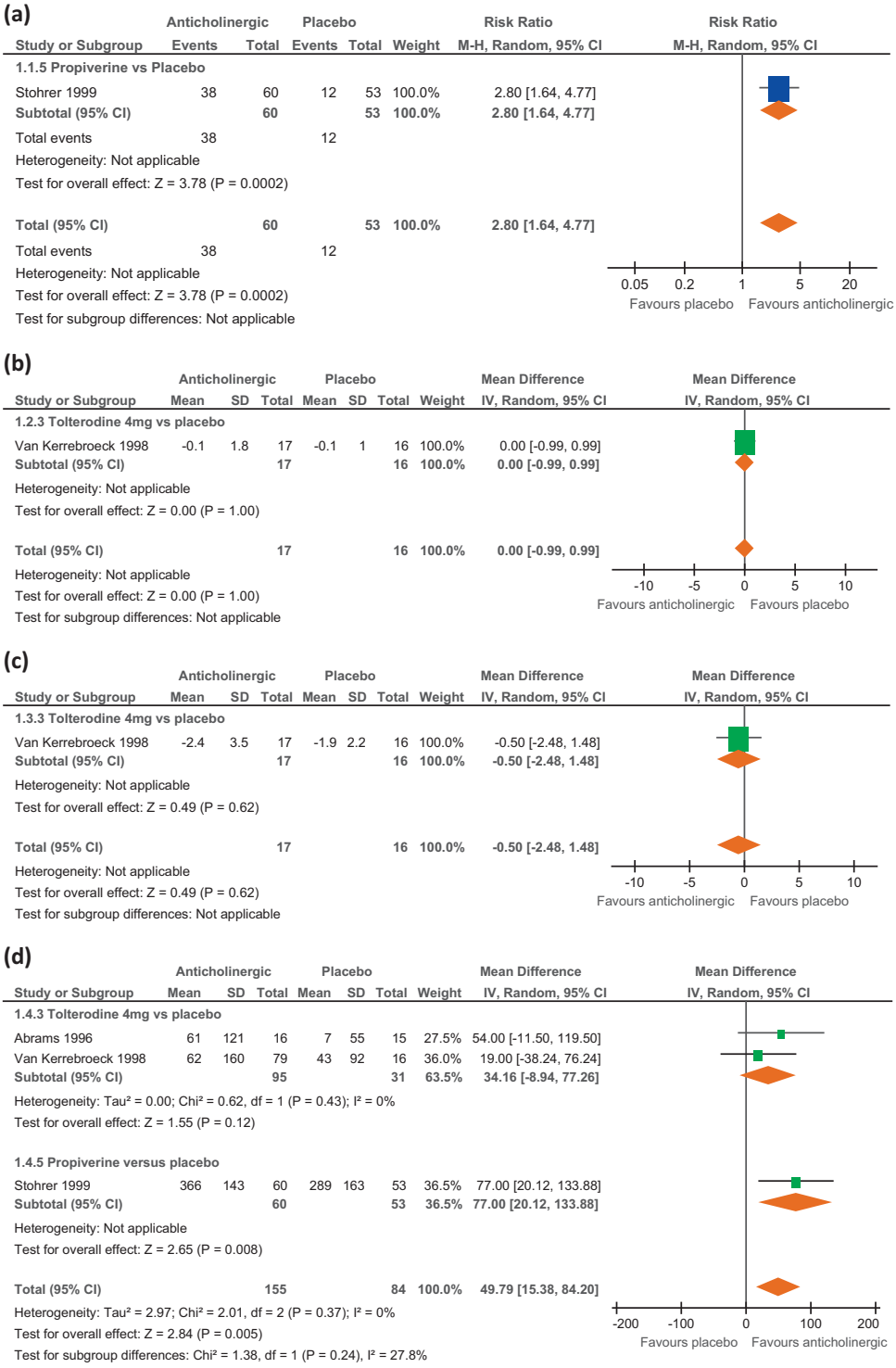
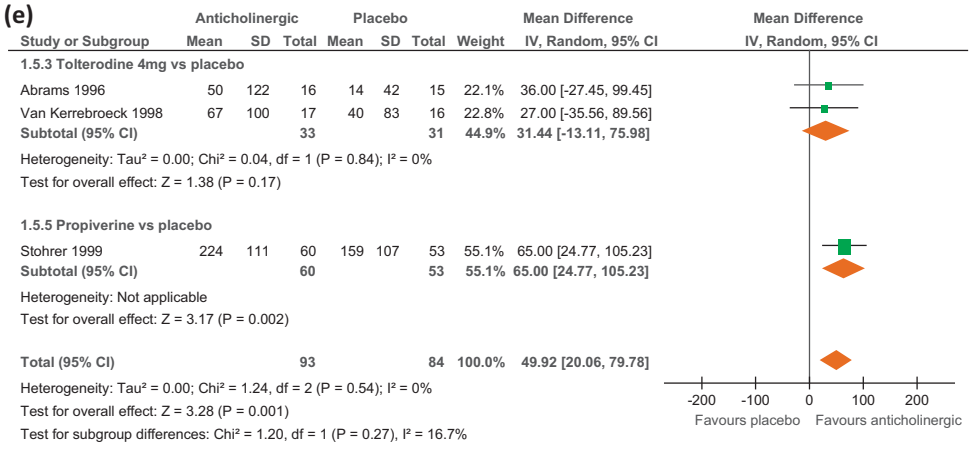
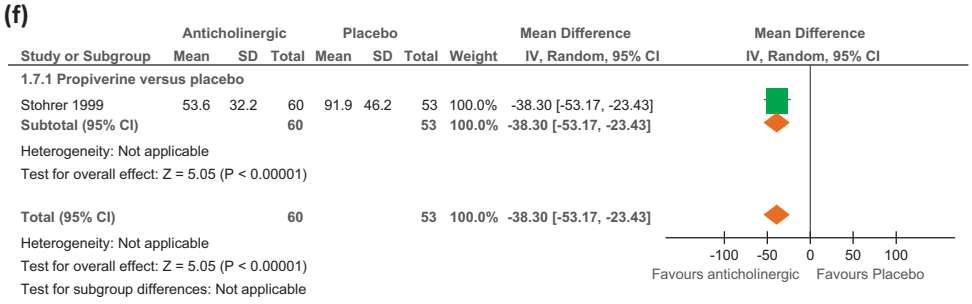
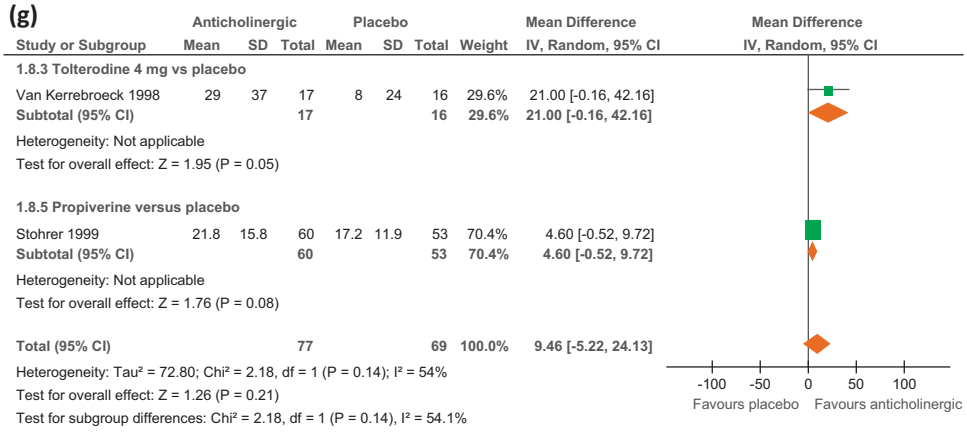


Fig. 2 – Anticholinergic drug compared with placebo: (a) patient-reported cure or improvement; (b) frequency episodes per 24 h; (c) incontinence episodes per 24 h; (d) maximum cystometric capacity; (e) volume at first contraction; (f) maximum detrusor pressure; (g) compliance; (h) residual volume; (i) adverse events; and (j) withdrawals because of adverse events. M-H = Manter-Haenszel; CI = confidence interval; SD = standard deviation; IV = inverse-variance method.







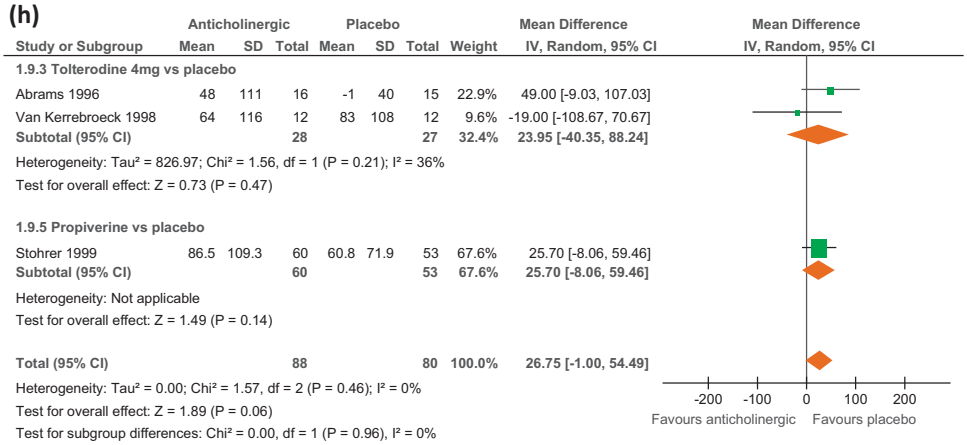
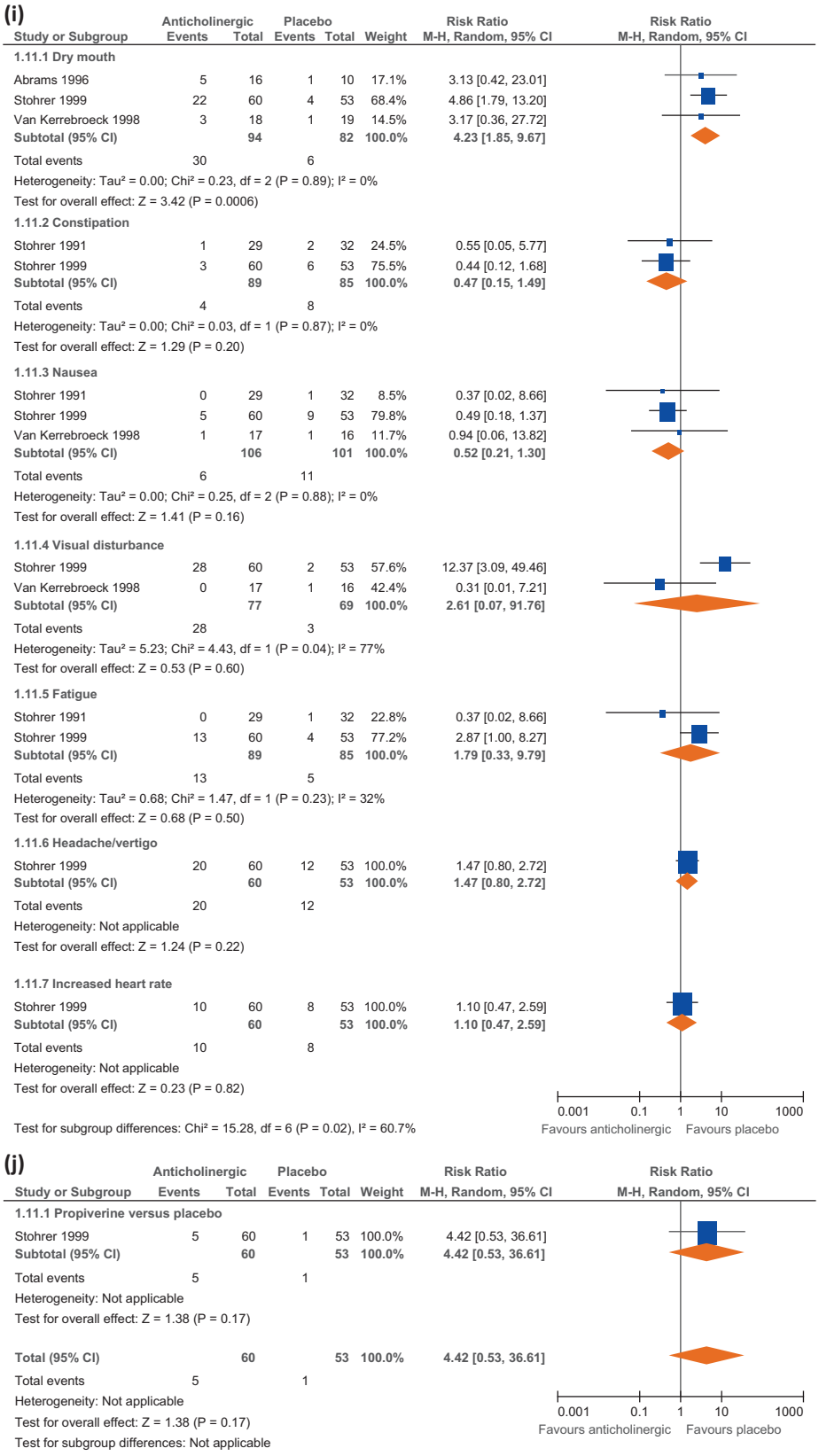


Fig. 2. (*Continued*)



CI = confidence interval; M-H = Manter-Haenszel; SD = Standard deviation; IV = inverse- variance method

Fig. 2. (*Continued*).

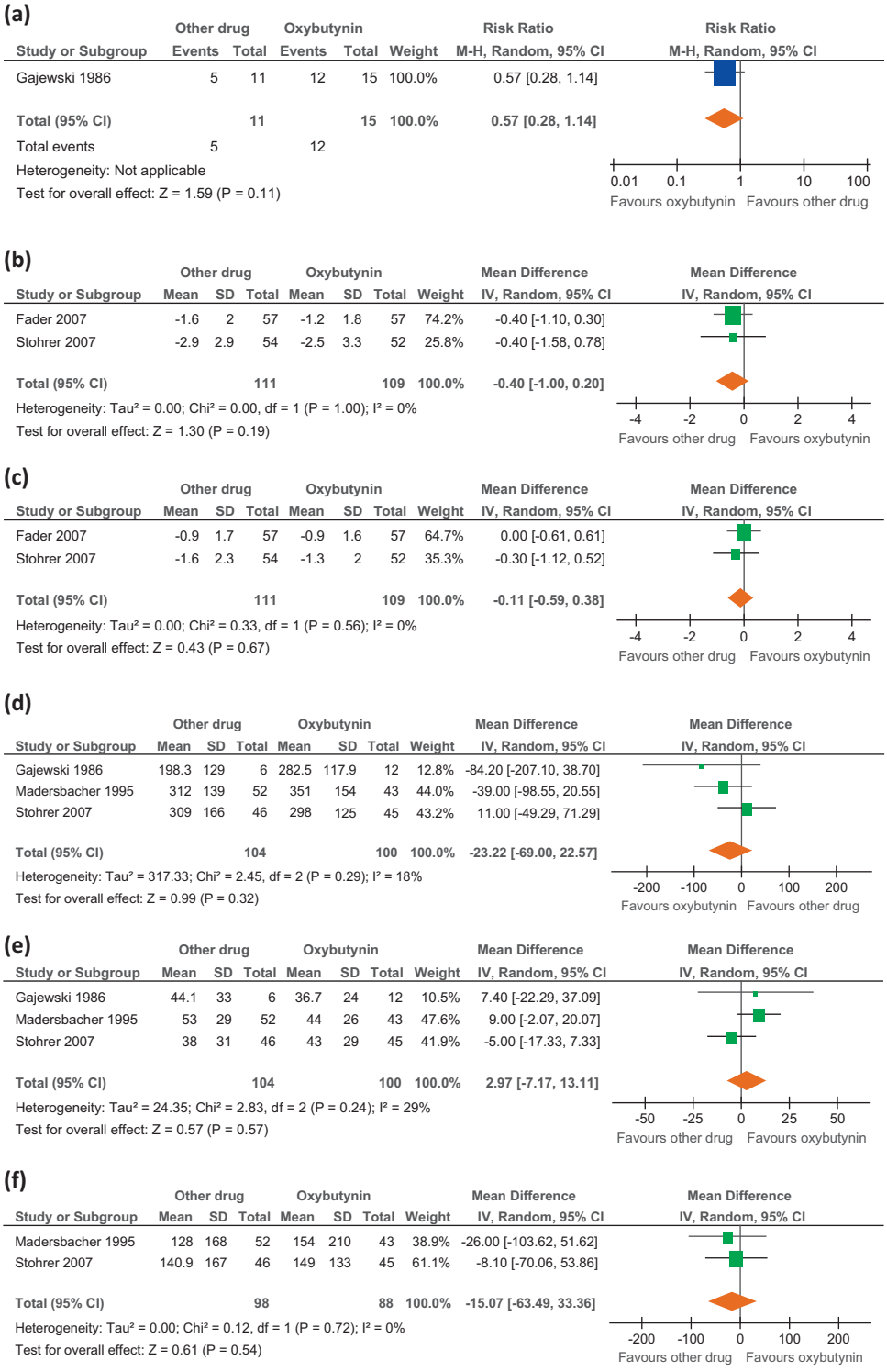
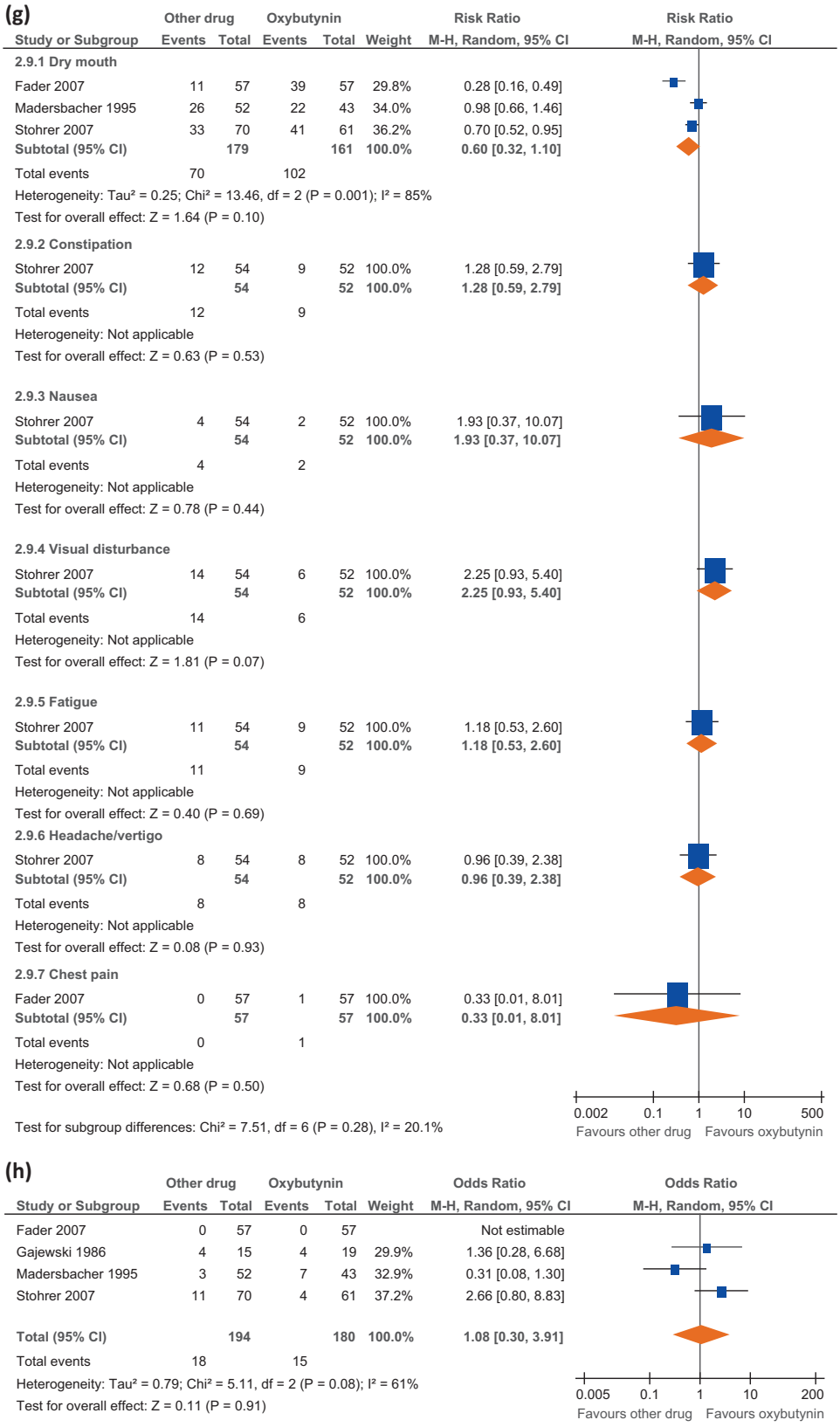


Fig. 3 – One anticholinergic drug compared with another: (a) patient-reported cure or improvement; (b) frequency episodes per 24 h; (c) incontinence episodes per 24 h; (d) maximum cystometric capacity; (e) maximum detrusor pressure; (f) residual volume; (g) adverse events; and (h) withdrawals because of adverse events. M-H = Manter-Haenszel; CI = confidence interval; SD = standard deviation; IV = inverse-variance method.



CI = confidence interval; M-H = Manter-Haenszel; SD = Standard deviation; IV = inverse- variance method

Fig. 3. (*Continued*).

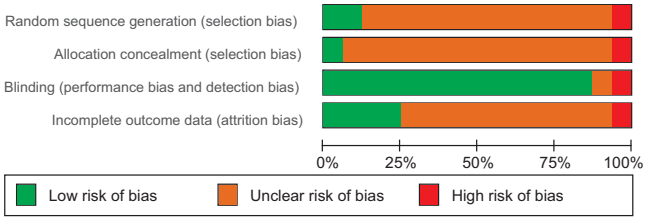


Fig. 4 – Risk of bias graph.

both idiopathic and neurogenic OAB symptoms; therefore, application of these results to patients with NDO is questionable.

In this systematic review, we only included RCTs/quasi-RCTs that evaluated the use of anticholinergic drugs in patients with NDO and showed that in patients with NDO, anticholinergic drugs are associated with higher rates of patient-reported cure/improvement of urinary symptoms compared with placebo (data from one study). Adverse events (such as dry mouth) were significantly higher with anticholinergic drugs. There was no significant difference in withdrawal of treatment because of adverse events when compared with placebo, but this finding could be because of short follow-up. Our results are similar to those of the Cochrane Review [33] for patients with idiopathic OAB, which showed that anticholinergic drugs were associated with statistically significant improvements in patients' symptoms and significantly higher dry-mouth rates, but they did not seem to have an effect on the numbers of withdrawals. Our results are in contrast to those of Nicholas et al. [34], who showed, in a systematic review including three RCTs, that there was little evidence to advocate the use of anticholinergic treatment for urinary symptoms secondary to multiple sclerosis, as there was no study comparing anticholinergics with placebo in patients with multiple sclerosis; each of the three RCTs included by Nicholas et al. [34] assessed different anticholinergics, so meta-analysis was not possible.

Interestingly, when we compared oxybutynin in patients with NDO with other anticholinergic drugs, there was no statistically significant difference in any of the outcome measures. Similar results were obtained when different doses of tolterodine (1–8 mg), trospium chloride (45–135 mg/d), and propiverine (15–60 mg/d and/or IR vs ER) were compared. It was noted that tolterodine (8 mg/d) was used off-license in one study and, when compared with a dose of 4 mg/d, showed significant increase in bladder capacity (however, with increased postvoiding residual urine volume). There were limited data from trials comparing different routes of administration of anticholinergic drugs from which to draw any conclusions. Our results are different from those of a number of systematic reviews [35–37] that have evaluated the different doses and routes of administration of anticholinergic drugs in patients with idiopathic OAB (ie, excluded patients with NDO) and showed that ER formulations should be preferred to IR formulations; for the latter, dose escalation might yield some improvement in efficacy with significant increase in adverse events; however, evidence from our review is limited by fewer RCTs.

Urodynamic data, especially data on intravesical pressure and its clinical significance to long-term renal function, are of particular importance and clinical relevance in patients with NDO. In a systematic review (without a meta-analysis), Stöhrer et al. [38] showed that anticholinergic treatment in NDO is associated with a 30–40% reduction of maximum detrusor pressure paralleled by an increase in maximum cystometric capacity of 30–40%. It was reassuring that our review showed similar results: The maximum cystometric capacity and the volume at first contraction were statistically significantly higher, while the detrusor pressure at highest contraction was statistically significantly lower, with anticholinergic treatment compared with placebo; however, there was no difference in urinary frequency episodes, incontinence episodes, or bladder compliance. Reassuringly, there was no evidence of significantly higher postvoiding residual urine volume with anticholinergics at the standard dose used in the review. These findings support the use of anticholinergic drugs in patients with NDO to help reduce their risk of long-term deterioration of renal function; however, this result should be taken with caution, as unfortunately these data refer to only very limited follow-up times.

Lower urinary tract dysfunction is known to be a multidimensional problem that affects various aspects of life. Therefore, assessment of any intervention should involve assessment of improvements in all aspects, including patient-reported cure, patient satisfaction, objective cure, and impact on QoL. Patient-reported cure was assessed on a three-point Likert scale by two studies [14,20]. QoL was assessed by only one trial [13] using a validated tool (King's Health Questionnaire); however, the data reported were not helpful, as the authors did not report the mean change with a measure of variation and were unable to provide it. Unfortunately, none of the trials attempted to compare the costs to health services, which can be another important dimension in decision making, especially for allocation of health resources.

This review has several strengths. The search was thorough, systematic, and without language restrictions. Two reviewers independently performed the study selection and data extraction to minimise errors. We contacted the authors for unpublished information. We adhered to the PRISMA [6] statement in reporting our review. There was statistically significant heterogeneity ($\geq$75%) in one of the secondary outcomes (dry-mouth rate, comparison 2), which after sensitivity analysis was no longer statistically significant. We performed sensitivity analysis and used the random effect model [7] throughout the meta-analysis, therefore reducing the impact of statistical heterogeneity. Our review has a number of limitations: There was methodological heterogeneity, as there were different types and doses of anticholinergic drugs compared with placebo and oxybutynin. There was a small number of studies included, with short follow-up in most studies. Patients in the overall study cohort were relatively young, with a mean age of 38.5 yr, so the

results may not be entirely generalisable to the population of patients who are treated. A subgroup analysis based on different neurologic pathology (spinal cord injury, multiple sclerosis, and others) was not possible because of the limited number of studies, and some studies included patients with all neurologic pathology. With one exception, all contacted authors were unable to provide additional information, as the studies were performed and published several years ago. None of the RCTs assessed the relatively new anticholinergic drugs such as solifenacin or fesoteridine. The randomisation process and allocation concealment were not reported in most studies.

We acknowledge that the RCTs in this specific population can be a challenge. Nevertheless, there is no alternative to good-quality, adequately powered RCTs with longer-term follow-up if we are to reach a robust conclusion on the effectiveness and tolerability of different anticholinergic drugs in patients with NDO.

4. Conclusions

This meta-analysis has shown that compared with placebo, anticholinergic treatment in patients with NDO is associated with better patient-reported cure/improvement. However, there is a higher incidence of adverse events, such as dry mouth, and no difference in withdrawal of treatment because of adverse events. None of the different anticholinergic drugs or different dosages assessed in this review was superior to another. Anticholinergic treatment was associated with a reduction in maximum detrusor pressure, which can be beneficial for long-term renal function.

Author contributions: Priya Madhuvrata had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Madhuvrata, Abdel-Fattah.
Acquisition of data: Singh, Hasafa.
Analysis and interpretation of data: Madhuvrata, Abdel-Fattah.
Drafting of the manuscript: Madhuvrata, Singh, Abdel-Fattah.
Critical revision of the manuscript for important intellectual content: Madhuvrata, Abdel-Fattah, Singh, Hasafa.
Statistical analysis: Madhuvrata, Singh.
Obtaining funding: None.
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Supervision: Madhuvrata.
Other (specify): None.

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