The effectiveness of parasympathomimetics for treating underactive bladder: A systematic review and meta-analysis

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Abstract

Aims: Biological rationale suggests that parasympathomimetics (cholinergic receptor stimulating agents) could be beneficial for patients with underactive bladder. However, no systematic review with meta-analysis addressing potential benefits or adverse effects exists. The aim of this review was to assess the effectiveness, both benefits and harms, of using parasympathomimetics for the treatment of underactive bladder. **Methods:** The protocol was registered in PROSPERO, and searches were undertaken in PubMed, Embase and CENTRAL, including randomised and non-randomised controlled trials of patients with underactive bladder, comparing parasympathomimetic to placebo, no treatment, or other pharmaceuticals. Risk ratios, odds ratios, and mean differences were calculated. **Results:** We included 12 trials with 3024 participants. There was a significant difference between parasympathomimetics and comparators (favouring parasympathomimetics) in the number of patients with urinary retention (RR 0.55, 95% CI 0.3 to 0.98, p=0.04, low quality of evidence). There was no difference in mean post-void volume overall (MD -41.4 mL, 95% CI -92.0 to 9.1, p=0.11, low quality of evidence). There was a significant difference at up to 1-week post-intervention, favouring parasympathomimetics (MD -77.5ml, 95% CI -90.9 to -64.1, p<0.001, low quality of evidence), but no difference at 1-month post-intervention. There was no difference in adverse events (OR 1.19, 95% CI 0.62 to 2.28, p=0.6, moderate quality of evidence). **Conclusions:** Overall, the evidence supporting the use of parasympathomimetics is of low quality, with relatively short follow-up durations. Overall, it is not possible to draw clear evidence-based conclusions from the current literature, presenting the use of parasympathomimetics in treating underactive bladder as a key area that requires future well-controlled clinical trials.

Keywords: Acetylcholine; Bethanechol; Carbachol; Cholinergic; Detrusor underactivity; Muscarinic agonist; Urinary bladder.

1 Introduction

Underactive bladder is an increasingly prevalent problem which commonly results in urinary retention, incomplete bladder emptying and other bothersome urinary symptoms[1]. Although a range of definitions have been provided in past literature[2-5], the currently accepted definition comes from a recent International Continence Society (ICS) terminology report, that underactive bladder is "characterised by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms"[6]. This ICS report also proposes underactive bladder as the clinical syndrome that includes urodynamic diagnosis of detrusor underactivity (defined as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying with a normal time span).

There are currently, however, no outcome-validated effective therapeutics for its management, treatment, or prevention. Prior studies have investigated the use of parasympathomimetics (muscarinic agonists) as a treatment, but much of the evidence may not have the academic or clinical rigor required to provide evidence-based support for the use of this class of medications in treating underactive bladder[7-9]. In particular, there are a range of adverse effects such as nausea, vomiting, diarrhea, sweating, salivation and headache, which also needs to be taken into account[10].

The M3 muscarinic receptor is responsible for contraction of the bladder muscle, which is necessary to facilitate voiding[11,12]. In normal bladder function, the receptor is activated by the neurotransmitter acetylcholine released from the nearby parasympathetic nerves. Parasympathomimetics, also called cholinergic receptor stimulating agents or cholinomimetic drugs, work by imitating or modifying the effects of acetylcholine[13].

Muscarinic agonists (i.e. bethanechol and carbachol) act directly on this G protein-coupled receptor, potentially acting to stimulate stronger contractions of the urinary bladder smooth muscle. Parasympathomimetics also include acetylcholinesterase inhibitors (i.e. neostigmine and distigmine), which inactivate the enzyme responsible for breaking down acetylcholine. This is thought to result in enhanced and prolonged receptor stimulation on the urinary bladder muscle cell membrane. Through these mechanisms of action, parasympathomimetics have the potential to facilitate voiding and assist with the overall detrusor muscle contraction, making them a candidate pharmaceutical for the treatment of underactive bladder.

Although parasympathomimetics potentially sit as the first-line pharmaceutical treatment option for underactive bladder[14], no meta-analyses have been completed regarding their effectiveness, that is, benefits or harms. With upcoming potential parasympathomimetics reaching Phase 2 clinical trials (i.e. ASP8302) and a renewed interest in detrusor underactivity and its symptom-based correlate, underactive bladder[7], there is a need for an updated and definitive assessment of the literature and available data. The aim of this review was primarily to evaluate the effectiveness of parasympathomimetics on the treatment of underactive bladder.

2 Materials and methods

The protocol for this systematic review was developed prospectively and registered in PROSPERO (CRD42020212409). The protocol was followed with minor deviations; these are reported in the methods section. The systematic review is reported following the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[15]. As this was a systematic review on published studies, no ethical approvals were required.

2.1. Literature search and inclusion of studies

We searched for published studies in PubMed, Embase (via Elsevier), and the Cochrane Register of Controlled Trials (CENTRAL), from inception until 23 September 2020. We searched clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform for additional completed or ongoing studies from inception until 23 September 2020. No date or language restrictions were applied to any of the searches. Fluent speakers of the relevant languages assisted to make inclusion or exclusion decisions where required (two articles written in Japanese, one in Arabic).

The search string was designed in PubMed by an experienced Information Specialist (J.C.) using a combination of Subject (MeSH) terms and keywords. The search string consisted of the following search concepts: Underactive Bladder AND Parasympathomimetic AND randomised controlled trial. The search string was translated for use in other databases by using the Polyglot Search Translator[16]. The complete search strings for all databases are provided in Appendix 1. In addition, on 3 December 2020 we conducted a backwards and forwards citation search, in Scopus, on all included studies.

We included randomised and non-randomised (e.g. alternate allocation) controlled trials of patients of any age, gender, or condition, who presented with underactive bladder (detrusor underactivity). However, studies including underactive bladder as an immediate outcome of

surgery were excluded. Studies in any clinical setting were included. We included studies of all reported parasympathomimetics, including muscarinic agonists, such as bethanechol and carbachol, and acetylcholinesterase inhibitors, such as distigmine, pyridostigmine and neostigmine. We included studies comparing the intervention to a placebo, or to another pharmaceutical. Although we did not pre-specify 'no treatment' as an includable comparator in the protocol, we included studies where the exact nature of the comparator could not be determined due to unclear reporting (but may have been 'no treatment'). We pre-specified the primary outcome as 'residual volume.' However, due to terminological differences (particularly in older studies), we extracted and reported data on both urinary retention and postvoid residual volume. The secondary outcomes were urinary flow and adverse events.

2.2. Screening and Data Extraction

Three review authors (A.M.S., C.P., V.V.) independently screened the search results, first in title and abstract, and subsequently in full text. Discrepancies in decisions were resolved by consensus or by referring to another author (C.M.). Three data extraction forms were used for this review: Table of Characteristics form, Outcomes form, and Risk of Bias form. Each of these forms were pre-piloted on two studies. Data from included studies were extracted independently by two authors (C.P. and V.V.), with discrepancies resolved by discussion, or by the third author (A.M.S.).

2.3. Risk of Bias

The risk of bias was assessed by two authors independently (C.P. and V.V.) with

discrepancies resolved by consensus or reference to other authors (A.M.S. or C.M.). Cochrane Collaboration's Risk of Bias tool 1[17] was used in preference to tool 2[18], as the former allows the assessment of biases from funding or conflict of interest issues, under the 'other bias' domain. The following domains were assessed: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective outcome reporting, and (7) Other bias (focusing on potential for biases due to funding or conflict of interest). Each potential source of bias was graded as low, unclear, or high. Each judgment was supported by a quote from the relevant trial.

2.4 Assessment of evidence using GRADE

The assessment of the quality of evidence using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) was not pre-specified in the protocol, however, was conducted (P.G.) on clinician advice[19]. (Appendix 2).

2.5. Data synthesis

Review Manager Software version 5.4 (Cochrane Collaboration, London, UK) was used to calculate the effect sizes. Data were sufficient (≥2 studies or comparisons reported the same outcome) to conduct meta-analyses for the incidence of urinary retention, mean postvoid residual volume, and adverse event outcomes. Data was not meta-analysable for the urinary flow outcome, and is therefore reported narratively. Dichotomous outcomes were reported as risk ratios (urinary retention) or odds ratios (adverse events) with 95% confidence intervals; the continuous outcome (mean postvoid volume) was calculated as a mean

difference with 95% confidence intervals. Random effects model was used for all meta-analyses.

2.6. Unit of analysis

The participant was used as the unit of analysis, where possible. However, where data on the number of individuals with outcomes of interest was not available, we extracted the information as it was presented in the study (e.g. mean flow rate or peak flow rate in each group). We planned to contact study investigators or sponsors to provide missing data if needed, but this was not required.

2.7. Assessment of heterogeneity

Heterogeneity was measured using the I^2 statistic.

2.8. Sensitivity analysis

We had planned to conduct sensitivity analyses by including versus excluding studies with three or more domains at high risk of bias. However, as none of the included studies were rated at high risk of bias for three or more domains, we did not conduct this. An ad-hoc sensitivity analysis was conducted to identify the source of high heterogeneity in the mean postvoid residual volume meta-analysis (Appendix 3).

2.9. Subgroup analysis

We had planned to conduct the following subgroup analyses: by gender, by condition/diagnosis, by intervention type, by comparator type, and by timepoint at which

the outcome was measured. There were sufficient data to conduct the following subgroup analyses: by intervention type (anticholinesterases vs choline carbamates), and by the timepoint at which the outcome was measured. We were unable to conduct the following subgroup analyses due to limited data: by gender, by condition/diagnosis, and by comparator type.

3 Results

3.1. Search Results

Database searches identified 982 references, and 365 additional references were identified from forward and backward citation searches and clinical registry searches. After deduplication, 1156 references were screened in title/abstract, and 1078 were excluded. Seventy-eight articles were screened in full text; 66 were excluded (64 full-text references and two ongoing clinical trials which did not have results available – see Appendix 4). Twelve studies were included in the review and ten were meta-analysed (Figure 1).

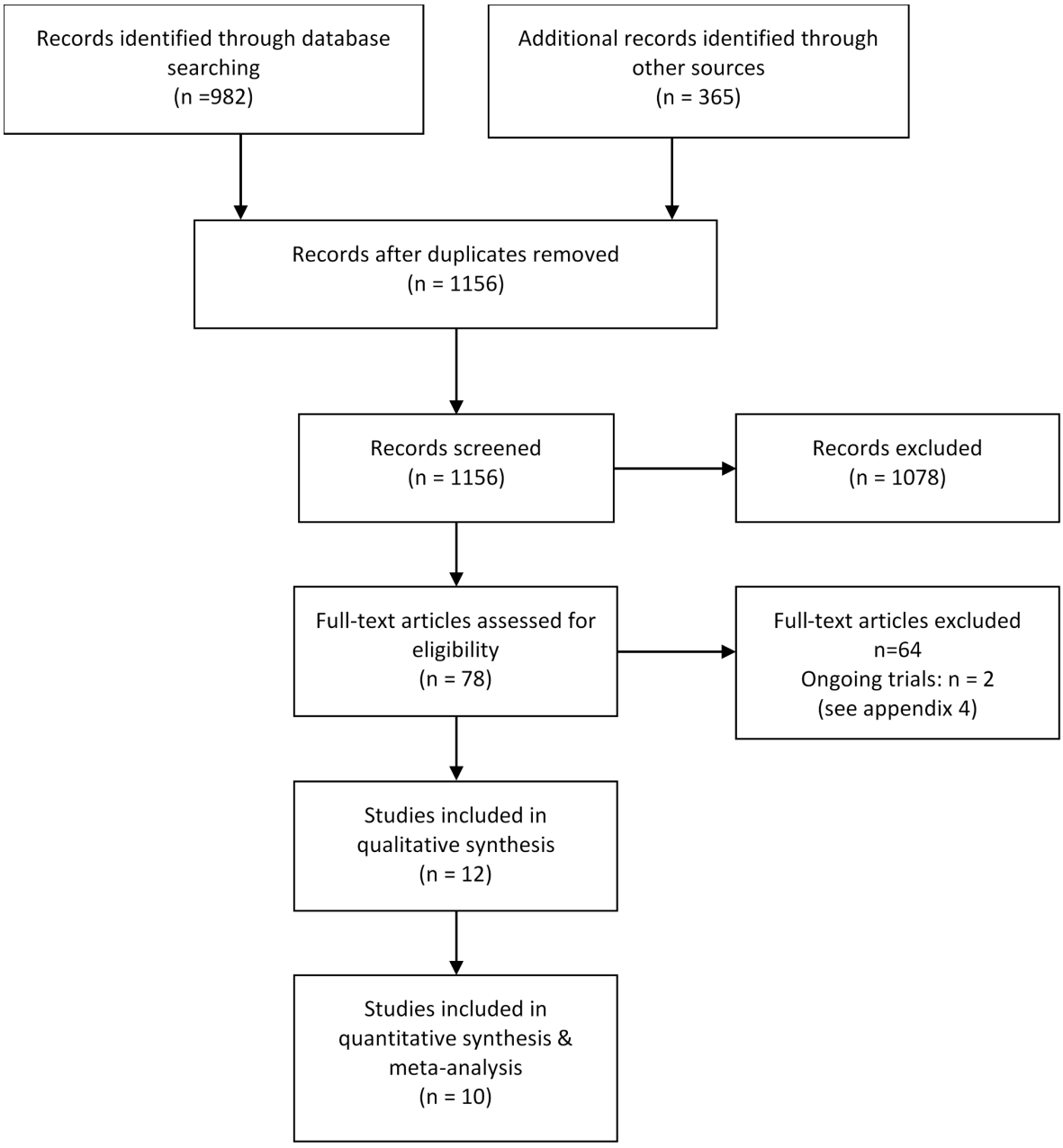

Figure 1: PRISMA Flow Diagram [15]. Appendix 4 contains the references and reasons for full-text excluded articles, and ongoing clinical trials which do not have results available.

3.2. Studies included

We included 12 trials (10 randomised controlled trials and two non-randomised controlled trials) of 3024 patients in aggregate (see Table 1). Three studies (25%) were conducted in the United States, with the remainder (one each) in The Netherlands, Egypt, Germany, Brazil, Thailand, Jordan, Malta, Indonesia, and the Philippines. Ten studies reported the duration of follow-up, which ranged from 3 hours to 6 months (median follow-up was 18 hours); two studies followed up patients for 1 month, and 1 study followed up patients for 6 months. Study size ranged from 36 to 1796 (median 100). Participant populations varied, but generally included patients in the community, patients scheduled for a surgical procedure, and patients post-surgery. Interventions included choline carbamates (typically bethanechol or carbachol) in nine studies, and anticholinesterases (neostigmine or distigmine) in three studies. Comparators were placebo, saline, another active drug, no treatment or unclearly reported. Administration was mostly oral (10 trials), or intravenous (one study), or intramuscular (one study), with varying doses and frequencies.

Table 1: Description and characteristics of studies included in the review.

Author Year Location	Study design	Follow-up Duration	No. of participants Total (each arm)	Participants	Age	Intervention Drug (route of administration), dose, frequency, duration	Comparator Drug (route of administration), dose, frequency, duration
Barrett 1981 United States [19]	RCT 4-arm	3 hours post-treatment	48 (12 in bethanechol 25mg, 12 in 50mg, 12 in 100mg, 12 in placebo)	Female patients; no evidence of bladder outlet obstruction or neurologic disease; residual urine vol. consistently >125ml	NR	A1: Bethanechol (oral), 1x, 25 mg A2: Bethanechol (oral), 1x, 50 mg A3: Bethanechol (oral), 1x, 100 mg	A4: Placebo (details NR)
Bowers 1987 United States [20]	RCT 4-arm	24 hours	108 (26 in bethanechol 25mg, 26 in 50mg, 29 in 5mg, 27 in no treatment)	Patients scheduled for anorectal procedure	NR	A1: Urecholine (oral), 25 mg, every 4 hrs for 24 hrs A2: Urecholine (oral), 50 mg, every 4 hrs for 24 hrs A3: Urecholine (subcutaneous), 5 mg, every 4 hrs for 24 hrs	A4: No urecholine (details NR)
Burger 1997 Netherlands [21]	RCT 3-arm	6 hours	249 (72 carbachol, 82 alfusozine, 95 placebo)	Patients who were operated on and were expected to leave the operating room without a catheter or a gastric tube	Mean 60	A1: Carbachol/diazepam (oral): 2mg Carbachol / 2mg diazepam; 1x A2: Alfusozine (oral): 2.5mg; 1x	A3: Placebo (oral): details NR
El Dahab 2011 Egypt [22]	CT 4-arm	12 hours	100 (25 neostigmine, 25 morphine/ neostigmine; 25 bupivacaine; 25 morphine)	Male patients, 20-50 years old with ASA class I, II	Mean 36 range: 20-50	A1: "Neostigmine group": 10 ml bupivacaine 0.5% + 2 ml normal saline cont. 5µg/kg neostigmine; 1x A2: "Morphine/neostigmine group": 10ml bupivacaine 0.5% + 1ml normal saline (cont. 2mg	A3: "Bupivacaine group": 10 ml bupivacaine 0.5% and 2ml saline; 1x A4: "Morphine group": 10 ml bupivacaine 0.5% + 2 mg morphine in 2ml normal saline; 1x

Author Year Location	Study design	Follow-up Duration	No. of participants Total (each arm)	Participants	Age	Intervention Drug (route of administration), dose, frequency, duration	Comparator Drug (route of administration), dose, frequency, duration
						morphine) + 1ml normal saline (cont. 5µg/kg neostigmine); 1x	
Fleming 1957 United States [23]	CT 2-arm	8-12 hours	1796 (821 bethanechol, 975 control)	Women in the postpartum period	NR	A1: Bethanechol (oral), 15 mg, every 4 hours for 6 doses total	Control: NR
Kemp 1997 Germany [24]	RCT 2-arm	6 months	40 (16 bethanechol, 24 control)	Patients who had a Wertheim-Meigs operation for cervical cancer, FIGO stage Ib or IIa	Mean 47 range 29-72	A1: Bethanechol chloride, 50mg, 3x/day, starting day 3 post-op (duration unclear)	A2: Control: no treatment (although received bethanechol if residual urine persisted >50ml after the 10th day post-operation)
Madeiro 2006 Brazil [25]	RCT 4-arm	30 days	79 (20 bethanechol, 20 cisapride, 20 bethanechol + cisapride, 19 control)	Patients 22-70 years old, with stage IV (FIGO) cervical cancer, and eligible for surgical treatment	Range 22-70	A1: Bethanechol (oral): 10 mg, every 8 h, for 30 days A2: Bethanechol + cisapride (oral): 10 mg, every 8 h, for 30 days	A3: Cisapride (oral): 10 mg, every 8 h, 30 days A4: Placebo (oral): 10 mg, every 8 h, 30 days
Manchana 2011 Thailand [26]	RCT 2-arm	1 month	62 (31 bethanechol, 31 control)	Patients with early-stage cervical cancer or endometrial cancer, who underwent standard type III radical hysterectomy	Mean 49 range 30-73	A1: Bethanechol (oral), 20 mg, 3x/day, 3rd to 7th postoperative day	A2: Placebo (oral), 20 mg, 3x/day, 3rd to 7th postoperative day
Rusan 1984 Jordan [27]	RCT 2-arm	36 hours	300 (150 bethanechol, 150 control)	Patients undergoing anorectal operations for benign conditions	Range 20-79	A1: Bethanechol (oral), 25 mg, every 6 hours, 6 total doses	A2: Control group (details NR)

Author Year Location	Study design	Follow-up Duration	No. of participants Total (each arm)	Participants	Age	Intervention Drug (route of administration), dose, frequency, duration	Comparator Drug (route of administration), dose, frequency, duration
Savona-Ventura 1991 Malta [28]	RCT 4-arm	Unclear	100 (22 distigmine, 23 phenoxybenzamine, 27 prostaglandin, 28 control)	Patients undergoing vaginal surgery for genital prolapse	NR	A1: Distigmine (oral), 5 mg daily, from 1st postoperative day (duration unclear)	A2: Phenoxybenzamine HCl (route NR), 10 mg 2x/day, from 1st postoperative day (duration unclear) A3: Prostaglandin F20 (intravesical), 7.5mg, 1x A4: Control (no pharmacological agents)
Senapathi 2018 Indonesia [29]	RCT 2-arm	Unclear	36 (18 neostigmine, 18 control)	Patients undergoing lower abdominal or lower extremity surgery under spinal anaesthesia	Range 18-50	A1: Neostigmine (intramuscular), 0.5mg, 1x	A2: NaCl 0.9% (intramuscular), 0.5mg, 1x
Uy 2011 Philippines [30]	RCT 2-arm	8 hours	106 (46 bethanechol, 60 control)	Patients who underwent anal surgeries under spinal anaesthesia	Mean 37, range 20-60	A1: Bethanechol (oral), 25 mg 1-hour post-op + 25 mg tablet 4-6 hours later	A2: Control (no medications)

3.3. Risk of bias and quality

Overall, the risk of bias was generally low (in particular, for random sequence generation, incomplete outcome data and selective reporting) or unclear (for allocation concealment and other bias – from funding and conflicts of interest). Blinding was at high risk of performance bias for participants and personnel for half of the included studies, due to lack of blinding (Figure 2).

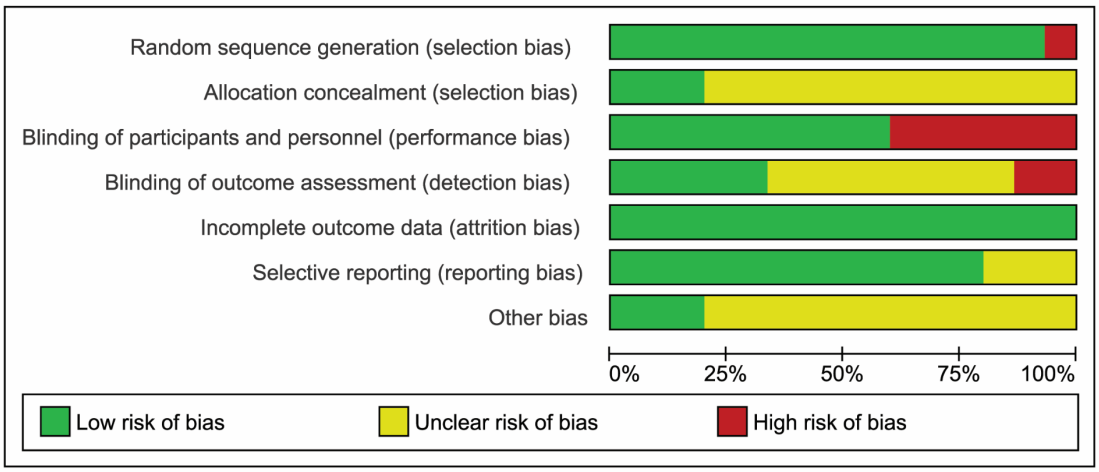

Figure 2: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

3.4. Primary outcomes: urinary retention and postvoid residual volume

3.4.a Incidence of urinary retention

Four studies reported on urinary retention. Two studies (three comparisons) reporting on this outcome were meta-analysable; the studies included a total of 400 patients. There was

no significant difference between parasympathomimetic and comparator in urinary retention by drug subgroup (anticholinesterase, choline carbamates), however, there was a significant difference (favouring parasympathomimetics) overall (RR 0.55, 95% CI 0.30 to 0.98, p=0.04, I^2=4%, Figure 3). The quality of evidence was low (Appendix 2).

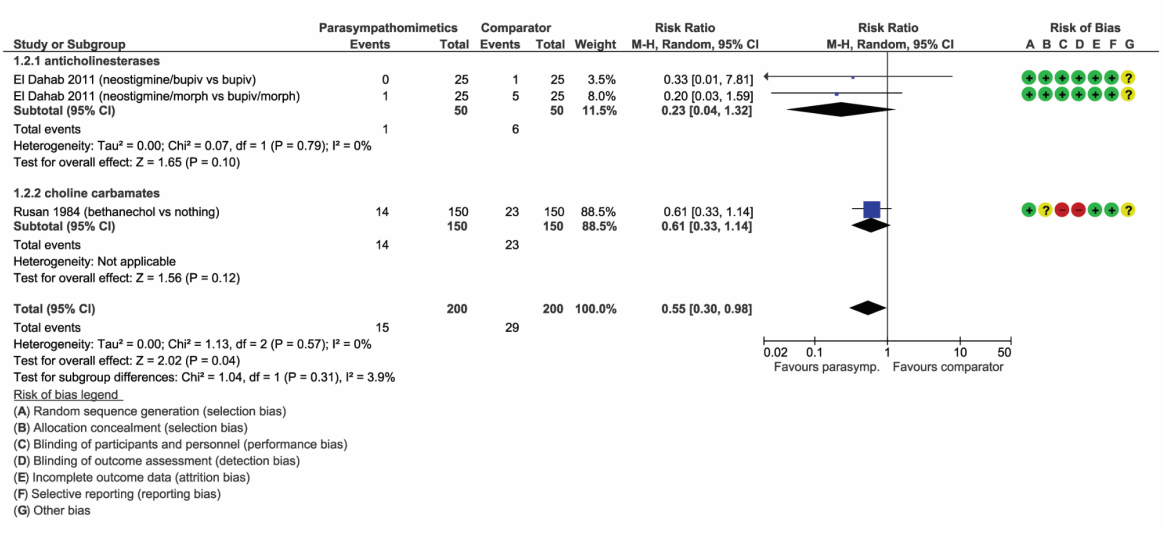

Figure 3: Incidence of urinary retention: parasympathomimetic vs comparator. Risk of bias legend: A, Random sequence generation (selection bias); B, Allocation concealment (selection bias); C, Blinding of participants and personnel (performance bias); D, Blinding of outcome assessment (detection bias); E, Incomplete outcome data (attrition bias); F, Selective reporting (reporting bias); and G, Other bias. Green colour indicates low risk of bias; yellow indicates unclear risk of bias; and red colour indicates high risk of bias. *bupi=bupivacaine, morph=morphine.

Two studies were not meta-analysable[20,21]. One trial, comparing three different doses of bethanechol to no bethanechol, found no difference in postoperative urinary retention

rates at 24 hours among patients undergoing anorectal procedure[20]. Another trial found the incidence of postoperative urinary retention did not differ between treatment groups (carbachol/diazepam, alfusozine, and placebo) at 6 hours post-operatively[21].

3.4.b Mean postvoid (residual) volume – subgrouped by pharmaceutical type

Eight trials in total reported on this outcome. Three trials (four comparisons), with 177 patients, were meta-analysable. There was a significant difference between the anticholinesterase group and the comparator (saline) group, favouring anticholinesterase (MD -77.5 ml, 95% CI -91.1 to -64.0, p < 0.001). However, there were no significant differences in mean postvoid (residual) volume between choline carbamate (bethanechol) and comparator (MD = -23.11 ml, 95% CI -67.6 to 21.4, p = 0.31), or overall (MD -41.4 ml, 95% CI -92.0 to 9.1, p = 0.11, Figure 4). Heterogeneity was very high (I^2 = 95%). The quality of evidence was low (Appendix 2).

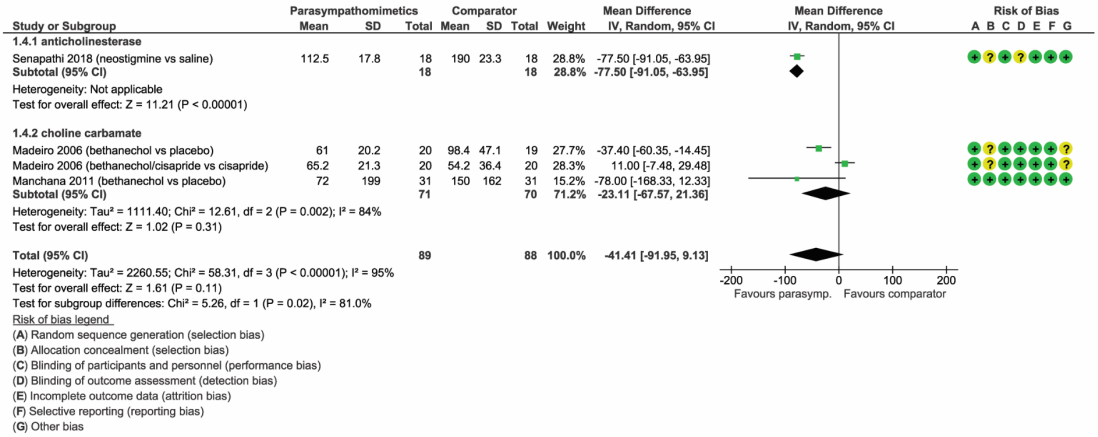

Figure 4: Mean postvoid (residual) volume, subgrouped by drug category.

In an ad-hoc sensitivity analysis, we identified that the high heterogeneity was the result of the inclusion of one trial[22]. Its removal decreased the I^2 from 95% to 0%, and increased the difference between groups to be significant, favouring parasympathomimetics (MD: -7.5 mL, 95% CI -91 to -64 mL, $p < 0.001$, $I^2 = 0\%$) (Appendix 3).

Five trials reported on residual volume but were not meta-analysable. Of those, three trials found no difference between the treatment and comparator groups in residual volume[23-25]. One trial found that 50% of patients in the bethanechol group reached the outcome of residual volume <50mL in 8 days vs 13 days in the control group (p<0.01, favouring bethanechol)[26]. One trial found that the mean amount of urine drained from patients in the bethanechol arm was significantly lower than in the no-treatment arm[27] (Table 2).

Table 2: Residual volume (non-meta-analysable studies).

Study	**Comparison**	**Results**
Barrett 1981	3 arms of bethanechol vs 1 arm placebo	"**no significant difference** between treatment and placebo groups" [in residual volume]
Fleming 1957	1 arm bethanechol vs 1 arm control	"**little or no difference** in the average residual urine between the two groups"
Kemp 1997	1 arm bethanechol vs 1 arm control	**Days to residual urine <50ml** (in days) reached by 50% of patients in each group: 13.0 in control group, 8.0 in bethanechol group, **p<0.01.**
Savona-Ventura 1991	1 arm distigmine bromide, 1 arm phenoxybenzamine HCL, 1 arm prostaglandin, 1 arm control	**No significant difference between** distigmine group and control group in the number of patients with ≥ 100 ml postoperative residual volume.
Uy 2011	1 arm bethanechol, 1 arm received nothing	"the **mean amount drained** from patients who needed catheterisation

		in the [nothing arm] was **significantly greater** than 400 cc (P=0.01)…mean amount drained from the patients that were given bethanechol was less than 400 cc."

3.4.c Mean postvoid (residual) volume – subgrouped by short-term versus longer-term

Two trials reported on the mean postvoid residual volume shortly (up to 1 week) after the intervention, and two trials (three comparisons) reported at 1-month post-intervention. There was a significant difference favouring parasympathomimetic shortly post-intervention (MD -77.5 ml, 95% CI: -90.9 to -64.1, $p < 0.001$, $I^2 = 0\%$, Figure 5). However, there was no significant difference at 1-month post-intervention (MD -10.4 ml, 95% CI -49.7 to 29.0, p=0.6), and heterogeneity was very high ($I^2 = 81\%$). The quality of evidence was low (Appendix 2).

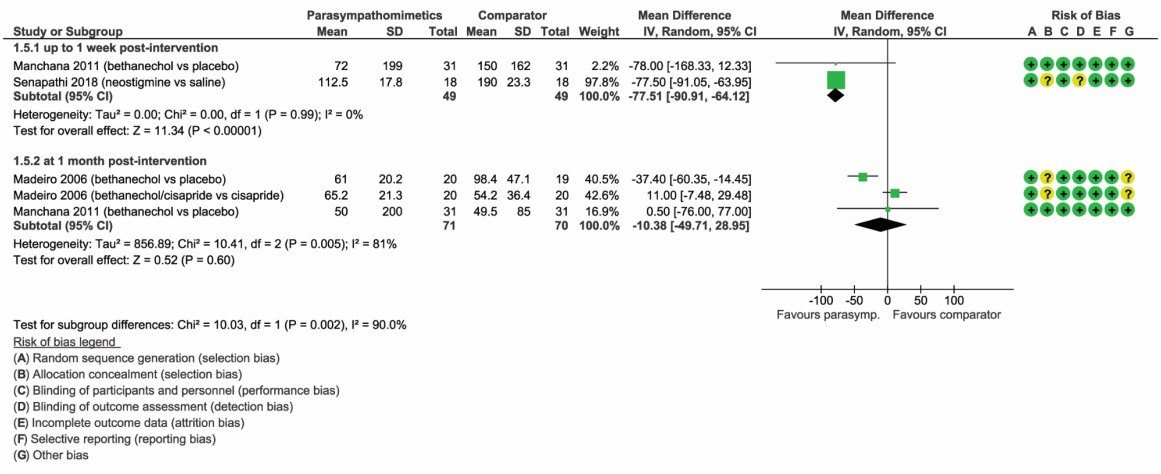

Figure 5: Mean postvoid (residual) volume, subgrouped by timepoint.

3.5. Secondary outcome: Urinary flow

Two studies (which could not be meta-analysed) reported on urinary flow; both reported mean (average) flow rate. One study[23] reported no differences in mean flow rate between bethanechol and placebo groups. One study[22] reported mean flow rate for bethanechol (mean 6.3 mL/second, SD 1.3), cisapride (mean 7.3, SD 2.0), bethanechol + cisapride (mean 6.9, SD 1.7) and placebo (mean 5.1, SD 1.7) groups. The value for the placebo group was significantly lower than for the remaining groups.

3.6. Adverse events

Eight studies (10 comparisons) reported on a variety of adverse events (Appendix 5). Two of the largest trials[24,27] found no adverse events in either group. There was no difference between anticholinesterases and comparators, between choline carbamates and comparators, or overall (OR 1.19, 95% CI 0.62 to 2.28, p = 0.60, I^2 = 25%, Figure 6). The quality of evidence was moderate (Appendix 2).

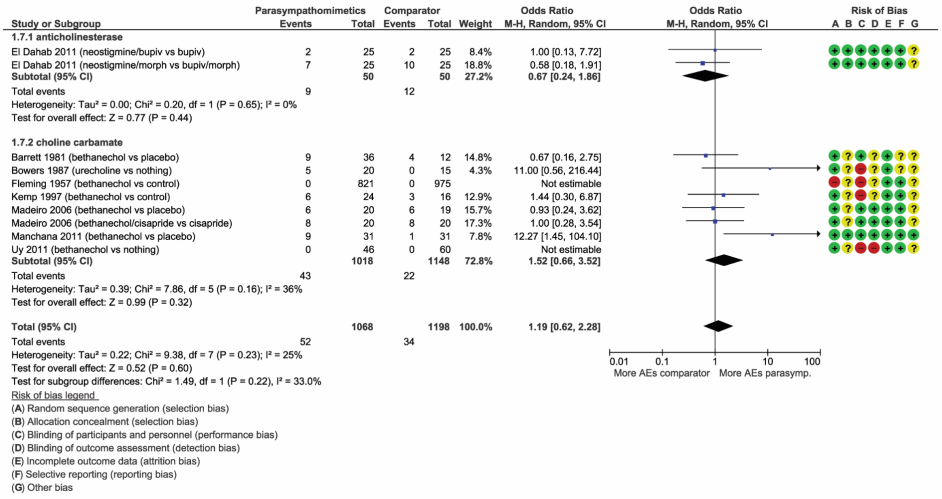

Figure 6: Adverse events for parasympathomimetics vs comparators. *bupi=bupivacaine, morph=morphine.

4 Discussion

Although the literature surrounding parasympathomimetics for treating underactive bladder has been systematically reviewed in the past, this is the first study to complete a formal meta-analysis of all relevant randomised and non-randomised controlled trials. We identified 12 relevant trials with 3024 participants. Meta-analyses significantly favoured parasympathomimetics for the number of patients with urinary retention, although there was no difference in mean post-void volume overall, or in adverse events. There was a significant difference favouring parasympathomimetics up to 1-week post-intervention, but not at 1-month post-intervention. However, the quality of the evidence was low (urinary retention, post-void volume) or moderate (adverse events), and the duration of follow-up was generally short. In addition, some additional parameters of interest, such as reports of nocturia, or urinary tract infections, were not assessed within any of the studies. Nonetheless, due to the current evidence (two trials reporting results up to 1-week post-intervention, and two trials reporting at 1 month), it is not feasible to identify any specific subgroup of patients who could potentially gain greater benefits from the parasympathomimetic therapy than others.

Based upon the available literature, there is only limited evidence supporting parasympathomimetics as an effective pharmaceutical treatment for underactive bladder. This finding is consistent with much of the current review literature, recommending clinicians consider alternative approaches for the management of this condition[10,14,28], with many of the beneficial effects identified in some literature [29] becoming non-significant upon meta-analysis and formal statistical appraisal. Nonetheless, for presentations such as high post-void residual volume, catheterization is the only recognized treatment option and as

such, there is a need to find alternative solutions.

However, the side effects of taking this class of pharmaceuticals may be less significant than commonly presented in literature surrounding this area[8,29,30]. Although individual studies reported some adverse health effects, such as nausea, vomiting, sweating, respiratory depression, hypotension, bradycardia and pruritis, there were no differences between groups across the 2250 participants and seven studies included in this meta-analysis, either overall, or when parasympathomimetics were subgrouped into specific drug types (anticholinesterase inhibitors or choline carbamates). However, for consideration is that 1796 of the participants included in these studies were postpartum women, in whom adverse event monitoring may be confounded by numerous other factors. Additionally, the data is confounded by the various intervention protocols used in these studies (dose, duration, etc.) and there is the possibility of some of the parasympathomimetic interventions underdosing in certain cases.

The need for future studies

For future studies, specific measurements should warrant inclusion to assess the viability of treatments on alleviating underactive bladder. We found that very few studies reported on urinary flow, either maximum flow rates or average flow rates, yet this may present a useful metric, as a characteristic of the most recent definition of underactive bladder is slow urinary flow rates[6]. In addition, many of the assessments were not necessarily those which have been identified as 'most important to patients'. A recent systematic review[31] identified that in males, improvements in urgency incontinence were more important to patients than

other symptoms in any pharmaceutical treatments, along with options which can avoid sexual side effects, provide rapid symptom improvements, and reduce the need for future surgeries. However, very few studies have reported on these metrics. It does highlight the fact that most of the symptoms assessed in past research may be out-of-touch with patient preferences.

In addition, follow-up studies should also assess reports of any alterations to nocturia, whether the parasympathomimetic drugs assist in shortening voiding times, or other affects that could result after their administration. It is also unclear whether there is a potential for tachyphylaxis from any repeated or continued administration of parasympathomimetic drugs. Additionally, there is an emerging awareness of coexisting overactive-underactive bladder [32], which, if present in any of the included patients, may confound the presented data. There were sufficient data to conduct subgroup analyses on intervention type (anticholinesterases vs choline carbamates), or even the timepoint at which the outcome was measured. We were also unable to conduct subgroup analyses by gender, condition/diagnosis, or comparator type due to limited data.

Some benefit could also be obtained by more rigorous testing of specific medications, such as neostigmine, where there is a paucity of research into its viability for treating underactive bladder. As newer parasympathomimetics are investigated for potential future pharmaceutical treatments (i.e. ASP8302), future studies could benefit from larger randomised controlled trials, as well as clear comparisons to placebos, rather than to have an alternative drug or intervention. With the studies included in this systematic review, over 10 separate comparators were used to assess the effectiveness of the various

parasympathomimetics on underactive bladder. Clear correlations to placebo interventions, with stringent study controls, would greatly assist in furthering the robustness of the understanding into the impact of parasympathomimetics.

5 Conclusions

This systematic review incorporates the first formal meta-analysis across the literature surrounding the use of parasympathomimetic drugs for the treatment of underactive bladder. Generally, low quality evidence suggests some benefits for this class of medication, with the additional finding that reports of their side effects during patient treatments are not as significant as the current literature suggests. However, it is not possible to draw clear evidence-based conclusions from the current literature, as it is confounded by very few studies, weak data, high heterogeneity, and a wide variety of patient presentations. It appears that the current recommendations by professional bodies (e.g. ICS, EAU), and conclusions in the literature, are valid, although the meta-analysis identified a clear lack of quality evidence in the field. Overall, the use of parasympathomimetics in treating underactive bladder has been identified as a key area which requires future well-controlled clinical trials on specific patient populations, placebo-based comparators, longer follow-ups, and the recording of a wider range of measurements of bladder functions.

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