Recent insights into pharmaceutical treatments for underactive bladder: a scoping review of recent studies

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Published in:
Australian and New Zealand Continence Journal

DOI:
10.33235/anzcj.30.1.4-10

ORIGINAL ARTICLE

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For referencing Phelps C, Tynan S and Moro C. Recent insights into pharmaceutical treatments for underactive bladder: a scoping review of recent studies. Australian and New Zealand Continence Journal 2024;30(1):4-10.

DOI https://doi.org/10.33235/anzcj.30.1.4-10

Submitted 23 November 2023, accepted 11 March 2024

ABSTRACT

Underactive bladder is a relatively prevalent condition, yet there is only limited research into its diagnosis, treatment, and management. This has increased interest in researching novel treatments for underactive bladder and enhancing understanding of the underlying mechanisms of its presentation. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews was followed as the guiding outline. An *a priori* protocol was developed prior to the commencement of any searching or database assessment and published online on the Open Science Framework, after which the PubMed database was searched for articles published over a five-year period from 1 April 2018 to 1 April 2023. Thirty records were identified, with eight included in the scoping review. Most studies were funded by industry, presenting the risk of considerable bias in study design or reporting. Overall, in the last five years, there have not been any new or upcoming treatments that present a consistent and evidence-based ability, across multiple articles, to alleviate underactive bladder. However, research is ongoing, and some receptor systems may hold some potential to assist in the prevention of the disorder.

Keywords detrusor underactivity, lower urinary tract symptoms, PRISMA, bladder dysfunction, urinary bladder

INTRODUCTION

Underactive bladder (UAB) is a lower urinary tract symptom complex characterised by slow urinary stream, hesitancy, and straining to void.[1] The symptoms of UAB are often associated with observations of detrusor underactivity (DU), which is the weakening or shortening of detrusor muscle contraction resulting in the incomplete or prolonged emptying of the bladder.[2] Symptoms of nocturia and frequency are also common complaints associated with UAB, as a result of incomplete emptying and urinary retention.[2,3] Although parasympathomimetics are often presented as the first-line pharmaceutical treatment option for UAB, the evidence supporting their success is often lacking.[4] As such, there is a continued need to review and summarise advancements in the field to identify upcoming or alternative treatments and expand knowledge of underactive bladder treatments.

The prevalence of lower urinary tract symptoms (LUTS) associated with UAB is approximately 9–28% in the adult population,[5] and this generally increases with age. Evaluations for non-neurogenic LUTS detected UAB in up to 28% of males aged under the age of 50 years, and 48% of those over the age of 70 years.[6] Similarly, UAB was detected in up to 45% of females aged over 70 years.[6] Furthermore, DU has been attributed to both myogenic and neurogenic aetiologies and may no longer be exclusively associated with the aging population.[7]

The absence of DU pathogenesis research corresponds to current ineffective treatment options for UAB.[8] Besides parasympathomimetics, treatment options include surgery, pharmacotherapy, intermittent catheterisation, and conservative methods.[8] Pharmaceutical treatments include a combination of alpha-adrenergic receptor blockers to reduce outlet obstruction pressure through decreased urethral sphincter tonicity and drugs that promote detrusor contractility, such as cholinergic agents.[8] Muscarinic agonists (bethanechol) and cholinesterase inhibitors (distigmine) in combination with alpha-blockers, or prostaglandin E2 and acotiamide, as separate

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medications, are used for bladder outflow resistance and to increase post-void residual volume (PVR).[8,9]

However, the efficacy of muscarinic agonists for DU has not been supported by recent literature, due to limited improvement, as well as limited data supporting the continued use of parasympathomimetics for bladder health.[4,9] In addition, cholinesterase inhibitors may have adverse side effects such as faecal incontinence, diarrhea, and urination,[8] affecting compliance rates as patients are less likely to continue prescribed medication. A recent systematic review and meta-analysis assessed the effectiveness of parasympathomimetics for the treatment of UAB and reported a paucity of evidence with short follow-up periods to support their use. This highlighted the need for well-controlled future trials to further warrant their use.[4] The European Association of Urology has emphasised the discontinued use of parasympathomimetics for UAB due to inadequate research and potential side effects, which must be considered for patient compliance.[10] Although there is increased occurrence of UAB with ageing populations and an increase in clinical prevalence, UAB and associated DU are primarily unrecognised and, subsequently, under-researched.[11]

REVIEW QUESTION

With an increasing prevalence in the diagnosis of UAB, and a paucity of viable treatment options, this review scopes the current literature over the last five years to identify any recent research developments that may be of interest to patients and healthcare professionals. This article is guided by the research question: Does recent research in the literature identify any potential tissue targets, or pharmaceutical medications, for the future treatments of underactive bladder?

METHODS

Protocol and registration

This scoping review is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[12] An *a priori* protocol was developed prior to the commencement of any searching or database assessment and published online through Open Science Framework (https://osf.io/z2hg4). It was hypothesised that underactive bladder remains an under-researched area, however, there will be suggestions in the literature for future alternative pharmaceutical therapies that may be effective. A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews and JBI Evidence Synthesis was conducted and no current or underway systematic reviews or scoping reviews on the topic were identified.

Eligibility criteria

This scoping review included all English language full-text articles published on PubMed (MEDLINE database). The PubMed database was searched for articles published over a five-year period from the dates 1 April 2018 to 1 April 2023. The search was undertaken to identify original research papers on pharmaceuticals for the treatment of any contractile disorders associated with UAB. Studies on humans and animals (both in vivo and in vitro) were included from any age, gender, or weight. Patients presenting with UAB as a consequence of surgery or injury were excluded. The review excluded reviews, abstracts, and clinical trials.

Search strategy

The following search string was employed

(formatted for the PubMed search):

("underactive bladder"[Title/Abstract]

OR UAB[Title/Abstract]

OR "detrusor underactivity"[Title/Abstract]

OR "bladder underactivity"[Title/Abstract]

OR "Urinary Bladder, Underactive"[Mesh])

AND (Drug[Title/Abstract]

OR medication[Title/Abstract]

OR pharmaceutical[Title/Abstract]*

OR pharmacotherapy[Title/Abstract]

OR alpha-blocker[Title/Abstract]

OR "adrenergic antagonists"[Title/Abstract]

OR "cholinesterase inhibitors"[Title/Abstract]

OR "muscarinic agonists"[Title/Abstract])

AND 2018/04/01:2023/04/01[dp]

NOT (Review[Publication Type]).

To identify the grey literature, a forward-backwards scan was undertaken by two independent authors (CP and ST) by searching the reference lists of the identified studies in the initial search to identify any additional studies not captured from the database search.

Types of Sources

This scoping review considered both experimental and quasi-experimental study designs, including: randomised controlled trials; non-randomised controlled trials; before and after studies; and interrupted time-series studies. In addition, analytical observational studies, including: prospective and retrospective cohort studies; case-control studies; and analytical cross-sectional studies were considered for inclusion. This review also considered descriptive observational study designs, including: case series; individual case reports; and descriptive cross-sectional studies for inclusion.

Study of evidence selection

Two independent authors (CP and ST) conducted the screening of the literature by an initial title and abstract scan followed by a full-text review. This was conducted using Covidence, an online screening and data extraction tool (covidence.org, Melbourne, VIC,

Australia). Data extraction was conducted manually using Microsoft Excel independently by the two authors (CP and ST). Discrepancies in screening and extractions were referred to a third independent author (CM) for resolution.

Data extraction

The primary outcome of studies included in this scoping review was the effectiveness of pharmaceuticals for underactive bladder treatment and management. This included parameters such as benefits observed, alleviation of any symptoms associated with UAB (infection, retention, stones etc.), follow-up periods, and adverse side effects experienced.

RESULTS

Search results

The electronic search on the PubMed database from 1 April 2018 to 1 April 2023 returned 28 articles, which were title and abstract screened, along with an additional two articles from forward-backwards searching. The outcomes of this screen resulted in eight articles that underwent full-text review. Of the 10 reviewed in full-text, eight met the inclusion criteria and were included in the final analysis of this scoping review (Figure 1).

Included studies

Eight studies were included in this scoping review, comprising a range of study designs and varied study populations (Table 1). Six studies were undertaken in Japan, one study in the United States and one study in Taiwan, in either research laboratories or medical institutions. Five studies included patient participants, and three studies included animals (such as monkeys and rats). Four studies included only female participants and three studies included both males (range 57–63.3%) and females (range 36.7–43%). One study did not have a formal control group. There was also variation in the age of participants, ranging from 24 weeks old to 82 years old.

DISCUSSION

Evaluation of the literature

The literature does provide insights into potential new treatments for underactive bladder. Although

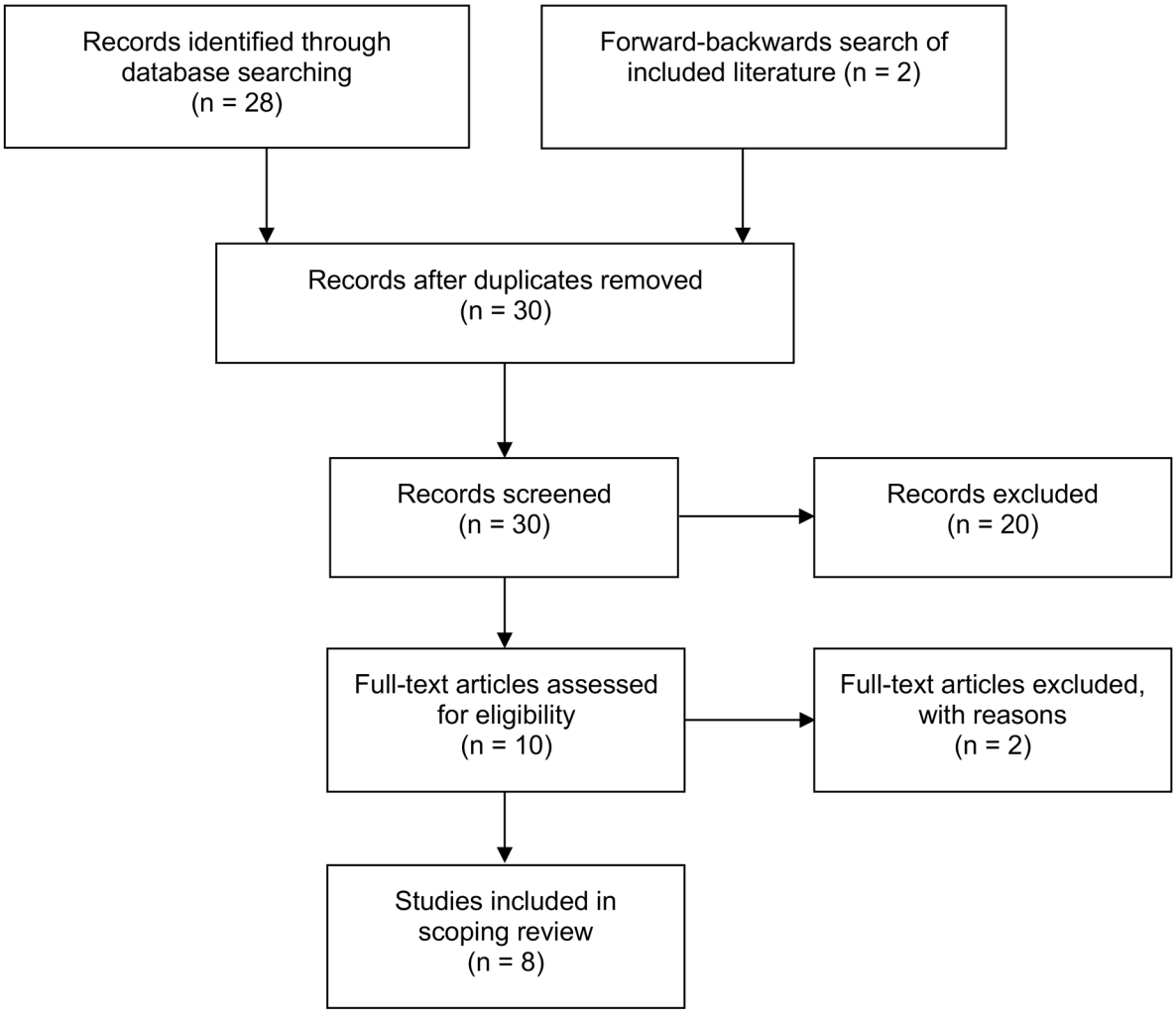

Figure 1. PRISMA flow chart for identification and inclusion of studies.

Table 1. General characteristics of included studies: participant information and study design.

Author, year location	Study design, follow-up	Participants	Number of participants (n in each arm)	Gender	Age	Intervention: Dose, frequency, duration	Comparator/s: Dose, frequency, duration
Chen et al[13] 2022 Taiwan	Retrospective. Video urodynamic study	Female patients unable to spontaneously void or with increased PVR (detrusor underactivity). All patients had contractility index scores (Pdet+5 × Qmax) of<100	409 (67 conservative CIC indwell catheter, 206 medical treatment, 87 transurethral incision of the bladder neck, 35 urethral sphincter botulinum, toxin A injection, 14 pelvic organ prolapse surgery)	0% male, 100% female	18 years (mean)	Either alpha blockers with or without cholinergic agent initially, if conservative treatment failed other treatment were suggested (dosage not stated).	Urethral sphincter BoNTA-A injection
Matsukawa et al[14] 2021 Japan	Comparative study using data from a prospective, open-label and non-randomised controlled trial	Patients experiencing LUTS and diagnosed via a DU pressure-flow study	126 (59 tadalafil, 67 silodosin)	100% male, 0% female	50–84 years	Tadalafil (5mg/day), 12 months	Silodosin (8mg/day), 12 months
Matsuya et al[15] 2018 Japan	*In vitro* isolated tissue and voiding characteristics	Cynomolgus monkeys (Macaca fascicularis)	46 (4 controls for radical hysterectomy, 42 experimental)	0% male, 100% female	3–8 years old	A1: EP2 and EP3 receptor dual agonist (ONO-8055)	A2: Distigmine
Sekido et al[16] 2020 Japan	Cystometry	STZ-induced diabetic Sprague-Dawley rats	23 (6 alpha-blocker, 8 cholinesterase inhibitor, 9 EP2/3 dual agonist)	100% male, 0% female	24 weeks old	A1:EP2/3 dual agonist (ONO-8055, 0.01 and 0.03 mg/kg, 1x oral dose)	A2: α-blocker (tamsulosin, 0.1 and 0.3 mg/kg, 1x oral dose) A3: cholisterase inhibitor (distigmine 0.3 and 1.0 mg/kg, 1x oral dose)
Sugimoto et al[17] 2019 Japan	Non-randomised single arm study	Patients 20 years old or younger with an IPSS of ≥8 points and a PVR of ≥50ml despite the use of an alpha-blocker plus a cholinergic drug.	7	57% male, 43% female	72–82 years	Acotiamide hydrochloride hydrate (100mg 3x/day, for 2 weeks)	NA

Author, year location	Study design, follow-up	Participants	Number of participants (n in each arm)	Gender	Age	Intervention: Dose, frequency, duration	Comparator/s: Dose, frequency, duration
van Till et al[18] 2022 Europe and Japan	Randomised, double-blind, placebo-controlled multicentre study	Patients experiencing symptoms of UAB (PVR > 100ml) without bladder outlet obstruction or observable overactive bladder	135 patients (65 ASP8302, 70 placebo)	Placebo: 57% male, 43% female ASP8302: 60.8% male, 39.2% female	Placebo: 61.1 years (mean) ASP8302: 62.8 years (mean)	ASP8302 (100mg/day), 4 weeks	Placebo (100mg/day), 4 weeks
Yonekubo-Awaka et al[19] 2022 Japan	Urodynamics	Sprague-Dawley rats	4–13	0% male, 100% female	9 weeks old	Silodosin (0.3 or 1mg/kg, for 4 weeks)	Urapidil (30 or 100mg/kg x1/day, for 4 weeks)
Yoshida et al[20] 2022 Japan	Multicenter, randomised, double-blinded, placebo-controlled phase 2 trial. 13 weeks	Participants >20 years of age with both voiding symptoms and OAB, PVR ≤ 300 mL, and a diagnosis of DU	60 (42 intervention; 18 control)	63.3% male, 36.7% female	70.8 years (mean)	A1: oral TAC-302 200mg, 2x daily, 12 weeks	A2: Placebo 2x daily, 12 weeks

Abbreviations:
PVR = post-void residual volume
DU = detrusor underactivity
IPSS = International Prostate Symptom score

activation of prostaglandin EP2 and EP3 did not cause major improvements in the rat bladder contractions,[16] there were some benefits, such as decreased postvoid residual volume. In addition, in some cases, voiding function was improved to the same degree as with parasympathomimetics[15] by using an EP2/EP3 dual agonist. As such, although consistent benefits have not been clearly identified, these suggestions promote prostaglandins as a receptor system that certainly warrants further investigation and potentially important in bladder contractions.[21–25]

Although recent literature has suggested that parasympathomimetics are unlikely to be helpful in alleviating underactive bladder,[4] Sugimoto et al[17] identified promising results for acotiamide (a non-selective muscarinic antagonist) towards increasing bladder pressure during voiding. This means that although only seven patients were included in this single-arm study, the potential for parasympathomimetics may not be entirely unevidenced by the research just yet.

Within the bladder tissue itself, there are a number of systems that could be impacted in underactive bladder. The most assessed is the muscarinic receptors, responding to acetylcholine.[26] This has also generated some interest in the M3 allosteric modulator ASP8302, which appears well tolerated, and may present some benefits to males with underactive bladder.[18] The urothelium also has systems that induce contraction in response to agonists, such as the alpha-adrenoceptor,[27] 5-HT,[28] and prostanoid[29] receptors. It is unclear how these systems are involved in overall bladder contractions, but any inhibition of the receptors or second messenger mechanisms may, in some way, inhibit bladder function and present as underactive bladder. Alternatively, mechanisms such as activation of the nitric oxide pathway[30] or beta-adrenoceptor[31] system may directly induce relaxation of the tissue itself. The nitric oxide system has been of partial recent interest, with both tadalafil and silodosin demonstrating some benefits towards the reduction of lower urinary tract symptoms in men with non-neurogenic detrusor underactivity.[14] As more research is conducted into the mechanisms underlying bladder physiology, and the receptors involved, systems such as these may present opportunistic areas for future research.

Of particular concern is the potential for high risk of bias within the literature. Six of the eight studies received funding from pharmaceutical companies with an interest in the treatment regimens. Although for each case the connection was clearly disclosed, this raises the prospect that independent, conflict-free research might be of interest to even the balance and reduce bias across the samples. This introduction of pharmaceutical findings would also make meta-analyses difficult, as the high risk of bias would limit the usefulness of the results presented in a broader context.

CONCLUSION

In conclusion, there remains limited recently published research into treatments for underactive bladder, and there is great variety in the methods used for their assessment, making summated and general conclusions challenging. Study findings are confounded by a potentially high risk of bias, due to a predominance of industry-funded studies. Nonetheless, pre-clinical research is ongoing and uncovering potential receptor systems that could be dysfunctional in the urinary bladder, presenting these as novel targets for future treatment development.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

The authors received no funding for this study.

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