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A Scoping Review of the Oral Treatment Options for the Management of Detrusor Sphincter Dyssynergia

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ABSTRACT

Background: Adult neurogenic lower urinary tract dysfunction may be associated with detrusor sphincter dyssynergia (DSD). Given the sparsity of the literature and the absence of official guidelines regarding the use of oral medications in the management of DSD, this scoping review aims to critically assess the available evidence to guide future research and practice.

Methods: We conducted a systematic scoping review of articles published from 1950 to July 2023 using PubMed, MedLine, Scopus and CINAHL databases to assess all oral treatment options for DSD. All study designs were included. The search was limited to English and French literature regarding human patients over 18 years of age with DSD.

Results: Of the 899 records screened, 15 studies were included, involving a total of 257 participants. Alpha-adrenergic blockers, nitric oxyde and muscle relaxants have been used in the treatment of DSD. A decrease of postvoid residual volumes and an improvement of symptom scores as well as urine flow rates were reported in several studies. Regarding the alpha-adrenergic blockers, five of the six studies that detailed postvoid residual volumes and subjective improvement noted benefits in most patients. Additionally, two of the three studies that addressed mean flow rate observed improvements in most patients. All six studies that documented adverse effects found side effects in only a slight minority of patients.

Conclusions: Alpha-adrenergic blockers are promising, but there is lacking evidence on the oral treatment of DSD. This study highlights the importance of conducting more studies to draw solid conclusions and stop treating these patients empirically.

1 | Introduction

Adult neurogenic lower urinary tract dysfunction (ANLUTD) has a prevalence of 40%–90% in patients with multiple sclerosis, 37%–72% in patients with Parkison's disease, 15% in patients with a stroke, 70%–84% in patients with spinal cord injuries, and 40%–60.9% in patients with spina bifida [1]. In some cases, NB may be associated with detrusor sphincter dyssynergia (DSD), an impaired coordination between the detrusor and urethral sphincters during voiding [2]. Some conditions commonly associated with DSD include multiple sclerosis, spinal cord injuries and spina bifida. It can sometimes also be caused by a spinobulbospinal tract disturbance occurring in transverse myelitis, HTLV-1 (Human T-lymphotrophic virus type 1) and stroke [3]. Patients with DSD experience voiding symptoms, such as urinary hesitancy, interrupted urinary stream, sensation of incomplete bladder emptying and double voiding [2].

Treatments should address voiding dysfunctions, improve overall quality of life [4], and avert possible complications such as repeated urinary tract infections or renal failure [2, 5]. Many treatment options aim to achieve these goals: oral medications, intermittent catheterization (IC), botulinum toxin-A injections in the striated sphincter, urethral stents (although not marketed in Canada anymore) and sphincterotomy [3]. Patients also often use self-catheterization or indwelling urethral catheters (IUC) [6]. If medications do not ensure adequate management of their

symptoms, they may resort to the other effective, but nonetheless more invasive alternatives.

Data regarding oral medication for the treatment of DSD are scattered and current clinical guidelines provide insufficient information for the evidence-based pharmacological management of DSD. Indeed, as of 2023, the Canadian Urological Association has no guidelines regarding the oral medication for DSD [7], nor do the American Urological Association (AUA) [8] and the European Association of Urology (EAU) [9]. However, the latter two do have an oral drug recommendation for voiding symptoms related to NB, stating that alpha-blockers may improve voiding parameters [8, 9]. These recommendations are not specific to DSD and therefore cannot be applied with certainty for this condition.

Although the evidence has never been synthetized, oral medications seem to be a good option to treat DSD. Not only do they have the potential to minimize voiding symptoms and DSD complications, but they also represent conservative alternatives for patients for which more invasive treatments such as surgery can still be avoided [2]. A recent review has recently examined possible treatment options in the treatment of DSD, but without sufficient emphasis on oral medications, which we deem to be an interesting and accessible alternative [10]. Therefore, this scoping review examines for the first time to our knowledge all possible oral treatment options for adults with DSD and their related effects on signs and symptoms of voiding dysfunction. It will further be discussed how poor the evidence on this topic is, and how important it is to do more research to draw clear conclusions on the oral treatment of DSD and stop treating these patients empirically.

2 | Methods

This scoping review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines [11]. We chose to not critically appraise the individual sources of evidence, since, as stated in the literature, scoping reviews aim to create a broad summary of the available evidence rather than a detailed quantitative or qualitative analysis. It is thus typically not required to perform a methodological appraisal or risk of bias assessment for the included sources [12]. The protocol was registered on PROSPERO (International prospective register of systematic reviews) under the number CRD42023446515.

2.1 | Data Sources

In this study, we conducted a search of research articles dating from inception to July 2023 using PubMed (United States National Libray of Medicine National Institutes of Health), MedLine (by EPSCO), Scopus (by Elsevier) and CINAHL (Cumulative Index to to Nursing and Allied Health literature by EBSCO) databases. A preliminary search using the terms "bladder sphincter dyssynergia treatment" was performed through PubMed to identify relevant key words for this literature review. The following key words were used in the final search: "neurogenic bladder," "bladder sphincter dyssynergia," "external urethral sphincter," "detrusor sphincter dyssynergia," "neurogenic urinary bladder," "oral treatment," "oral therapy," "PO treatment," "PO therapy," "pharmacologic treatment," "pharmacologic therapy," "pharmacotherapy," "drug therapy," "drug treatment" and "medication." Additionally, we manually searched the reference lists of included studies and relevant reviews or guidelines to identify any additional articles. To explore the gray literature, we searched conference abstracts of the International Continence Society (ICS) using the keyword "dyssynergia". Further details about the search strategy are available in Appendix 1.

The only MeSH term used was "neurogenic urinary bladder" with "drug therapy" as a subheading, whilst the CINAHL subject heading used was "neurogenic bladder" with that same subheading. No subject heading was used in Scopus. We also restricted the search to an adult population by using the words "adult," "woman" and "man".

2.2 | Selection Process

The method was first validated by two authors (S.I., L-M.T) and the search as well as data extraction were then performed independently by two others (M-A.B., A.T.). After removal of duplicates, each record was first screened considering the title and abstract by both of these two reviewers. Thereafter, a second screening based on the full text was undertaken to verify the eligibility criteria. Disagreements were mediated with the help of a third researcher (S.I.).

2.3 | Eligibility Criteria

Only registered online and peer-reviewed articles were considered. All sample sizes, studies and abstracts, regardless of their publication dates, were included. Systematic reviews were excluded but all other types of study designs were included, among others randomized controlled trials, quasi-experimental trials, cohort studies, case reports and case series. Studies with or without a comparator group were included, with no specific healthcare or geographic setting. Studies included were limited to English and French literature regarding human patients over 18 years of age and with an ANLUTD regardless of treatment or follow up duration. Because little research has been done on DSD, we included studies that were not specific to DSD, but still somewhat reported the outcomes of oral drugs on the treatment of DSD. Additionally, we included studies that presented outcomes for DSD patients grouped with patients having other types of ANLUTD. Articles were also included if they evaluated the effects of an oral treatment for DSD. Eligible outcomes included subjective improvement in voiding symptoms, postvoid residual (PVR) and urine flow rate, but the latter outcomes did not all have to be available in the studies for us to include them. No restrictions were applied for the comparison group.

2.4 | Data Extraction

The following characteristics were extracted: study design, patient's neurological disease, patient's sex and age, type of

medication, treatment duration and follow-up time, along with outcomes measured by patient questionnaire and by urodynamic testing. Regarding the outcomes, we focused on patient satisfaction as well as improvement of voiding symptoms, PVR and urine flow rate. Studies were grouped according to treatment type for DSD.

3 | Results

3.1 | Literature Search

As shown by the PRISMA flow diagram presented in Figure 1, the primary search yielded 1058 records, but 758 were screened after the removal of the duplicates. Of that, 158 were assessed for eligibility based on their title and abstract, and 15 were included in our study based on their full text. A total of 141 added records were identified by citation searching, other authors' publications searching, reference searching and other articles searching in PubMed from three of the most relevant articles that we had previously included [13–15] as well as from 18 systematic reviews that we found [3, 5, 10, 16–30]. No relevant abstracts were found on the International Continence Society database.

Table 1 reports the characteristics of included studies and patients. Table 2 reports the main outcomes observed in studies that evaluated oral drugs for DSD. Adverse effects associated with these treatments are detailed in Table 3.

3.2 | Study Design and Patient Characteristics

Nine case series, three case reports and three cohort studies were included. Two of the cohort studies were not available in French or in English, so data were extracted from their abstracts. Six records focused exclusively on male patients, whilst six included or were limited to only female patients, for a total of 257 patients whose data was included in this literature review. Patient age ranged from 18 to 84 (Table 1). All of them had an ANLUTD with DSD, sometimes associated with an overactive bladder or external urethral sphincter spasticity. Their urological condition was related to multiple sclerosis, spinal cord injury, brain or peripheral nervous system lesions, myelopathy, multiple-system atrophy or traumatic surgery. Moreover, studies were published between 1975 and 2010.

3.3 | Muscle Relaxants

Among the three studies that focused on muscle relaxants, all reported a reduction in PVR, while two reported an improvement in voiding symptoms as well. However, none showed an improvement in flow rate, as seen in Table 2. The follow-up time ranged between 12 days to 6 months.

As shown in Table 3, reported side effects ranged from none with baclofen, to overall weakness, dizziness, fatigue or malaise with dantrolene sodium [31, 32]. All side effects were transitory, except in one of the DSD cases. The authors also noted that at

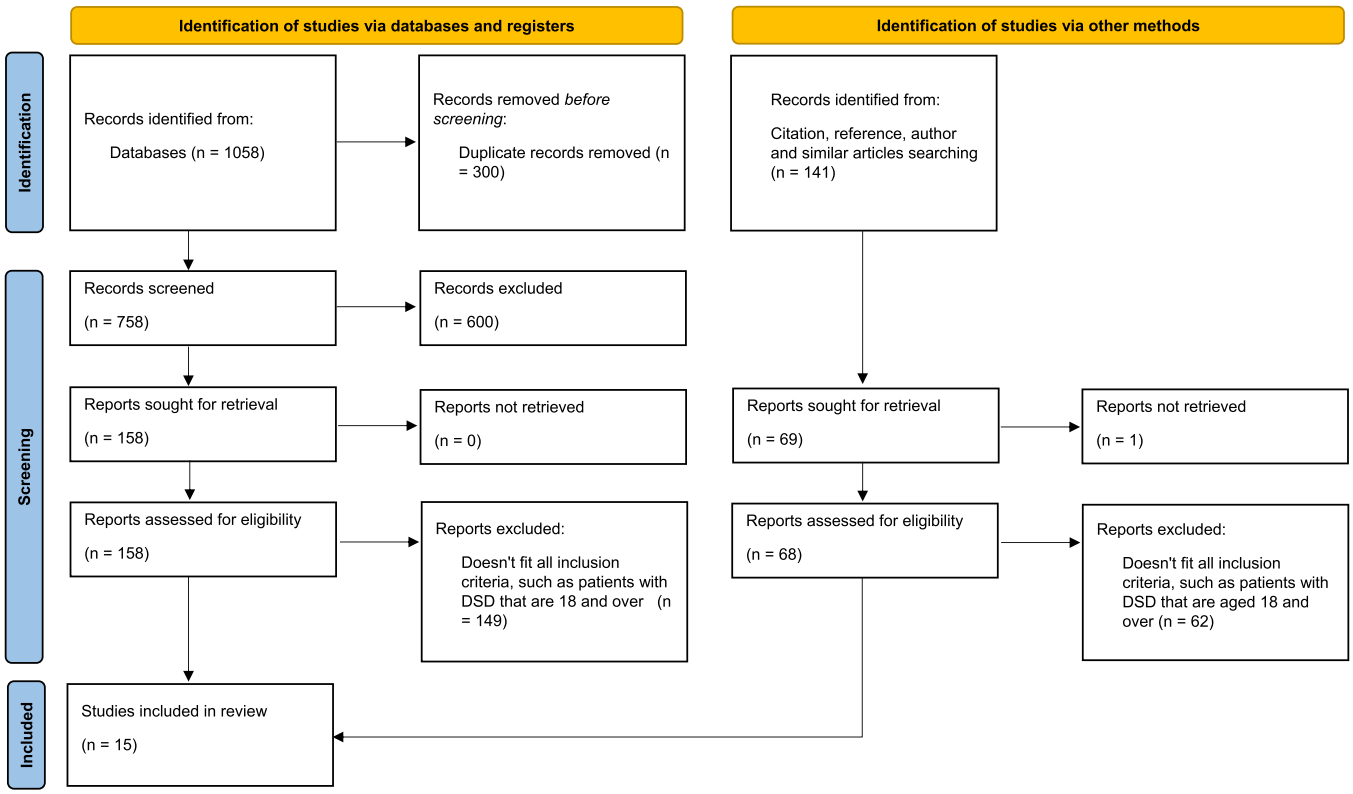

FIGURE 1 | PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

TABLE 1 | Patient's and included studies' characteristics.

Authors	Patients' neurological disease/bladder problems	n	Medication name	Patients's sex	Patients' age (mean)	Study design
Muscle relaxants						
Kiesswetter and Schober (1975) [31]	MS/OAB with DSD	1	Baclofen	Male	68	Case report[a]
Hackler and al. (1980) [32]	SCI/EUS spasticity and DSD	4	Dantrolene sodium	NR	18–45[b]	Case series
Leyson et al. (1980) [33]	SCI/DSD	25	Baclofen	All male	19–61[b]	Case series
Alpha adrenergic blocking agents						
Hachen (1980) [34]	SCI/automatic bladder with DSD and EUS spasticity	34	Phenoxybenzamine hydrochloride	All male	36–50[b]	Case series
Buczyński (1984) [35]	SCI/DSD	NR	Phenoxybenzamine	NR	NR	Case series
Gotoh and al. (1980) [36]	CVA or SCI/DSD	61	Prazosin	NR	NR	Abstract from cohort study
Jensen (1981) [37]	MS or myelopathy/OAB with DSD	5	Prazosin	3 males, 10 females[b]	20–67 (44)[b]	Case series
Chancellor and al. (1993) [38]	SCI/DSD	15	Terazosin	All male	18–45	Case series
Perkash (1995) [13]	SCI/DSD	11	Terazosin	All male	26–74 (54)[a]	Case series
Yasuda and al. (1996) [14]	Brain lesions, spinal cord diseases, PNS diseases, combination of conditions/DSD	25	Urapidil	27 males, 20 females[b]	20–84 (62.9)[b]	Cohort study
		16		28 males, 16 females[b]		
Stankovich and al. (2004) [39]	NR/DSD	28	Tamsulosin	8 males, 20 females	NR	Abstract from cohort study
Ito and al. (2006) [40]	Multiple-system atrophy/OAB with DSD	18	Prazosin, urapidil, moxisylyte or tamsulosin	141 males, 104 females[b]	40–78 (59)[b]	Case series
Decavel and al. (2007) [41]	Dysbaric myelitis/complete urinary retention with DSD	1	NR	Female	21	Case report
Nitric oxyde						
Reitz and al. (2004) [15]	SCI/OAB with DSD	12	Isosorbide dinitrate	All male	29–36 (32)	Case series
Cholinergic agonist agent and antibiotic						
Justiz and al. (2010) [42]	Endoscopic lysis of adhesions for severe scarring of the epidural space/DSD	1	Bethanecol and nitrofurantoin	Female	73	Case report

Abbreviations: CVA, cerebral vascular attack; DSD, detrusor-sphincter dyssynergia; EUS, external urethral sphincter; MS, multiple sclerosis; n, number of patients with DSD; NR, not reported; PNS, peripheral nervous system; Pt, patient; SCI, spinal cord injury.

[a]This case report was included in a case series study that reported other cases of neurogenic bladder that were not DSD.

[b]Not specific to DSD patients; the authors did not differentiate the results between patients who had DSD and those who did not.

TABLE 2 | Studies that evaluated oral drugs as a treatment for destrusor-sphincter dyssynergia.

Authors	Medication name	Maximum medication dosage	Follow-up time	Success rate	Description or % of improved maximum PVR after treatment (mL)	Description or % of improved mean flow (mL/s)	Improvement in voiding symptoms	Further details of study
Muscle relaxants								
Kiesswetter and Schober (1975) [31]	Baclofen	20 mg, TID	12 days	100.0%	Baclofen restored the normal condition.	NR	Baclofen restored the normal condition.	
Hackler and al. (1980) [32]	Dantrolene sodium	400–600 mg, QID	2–5 weeks	50.0%	50.0% (≤ 5100)	NR	NR	
Leyson and al. (1980) [33]	Baclofen	80–160 mg, divided in three doses daily	6 months	76.0%[a]	76.0%[a] (≤ 90)	NR	NR	
Alpha adrenergic blocking agents								
Hachen (1980) [34]	Phenoxybenzamine	20 mg, BID	1 month	4.8%[a]	4.8%[a,b] (≤ 75)	NR	NR	
Buczyński (1984) [35]	Phenoxybenzamine	30 mg, DIE	2 weeks	80% when adminstered within 3 months after spinal cord injury.	NR	NR	NR	
Gotoh and al. (1990) [36]	Prazosin	NR	NR		The amount of residual urine significantly decreased for all except in patients with lumbar cord injury with complete paralysis.	NR	Better response rates in subjective improvement amongst patients with CVA or SCI with incomplete paralysis, compared to complete paralysis.	The rates of needing CIC did not change.
Jensen (1981) [37]	Prazosin	1 or 2 mg, TID	2–8 weeks		NR	40.0%	Subjective improvement in micturition.	
Chancellor and al. (1993) [38]	Terazosin	5 mg, DIE	4–12 weeks		NR	No significant improvement.	NR	

(Continues)

TABLE 2 | (Continued)

Authors	Medication name	Maximum medication dosage	Follow-up time	Success rate	Description or % of improved maximum PVR after treatment (mL)	Description or % of improved mean flow (mL/s)	Improvement in voiding symptoms	Further details of study
Perkash (1995) [13]	Terazosin	1–2 mg, BID	One week		NR	NR	Subjective improvement in 50% of patients[a].	
Yasuda and al. (1996) [14]	Urapidil	15 mg TID	4 weeks	19.5%	91.5%[a] (mean 125.5 mL within the success group)	91.5%[a] (11.4)	The sum of obstructive symptom scores was decreased significantly in all groups[a].	
		15 mg TID for 2 weeks, followed by 30 mg TID for 2 weeks			55.8%[a] (mean 99.3 mL within the success group)	93.0%[a] (11.4)		
Stankovich and al. (2004) [39]	Tamsulosin	0.4 mg, DIE	2 months		There was a significant decrease in the volume of the residual urine.	There was an increase in maximal flow rate.	QoL raised in 96% of patients and by 58%.	
Ito and al. (2006) [40]	Prazosin, urapidil, moxisylyte or tamsulosin	1–3 mg, 30 mg, 30 mg, 0.1–0.2 mg, each DIE	2 months	44.4%	NR	NR	NR	The effectiveness of alpha blockers was not clearly associated with DSD.
Decavel and al. (2007) [41]	NR	NR	NR	100.0%	No more urinary retention after treatment.	NR	The patient still experienced painful urination in the morning.	
Nitric oxyde								
Reitz and al. (2004) [15]	Isosorbide dinitrate	10 mg, one dose only	15 min		100.0% (73 mL)	NR	Improvement of EUS pressure at rest and during dyssynergic contraction.	PVR was only evaluated in 6 patients, who all used suprapubic triggering for bladder emptying.

(Continues)

TABLE 2 | (Continued)

Authors	Medication name	Maximum medication dosage	Follow-up time	Success rate	Description or % of improved maximum PVR after treatment (mL)	Description or % of improved mean flow (mL/s)	Improvement in voiding symptoms	Further details of study
Cholinergic agonist agent and antibiotic								
Justiz and al. (2010) [42]	Bethanecol and nitrofurantoin	NR	Bethanecol for 3 years, and another 3 years with added nitrofurantoin	100.0%	Nitrofurantoin allowed the patient to void spontaneously with subsequent residual volumes of 35 mL.	NR	Nitrofurantoin allowed the patient to void spontaneously with subsequent residual volumes of 35 mL.	No improvement in urodynamics for 3 years on bethanecol, but major improvement after starting a course of nitrofurantoin, even after resolution of the infection.

Abbreviations: CIC, clean intermittent catheterization; CVA, cerebral vascular attack; DSD, detrusor-sphincter dyssynergia; EUS, external urethral sphincter; IC, intermittent catheterization; MS, multiple sclerosis; n, number of patients with DSD; NR, not reported; PNS, peripheral nervous system; Pt, patient; PVR, post-void residual; QoL, quality of life; SCI, spinal cord injury.
[a]Not specific to DSD patients; the authors did not differentiate the results between patients who had DSD and those who did not.
[b]Not signifiant.

600 mg doses of dantrolene sodium, hepatotoxicity was a possibility [32]. Baclofen induced some somnolence in quadriplegics, as well as weakness of the upper extremities in paraplegics. Nonetheless, adverse effects only occurred in that study if the drug dosage was increased suddenly within the first 3 days of treatment, and usually in patients over 45 years old [33] (Table 3).

3.4 | Alpha-Adrenergic Blocking Agents

Studies on alpha-adrenergic blocking agents had a follow-up time that ranged between one to 12 weeks. All were non-selective, except for tamsulosin, which is selective for the alpha-1A receptors.

PVR decreased significantly in the groups treated with prazosin, urapidil and tamsulosin (Table 2) [14, 36, 39]. Nonetheless, the PVR improvement was not significant amongst lumbar cord injury patients with complete paralysis treated with prazosin [36]. While there was an improvement in the maximal flow rate amongst patients treated with tamsulosin [39], it was not the case with terazosin [38]. Subjective improvement was noted by both groups of patients treated with prazosin [36, 37], by half of the patients treated with terazosin [13], and an improvement of the quality of life in almost all patients who took tamsulosin [39]. Yet, some patients treated with alpha-blocking medications still experienced painful urination in the morning [41].

The following side effects were reported amongst patients taking alpha-adrenergic blocking agents: dizziness, lethargy, nasal obstruction, diarrhea, hot flashes and exacerbation of urinary frequency and urinary incontinence (Table 3).

3.5 | Nitric Oxyde

The effects of the treatment with isosorbide dinitrate was evaluated in all patients after 15 min, and showed a significant reduction of PVR. There was also an improvement of external urethral sphincter pressure at rest and during dyssynergic contraction (Table 2). Headache, low blood pressure and increased heart rate (only for 30 min, with no clinical significance) were the main adverse effects reported [15] (Table 3).

3.6 | Cholinergic Agonist and Antibiotic

Finally, the patient who first took bethanecol for 3 years did not show improvement of urodynamics during that period. However, the addition of nitrofurantoin allowed the patient to void spontaneously and with PVR under 35 ml; that treatment was thus maintained for three additional years (Table 2). That patient did not suffer from any adverse effect [42] (Table 3).

4 | Discussion

4.1 | Interpretation

The objective of this scoping review was to examine all possible oral treatment options and their related effects in the

TABLE 3 | Studies that evaluated adverse effects of oral drugs as a treatment for detrusor-sphincter dyssynergia.

Authors	Medication name	Negative effect rate	Adverse effects encountered (%)	Further details of study
Muscle relaxants				
Kiesswetter and Schober (1975) [31]	Baclofen	0.0%		
Hackler and al. (1980) [32]	Dantrolene sodium	80.0%[a]	Overall weakness, dizziness, fatigue and malaise	All side effects were transitory, except in one of the DSD cases. At 600 mg doses, hepatotoxicity is a possibility.
Leyson and al. (1980) [33]	Baclofen	NR	Somnolence in quadriplegics, weakness of the upper extremities in paraplegics	Adverse effects occured only if the drug dosage was increased suddenly within the first 3 days of treatment and usually in patients over 45 years old.
Alpha adrenergic blocking agents				
Hachen (1980) [34]	Phenoxybenzamine hydrochloride	0.0%		Phenoxybenzamine may aggravate orthostatic hypotension in tetraplegics.
Jensen (1981) [37]	Prazosin	20.0%	Transient dizziness (20.0)[a]	BP was unaltered.
Chancellor and al. (1993) [38]	Terazosin	13.3%	Dizziness and lethargy at a 5 mg dosage (13.3)	Subjective erectile dysfunction not significantly altered, nor was the systolic BP.
Perkash (1995) [13]	Terazosin	10.7%[a]	Syncope (3.6)[a], lethargy (3.6)[a], body rash (3.6)[a]	Patients may not have antegrade ejaculation and may have significant postural hypotension.
Yasuda and al. (1996) [14]	Urapidil	2.1%[a] in the first group, 4.7%[a] in the second group	Mild numbness (2.2)[a] in the first group, hot flashes (2.5)[a] and mild dizziness, nasal obstruction and diarrhea (2.5)[a] in the second group	The patient who experienced hot flashes had to discontinue the treatment, whilst the others could continue taking the drug.
Ito and al. (2006) [40]	Prazosin, urapidil, moxisylyte or tamsulosin	20.0%[a]	Syncope (8.3 with prazosin, 5.6 with moxysylyte, 11.1 with tamsulosin)[a], diarrhea (2.5)[a], exacerbation of urinary frequency and incontinence (10.0)[a]	The drug was withdrawn in all the patients who encountered these adverse effects.
Nitric oxyde				
Reitz and al. (2004) [15]	Isosorbide dinitrate	58.3%	Mild headache (58.3)	The BP was lowered and HR was increased, but only for up to 30 min and without any clinical significance.
Cholinergic agonist agent and antibiotic				
Justiz and al. (2010) [42]	Bethanecol and nitrofurantoin	0.0%		Some of nitrofurantoine's metabolites may cause pulmonary and hepatic toxicity, and peripheral neuropathy.

Abbreviations: BP, bloop pressure; CVA, cerebral vascular attack; DSD, detrusor-sphincter dyssynergia; EUS, external urethral sphincter; HR, heart rate; MS, multiple sclerosis; n, number of patients with DSD; NR, not reported; PNS, peripheral nervous system; Pt, patient; SCI, spinal cord injury.

[a]Not specific to DSD patients; the authors did not differentiate the results between patients who had DSD and those who did not.

management of DSD. A thorough literature search following the PRISMA-ScR guidelines was conducted, and older studies were also included. Results showed that a variety of drugs have been used for the management of DSD: alpha-adrenergic blocking agents, muscle relaxants, nitric oxyde and cholinergic agonists and nitrofurantoin. However, the literature is limited and was often published many years ago as it will be discussed further.

Stimulation of the alpha receptors by catecholamines causes contraction of the smooth muscle fibers [34]. These receptors are present in high density in the bladder [13], especially in the outlet region [14]. Alpha-adrenergic blocking agents thus allow the relaxation of the bladder, urethra and external urethral sphincter [15], which explains why they reduced PVR, improved flow rate and voiding symptoms of patients. In this scoping review, all reported medications were non-selective, except for tamsulosin, which is selective for the alpha-A1 receptors. Reported side effects were dizziness, lethargy, syncope, body rash, numbness and hot flashes [13, 14, 34, 37–40] The use of alpha-adrenergic blocking agents seems to be the most clinically promising to date as they are stated as possible treatment options for DSD in the guidelines of the various learned societies [7–9]. While urapidil showed effectiveness in managing DSD symptoms and is indeed used in Europe, it is not approved in Canada nor in the United States. It is important to take under consideration that the presence of other obstructive disorders, such as benign prostatic hyperplasia or dysfunctional voiding, introduces a possible bias when reporting the efficacy of alpha-adrenaergic blocking agents. Indeed, their efficacy could be partially explained by a relief of other obstructive etiologies and not only DSD.

Muscle relaxants also showed positive effects in the management of DSD. They have a depressant action on the activity of diverse nerve cells. Regardless of their various sites of action, they lower the external sphincter resistance [32, 33]. They may induce overall weakness, dizziness, fatigue and malaise [31–33]. All muscle relaxants related studies were published in 1980 or earlier. Since then, because of the presence of significant side effects and better treatment alternatives, the Canadian, American and European urology guidelines do not encourage the use of muscle relaxants anymore in the treatment of DSD [8–10]. However, our exhaustiveness still led us to report these results.

Nitric oxyde is an inhibitory neurotransmitter in the lower urinary tract. It is naturally synthesized by parasympathetic nerve cells present across the bladder and urethra and plays a role in the relaxation of the external urethral sphincter. Only one study focused on nitric oxyde and reported headache as a side effect [15]. As of today, it is clinically irrelevant in the treatment of DSD. Because of potential side effects and medication alternatives, the Canadian, American and European urology guidelines do not encourage the use of nitric oxyde [8–10]. Once again, our exhaustiveness still led us to report these results.

A study reported favorable outcomes with the combination of a cholinergic agonist (bethanecol) and nitrofurantoin, and no side effect was reported. The latter works as an antibiotic by releasing toxic metabolites of its nitro group. It is thought that the presence of a nitro group may explain why this antibiotic reduces bladder outlet obstruction caused by DSD [42], which translates in an improvement of voiding functions. Only one patient was included in that study, which unfortunately precludes drawing any clinical recommendation. That information still seemed relevant to be reported, as this study aims to identify every oral medication that has been used in the treatment of DSD to date.

4.2 | Limitations

The main limitation of this study is the fact that few studies could be included because little research has been done on oral medication for DSD. To counter that issue, we used wide keywords to find studies that were not necessarily fully specific to DSD, but still somewhat reported the outcomes of oral drugs on the treatment of DSD. However, by doing so, the extracted data were not always entirely exclusive to DSD patients. Moreover, some of the studies included were old and, in some cases, the reported medications are not even of use for DSD nowadays. We still decided to include them with the intention of being as exhaustive as possible. Some key data were also missing in a few studies. For example, patient age was not always mentioned, in which cases we assumed that all patients were over 18. We included all relevant studies, even if results for the outcomes of interest were not all reported or measured. Full text articles were available for most of the studies included, however, in a few cases, only the abstracts were available in French or in English. Amongst the studies included, only one had a placebo group. Most studies also had small sample sizes; only five of them included over 20 patients. Indeed, most studies were case series or reports, which makes it harder to draw any conclusions regarding the treatment efficacy. Finally, we mentioned whether most patients in the included studies had an improvement in the reported outcome measures but could not report whether this had a significant clinical impact. In future studies, factors such as converting someone from CIC to voiding or reducing CIC use should be considered. Quality of life questionnaires could also be used.

5 | Conclusion

This scoping review reveals that several oral medications have been used for the treatment of DSD. While some of these drugs are no longer recommended or used for DSD, the most promising oral treatment option appears to be alpha-adrenergic blocking agents. Perhaps, in future studies, aiming more specifically at alpha-1a adrenergic blockers would have a more targeted effect while also minimizing adverse events.

The literature is limited, was often published many years ago, and available papers do not have an adequate design to provide an evidence base for treatment decisions. Further studies using rigorous study design such as randomized controlled trials are essential to draw clear conclusions on the efficacy of oral drugs in the treatment of DSD, as they could significantly delay the use of more invasive treatment alternatives, such as catheterization, botulinum toxin injection and sphincterotomy. As we

are sailing blindly by treating DSD patients without relying on any solid evidence regarding oral medications, this review thus highlights the importance of conducting more studies to stop treating these patients empirically and start applying evidence-based treatments.

Ethics Statement

This scoping review did not involve direct interaction with human subjects, and as such, ethical approval was not required. All data used in this review were obtained from previously published studies. This manuscript includes the use of the PRISMA Flow Diagram, which is available for public use. The diagram has been adapted and the source appropriately cited in accordance with the PRISMA guidelines. No other materials from third-party sources have been reproduced. This study does not involve a clinical trial and thus does not require clinical trial registration.

Consent

As this study is a scoping review of published literature, no patient consent was required. The patients involved in the studies included in this review had previously consented as part of the original research.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting this scoping review are derived from publicly available articles cited within the manuscript. No new data were generated for this review.

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Appendix 1

Example of the search strategy used on PubMed

(((“neurogenic bladder*“[Title/Abstract] OR “bladder sphincter dyssynergia”[Title/Abstract] OR “external urethral sphincter*“[Title/Abstract] OR “detrusor sphincter dyssynergia”[Title/Abstract] OR “neurogenic urinary bladder*“[Title/Abstract]) AND (“oral treatment*“[Title/Abstract] OR “oral therap*“[Title/Abstract] OR “po treatment*“[Title/Abstract] OR “po therap*“[Title/Abstract] OR “pharmacologic treatment*“[Title/Abstract] OR “pharmacologic therap*“[Title/Abstract] OR “pharmacotherap*“[Title/Abstract] OR “drug therap*“[Title/Abstract] OR “drug treatment*“[Title/Abstract] OR “medication*“[Title/Abstract])) OR (“urinary bladder, neurogenic/drug therapy”[MeSH Terms])) AND (“adult*“[All Fields] OR “womans”[All Fields] OR “women”[MeSH Terms] OR “women”[All Fields] OR “woman”[All Fields] OR “women s”[All Fields] OR “womens”[All Fields] OR “womans”[All Fields] OR “women”[MeSH Terms] OR “women”[All Fields] OR “woman”[All Fields] OR “women s”[All Fields] OR “womens”[All Fields] OR “men”[MeSH Terms] OR “men”[All Fields] OR “men”[MeSH Terms] OR “men”[All Fields] OR “man”[All Fields]).