

Urologic Agents for Treatment of Bladder Dysfunction in Neurologic Disease

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Published online: 25 January 2014

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This article is part of the Topical Collection on *Neurologic Manifestations of Systemic Disease*

Keywords Detrusor overactivity · Anticholinergics · Neurogenic bladder · Antimuscarinics · Intravesical therapy · Percutaneous tibial nerve stimulation · Sacral nerve stimulation · Neurologic disease · Bladder dysfunction · Treatment

Opinion statement

Bladder dysfunction, which is commonly associated with neurologic disorders, can present in myriad ways, from complete retention of urine to total urinary incontinence. The multiple options for treating neurogenic bladder dysfunction range from minimally invasive lifestyle changes to major surgical interventions. Interventions may be driven by patient-reported nuisance or by medical necessity, as in the case of impaired compliance with associated upper urinary tract compromise. Pharmacologic treatment has long been the mainstay in the management of bladder dysfunction, particularly for overactive bladder symptoms [1]. While there are many different medications for overactive bladder dysfunction, most are in the category of antimuscarinics. Each medication has a slightly different side effect profile, which may be important in the drug selection process [2]. When these are not tolerated or are ineffective, beta agonists, phosphodiesterase inhibitors, tricyclic antidepressants, and the gamma aminobutyric acid (GABA)-B agonist baclofen can be added or substituted. For difficulty emptying, alpha adrenergic antagonists can be used [3]. Intravesical options are also available for overactive bladder (OAB) symptoms. The most common is botulinum toxin, which works by decreasing the activity of the detrusor smooth muscle, thereby decreasing OAB symptoms [4]. Percutaneous nerve stimulation may also be used [5•].

Introduction

Normal bladder function involves two phases: storage and emptying. A normal functioning bladder must have adequate compliance to store urine without leak-

age or reflux as a result of elevated intravesical pressure. During the emptying stage, the bladder must contract and the urinary sphincter (made up of smooth

and striated muscle) must synergistically relax to allow adequate urinary flow and complete bladder emptying. Bladder dysfunction results from a failure to properly store urine or to properly empty. The bladder is controlled by a complex neurologic network, including both autonomic (sympathetic and parasympathetic) and somatic innervation. All neuronal connections must work together to achieve proper urologic function. Neurologic diseases can affect both emptying and storage of urine. Bladder function can be impeded in demyelinating central nervous system diseases, such as multiple sclerosis, which can cause bladder overactivity and associated incontinence, as well as impaired emptying secondary to detrusor sphincter dyssynergia.

There are many considerations when treating patients with bladder dysfunction stemming from neurological disease, the first of which is to determine whether the patient primarily has overactive bladder dysfunction or emptying dysfunction. There are several lifestyle changes that can be made for both. For overactive bladder symptoms, reduction in caffeine and restriction of artificial sugars and alcohol have been found to be helpful [2]. It can also be helpful to have patients commit to timed voiding (voiding at specific intervals prior to the onset of urgency symptoms) and to keep a voiding diary [2]. For difficulty emptying, pa-

tients can be instructed to double-void (attempting to void again, with or without the use of Valsalva maneuver or direct bladder compression, following a normal volitional void). If retention of urine is not responsive to conservative options or if patients experience untoward effects from retained urine, they can also be taught to do intermittent self-catheterization.

Pharmacologic treatment is usually the second step in treatment of bladder dysfunction. For OAB, the major category of medications is the antimuscarinics, which differ from each other in central nervous system penetration that produces sedation and in other adverse effects (see below).

Surgical options include neurostimulation with sacral neuromodulation. In this procedure, a tined-lead electrode is implanted directly into the S3 foramen adjacent to the sacral nerve plexus and connected to a battery source, which then uses electrical stimulation to control frequency, urgency to void, and urge incontinence [1]. More permanent surgical options, including sphincterotomy for difficulty emptying, are rarely used due to their irreversible nature and risk for complications from surgery itself. As a last resort, bladder augmentation or urinary diversion surgery can be performed, but this is reserved for patients with poor bladder compliance and potential for damage to the upper urinary tract [3].

Treatment

Diet and lifestyle

For overactive bladder symptoms:

- Caffeine restriction can decrease OAB symptoms
- Restriction of artificial sugar/alcohol or other irritant can decrease symptoms.
- Reduction of excessive fluid intake can decrease OAB symptoms.
- Timed voiding/bladder training can diminish bladder urgency and associated leakage by consistently voiding at defined intervals prior to the sensation of bladder urgency.
- Urge suppression strategies can lessen the intensity of or diminish involuntary contractions, preventing leakage.
- Kegel exercises can increase pelvic floor muscle strength and the urinary sphincter's ability to hold urine. They can also cause reflexive relaxation of detrusor smooth muscle, lessening urgency and diminishing involuntary bladder contractions.
- Treatment of constipation can lessen OAB symptoms.

For difficulty emptying:

- Pelvic floor relaxation during voiding can improve bladder emptying by allowing the urethral sphincter and surrounding pelvic floor muscles to relax with each void
- Double voiding, which involves voiding or attempting to void a second time with or without the use of Valsalva or compression within a few minutes of the first void, gives the bladder another opportunity to empty

Non-pharmacologic intervention for difficulty emptying:

- Clean intermittent catheterization can be used when the patient is unable to empty effectively on their own. A catheter is inserted in the bladder every 3–8 hours in lieu of or following voiding.
- An indwelling urethral catheter or suprapubic tube can be used to drain the bladder in patients unable to catheterize themselves. This is a last-resort option due to the risk of complications from an indwelling foreign body (urinary tract infection, tract erosion, need for a bag, odor, accidental spillage of the bag, and loss of cycling of the bladder).

Pharmacologic treatment

Overactive bladder

Drug therapy is used for OAB symptoms primarily to decrease urinary frequency, lessen bladder urgency, and reduce episodes of urinary incontinence. Drug therapy can also effectively relax detrusor smooth muscle to lower intradetrusor pressure in patients with poor bladder compliance. Anti-cholinergics and anti-muscarinics are the mainstays of treatment, but when these are not tolerated or are ineffective, beta agonists, phosphodiesterase inhibitors, and tricyclic antidepressants can be added or substituted. Drug therapy with alpha-adrenergic agents can be initiated when poor bladder emptying is encountered.

Specific drugs	anticholinergics – oxybutynin
Standard dosage	oral: 5 mg IR/5–15 mg ER (Ditropan XL); patch 3.9 mg/day (Oxytrol); 3 % gel 64 mg/day (Gelnique) [6]
Contraindications	Narrow-angle glaucoma, urinary retention, gastroparesis, intestinal obstruction
Main drug interactions	interacts with potassium salts and slows passage through the GI tract
Main side effects	Most common side effects include dry mouth, dry eyes, blurred vision, dizziness, drowsiness, and mild constipation [2]. CNS side effects such as cognitive dysfunction, memory impairment, and headache are rare.
Cost/cost effectiveness	5 mg tab (100) \$328.40, 10 mg tab (100) \$328.75, 15 mg tab (100) \$336.95; Oxytrol 3.9 mg/24-hr patches: 8/\$250.80 or 24/\$731.48 [7]
Specific drugs	antimuscarinics – tolterodine (Detrol) [8]
Standard dosage	1–2 mg daily IR, 2–4 mg LA
Contraindications	narrow-angle glaucoma, urinary retention, gastroparesis, intestinal obstruction

Main drug interactions	metabolized by the cytochrome P450 system
Main side effects	dry mouth, dry eyes, mild constipation, and blurred vision; tachycardia, QT prolongation (never more than 500 msec) and CNS side effects are rare [2]
Cost/cost effectiveness	Capsule, 24-hour Detrol LA oral 2 mg (90): \$734.24, 4 mg (90): \$734.24. Capsule, 24-hour Detrol oral 1 mg (140): \$679.08, 2 mg (140): \$696.65. Capsule, 24-hour tolterodine tartrate oral 1 mg (90): \$297.83, 2 mg (90): \$305.69 [7]
Specific drugs	antimuscarinics – trospium (Sanctura) [9]
Standard dosage	20 mg IR/60 mg ER
Contraindications	narrow angle glaucoma, renal failure, urinary retention, gastroparesis, intestinal obstruction
Main drug interactions	can interact with other drugs that are eliminated by the renal tubules, causing both drugs to build up in the system; common interactions through this mechanism occur with ranitidine and metformin
Main side effects	same as above; trospium is made up of quaternary amines which have fewer CNS side effects; common side effects are constipation and fatigue [2]
Special points	quaternary amines cross the blood–brain barrier less often, resulting in fewer CNS side effects; trospium is metabolized primarily by the kidneys (as opposed to the liver, which metabolizes the vast majority of the other antimuscarinics)
Cost/cost effectiveness	Capsule, 24-hour (Sanctura XR oral) 60 mg (90): \$673.68, Capsule, 24-hour (trospium chloride ER Oral) 60 mg (90): \$606.30. Tablet (Sanctura oral) 20 mg (90): \$381.58. Tablet (trospium chloride oral) 20 mg (90): \$255.39 [7]
Specific drugs	solifenacin (VESIcare) [10]
Standard dosage	5–10 mg daily
Contraindications	same as above; glaucoma, urinary retention
Main drug interactions	metabolized by cytochrome P450 enzymes, tertiary amine
Main side effects	same as above, possibly less dry mouth than tolterodine
Cost/cost effectiveness	5 mg (90): \$730.46, 10 mg (90): \$730.46 [7]
Specific drugs	darifenacin (Enablex) [6]
Standard dosage	7.5 or 15 mg/day
Contraindications	same as above; urinary retention, glaucoma
Main drug interactions	slows down gastric emptying, should not be combined with other medications that slow gastric emptying
Main side effects	dry mouth, constipation, headache, blurred vision, tachycardia, QT prolongation
Cost/cost effectiveness	(Enablex oral) 7.5 mg (90): \$647.31, 15 mg (90): \$647.31 [7]
Specific drugs	fesoterodine (Toviaz) [11]
Standard dosage	4–8 mg daily
Contraindications	same as above; glaucoma, urinary retention
Main drug interactions	same as tolterodine

Main side effects	same as tolterodine
Special points	breaks down to the same end product as tolterodine
Cost/cost effectiveness	(Toviaz oral) 4 mg (90): \$597.66, 8 mg (90): \$597.66 [7]
Specific drugs	beta agonists – mirabegron (Myrbetriq) [12•]
Standard dosage	25–50 mg daily
Contraindications	uncontrolled hypertension
Main drug interactions	metabolized by CYP450, can interact with other drugs hepatically metabolized
Main side effects	hypertension, urinary retention, headache, tachycardia
Cost/cost effectiveness	(Myrbetriq oral) 25 mg (90): \$750.60, 50 mg (90): \$750.60 [7]
Specific drugs	phosphodiesterase inhibitors – sildenafil (Viagra) [13]
Standard dosage	50–100 mg daily
Contraindications	none
Main drug interactions	when combined with alpha blockers, can cause hypotension
Main side effects	hypotension, vision changes, headache
Special points	reduced LUTS symptoms in patients taking it for erectile dysfunction, relaxes smooth muscle, including the detrusor, and also relaxes the smooth muscle of the outflow tract
Cost/cost effectiveness	Tablet (Revatio oral) 20 mg (90): \$2315.05 Tablet (sildenafil citrate oral) 20 mg (90): \$1818.46 Tablet (Viagra oral) 25 mg (90): \$2880.48, 50 mg (90): \$2880.48, 100 mg (90): \$2880.48 [7]
Specific drugs	tricyclic antidepressants – imipramine [14]
Standard dosage	150–300 mg daily
Contraindications	recent MI
Main drug interactions	class IA antiarrhythmics due to increase in QT
Main side effects	orthostatic hypotension, syncope, QT prolongation
Special points	helpful in groups of patients who have failed anti-muscarinic therapy alone, decreases bladder contractility and increases outlet resistance
Cost/cost effectiveness	Capsule (imipramine pamoate oral) 75 mg (90): \$1517.19, 100 mg (90): \$1517.19, 125 mg (90): \$1517.19, 150 mg (90): \$1517.19 Capsule (Tofranil-PM oral) 75 mg (90): \$1995.60, 100 mg (90): \$2035.11, 125 mg (90): \$2074.65, 150 mg (90): \$2114.13 Tablet (imipramine HCl oral) 10 mg (100): \$42.96, 25 mg (100): \$71.75, 50 mg (100): \$121.85 Tablet (Tofranil oral) 10 mg (90): \$704.01, 25 mg (90): \$716.58, 50 mg (90): \$729.15 [7]
Specific drugs	baclofen [2]
Standard dosage	20–80 mg/day [6]
Contraindications	caution in patients with psychiatric disorders
Main drug interactions	can combine with antihistamines to cause increased sedation
Main side effects	drowsiness, insomnia, rash, pruritus, sudden withdrawal can cause hallucinations

Cost/cost effectiveness	(baclofen oral) 10 mg (100): \$59.65, 20 mg (100): \$106.99 [7]
Specific drugs	Desmopressin [2]
Standard dosage	0.2–0.6 mg/day at bedtime PO
Contraindications	cannot be used in patients with severe renal impairment, can cause hypotension and therefore should be used in caution in patients with cardiac history
Main drug interactions	can combine with heparin to increase activity, reduced activity seen in patients taking lithium
Main side effects	hyponatremia, and therefore the need to restrict fluid intake one hour before taking the medication and 8 hours after
Cost/cost effectiveness	Tablet 0.1 mg tab: \$287.97 (90), 0.2 mg tab: \$521.97 (90)

Pharmacologic therapy

Difficulty emptying

Specific drugs	alpha-adrenergic antagonists –tamsulosin (Flomax); doxazosin (Cardura), terazosin (Hytrin), silodosin (Rapaflo), alfuzosin (Uroxatral) [3]
Standard dosage	tamsulosin 0.4 mg daily, generally given at bedtime
Contraindications	risk of increased drug levels if combined with hepatic metabolism inhibitors
Main drug interactions	risk of hypotension when combined with other alpha blockers
Main side effects	orthostatic hypotension
Special points	best used for patients with hesitancy, poor urinary stream, straining to urinate, incomplete bladder emptying, and outflow obstruction [15]
Cost/cost effectiveness	0.4 mg tab (100) \$623.83 [7]

Interventional procedures

Standard procedure	intravesical botulinum neurotoxin type A (BoNT-A) [4]
Contraindications	difficulty emptying, acute UTI
Complications	can cause acute urinary retention, UTI
Special points	BoNT-A for overactive bladder/detrusor overactivity – inject 200 units reconstituted in 10–20 ml of injectable saline in approximately 10–20 sites throughout the bladder. Intrasphincteric injection can be used when detrusor sphincter dyssynergia prevents emptying
Cost/cost effectiveness	2-year period cost was \$4,392 [16]
Standard procedure	percutaneous tibial nerve stimulation (PTNS) [5]
Contraindications	skin infection, inflammation at malleolus
Complications	none
Special points	minimally invasive treatment useful in medically refractory overactive bladder symptoms [17]
Cost/cost effectiveness	\$1,773 for 12 weekly percutaneous tibial nerve stimulation treatments; cumulative discounted 2-year costs were \$3,850 for PTNS [18••]; PTNS

	compared to the oral option tolterodine was found to be a greater cost initially but more cost-effective over time [19••]
Standard procedure	intrathecal baclofen [2]
Contraindications	active infection
Complications	seizures, meningitis, pump pocket infection
Special points	used in patients with detrusor overactivity due to spasticity from spinal cord lesions in the setting of concomitant muscle spasticity
Cost/cost effectiveness	used very infrequently, and therefore cost effectiveness data not available

Surgery

Surgery for neurogenic bladder dysfunction is a last resort due to the permanent nature of most of the procedures. In addition, patients with neurogenic bladder dysfunction can have changes in dysfunction status over time.

Standard procedure	InterStim neuromodulation [1]
Contraindications	anatomical abnormalities of the sacrum, skin infection/inflammation over the sacrum, mental inability of the patient to use the device. Should be removed before a patient gets an MRI (except head) and turned off if a patient becomes pregnant
Complications	infection of the pocket leading to need for removal, lead migration, lead fracture, failure of device
Special points	this is the most commonly used non pharmacological modality for overactive bladder symptoms, can also be used for non-obstructive urinary retention [20]
Cost/cost effectiveness	\$1,857 for test sacral nerve stimulation. For ongoing therapy, the cost of the sacral nerve stimulation surgical implant was \$22,970; cumulative discounted 2-year costs were \$14,160 for sacral nerve stimulation [18••]
Standard procedure	sphincterotomy [2]
Contraindications	Patients who desire continence, anatomic obstruction such as BPH or bladder neck contracture
Complications	Urinary incontinence, urinary extravasation, and erectile dysfunction are possible but less likely if the cut is made at the 12 o'clock position
Special points	rarely done now due to its semi-permanent nature; intrasphincteric Botox is more commonly used. The procedure involves incision of the external urethral sphincter to allow better urinary flow, most commonly used in detrusor sphincter dyssynergia to release the poorly relaxing sphincter, can be done with a knife or laser
Cost/cost effectiveness	no data available
Standard procedure	urethral stenting (UroLume) [2]
Contraindications	bladder neck contracture, urethral stones, patient who desires continence
Complications	stent can migrate into the bladder and cause bladder calcifications, migrate proximal or distal to the sphincter, and fail
Special points	rarely done due to its semi-permanent nature; the procedure involves the placement of a urethral stent to allow the striated sphincter to remain open
Cost/cost effectiveness	no data available

Standard procedure	bladder augmentation – enterocystoplasty or autoaugmentation [2]
Contraindications	patients unwilling or unable to perform intermittent catheterization; enterocystoplasty cannot be done in patients whose intestinal tract is compromised, such as patients with inflammatory bowel disease
Complications	urine leak from surgical anastomosis, bladder calculi, UTI with enterocystoplasty and the use of intestinal segment are complications that come with any bowel surgery, including adhesions and small bowel obstructions.
Special points	primarily used in patients with poorly compliant bladders; patients have to be able to catheterize because ability to void is not guaranteed; bladder augmentation is a viable option in patients whose upper tracts and kidneys are being compromised by inability to properly empty.
Cost/cost effectiveness	no data available

Assistive devices

Urinary collection devices

Specific device	bedpan/urinal
Special points	ease ability to urinate because the patient does not have to get up to urinate
Usage	can be used with patients who are less mobile or have fall risk
Cost/cost effectiveness	very low-cost
Specific device	commode
Usage	can be used for patients who have slow gait, can be set up nearby to prevent accidents
Cost/cost effectiveness	very low-cost, usually covered by insurance
Specific device	diapers/incontinence pads
Usage	can be worn to prevent accidents from leaking onto clothes
Cost/cost effectiveness	Relatively low-cost and can improve quality of life because patients are not as afraid of being farther away from a bathroom; sometimes covered by insurance

Physical/speech therapy and exercise

Specific therapy	pelvic floor muscle therapy (PFMT)
Usage	pelvic muscle exercises taught by a healthcare professional
Special points	usually used in combination with a pharmacological agent to improve overactive bladder symptoms by strengthening the pelvic floor muscles
Specific therapy	biofeedback
Usage	can be used to train a patient to control any bodily function
Special points	depends on the patient's efforts and skill of the therapist; utilizes EMG sensors attached to a computer terminal so that patients get visual and/or auditory feedback when they are contracting their muscles properly

Emerging therapies

MRI-compatible neuromodulation would be an extremely useful modality in the neurologic population where bladder symptoms are mixed in nature, as neuromodulation can improve both emptying function and overactive bladder symptoms. MRI compatibility would allow patients whose neurologic disease is monitored with MRI to benefit from care.

PTNS is very effective for decreasing overactive bladder symptoms; however, its major cost and inconvenience comes from having to go to the doctor's office weekly for 12 weeks, followed by a maintenance regimen. Home units for stimulation of the tibial (or other accessible peripheral) nerve would allow patients to institute therapy at home without the added cost and burden of weekly health care visits [21].

Compliance with Ethics Guidelines

Conflict of Interest

Eliza Lamin declares that she has no conflict of interest.

Ariana L. Smith has received grant support from the NIH/NIDDK P20 Award.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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