Invited Review

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BLADDER DYSFUNCTION IN PERIPHERAL NEUROPATHIES

AHMET Z. BURAKGAZI, MD, BANDER ALSOWAITY, MD, ZEYNEP AYDIN BURAKGAZI, BS, DOGAN UNAL, MD, AND JOHN J. KELLY, MD

EDUCATIONAL OBJECTIVES Upon completion of this monograph, the reader will acquire skills to: (1) describe the normal neuroanatomy and neurophysiology of the bladder and micturition, (2) describe the causes of bladder dysfunction caused by various neuropathies, (3) seek and recognize the symptoms of bladder dysfunction in neuropathy patients, (4) describe the tests necessary to diagnose the nature of bladder dysfunction, and (5) describe the proper pharmacologic and non-pharmacologic treatment of bladder dysfunction.

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BLADDER DYSFUNCTION IN PERIPHERAL NEUROPATHIES

AHMET Z. BURAKGAZI, MD,1 BANDER ALSOWAITY, MD,1 ZEYNEP AYDIN BURAKGAZI, BS,2 DOGAN UNAL, MD,3 and JOHN J. KELLY, MD1,4

1 Department of Neurology, George Washington University, 2150 Pennsylvania Avenue NW, Suite 7-404, Washington, DC 20037, USA
2 Pharmacist, Washington, DC, USA
3 Department of Urology, School of Medicine, Fatih University, Ankara, Turkey
4 Department of Neurology, George Washington University, Washington, DC, USA

ABSTRACT: Normal bladder function depends on the complex interaction of sensory and motor pathways. Bladder dysfunction can develop as a result of several neurological conditions. It can happen in a number of ways, including diabetic cystopathy, detrusor overactivity, bladder outlet obstruction, and urge and stress urinary incontinence. Diabetic neuropathy is the most common cause of peripheral neuropathy–associated bladder dysfunction. Guillain–Barré syndrome (GBS), human immunodeficiency virus (HIV)-associated neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), and amyloid neuropathy are other major causes. The diagnosis of bladder dysfunction should be established by the history of neurological symptoms, neurological examination, and urological evaluation. Functional evaluation of the lower urinary tract includes cystometry, sphincter electromyography, uroflowmetry, and urethral pressure profilometry. Management of urinary symptoms in patients with bladder dysfunction is usually supportive. In some cases, alpha-blocker and/or anti-muscarinic agents are needed to help improve urinary function. Intermittent self-catheterization is needed occasionally for patients with slow and/or poor recovery.

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INVITED REVIEW

BLADDER DYSFUNCTION IN PERIPHERAL NEUROPATHIES

Normal bladder function in humans depends on the complex interaction of sensory and motor pathways at numerous levels in the central and peripheral nervous systems. Bladder dysfunction (BD) can develop as a result of several neurological conditions. Understanding the neuroanatomy of the urinary system provides better insight into the pathogenesis of BD. The bladder wall is formed by three layers of interdigitating smooth muscle (the detrusor muscle) and works as a vesicle for the storage and evacuation of urine. The internal sphincter is the part of the detrusor muscle that is localized at the junction of the bladder neck and urethra. This sphincter is not anatomically isolated but functions as a physiological sphincter.

Reflex bladder contractions are activated by sympathetic, parasympathetic, and somatic nerves from the spinal cord. The preganglionic parasympathetic efferent nerves arise from the S2–S4 spinal nerves. The axons run a long distance within the pelvic nerves to the ganglia (pelvic plexus), which are located close to the bladder. Acetylcholine (ACh) is the main neurotransmitter for both pre- and postganglionic parasympathetic fibers. 

The preganglionic sympathetic efferent fibers arise from the thoracolumbar segment of the spinal cord at T10–L2. Those fibers intermingle with somatic efferents from spinal nerves and synapse in one of the nearby paravertbral ganglia of the sympathetic chain, which continue peripherally with associated somatic segmental fibers. Alternatively, some fibers pass through the paravertebral ganglia and synapse with one of the prevertebral or collateral ganglia on the aorta or internal iliac vessels, such as the inferior mesenteric ganglia, then continue inferiorly as the hypogastric nerves. Some fibers pass through both pre- and paravertebral ganglia and synapse with the end organ. The main neurotransmitter for postganglionic sympathetic fibers is norepinephrine, and for preganglionic sympathetic fibers it is ACh.

The preganglionic somatic efferent nerves originate from the nucleus of Onuf (at S2–S4) in the
The nerve fibers travel within the pudendal nerve to the external urethral sphincter. In addition, afferent nerves are located in the detrusor muscle and the suburothelium. The afferent nerve fibers form plexiform structures beneath the urothelial lining (more prominent in the trigone and bladder neck and relatively sparse in the bladder dome), with some nerve ends extending into the urothelium. The afferent fibers travel within pelvic, hypogastric, and pudendal nerves. Two types of afferent nerves have been described: (1) myelinated A\(\delta\) fibers, which respond to normal bladder distention and the main afferent nerve during normal micturition; and (2) unmyelinated C fibers, which respond to chemical irritation or cold, and are usually silent normally, but appear to be more active during pathological conditions.

During the storage phase, the bladder and the internal urethral sphincter are predominantly activated by the sympathetic nervous system. Activation of the sympathetic nervous system leads to contraction of smooth muscles in the bladder base and proximal urethra via activation of \(\alpha\)-adrenergic receptors (the \(\alpha_1\) subtype is the main subtype in the urethra and prostate) and relaxation of the detrusor via activation of \(\beta\)-adrenergic receptors (\(\beta_2\) and \(\beta_3\) are the main receptors located in the lower urinary tract) in the bladder body. Overall, sympathetic nervous system activation provides urinary accommodation and inhibition of the micturition reflex.

During the voiding phase, which is initiated voluntarily from the cerebral cortex, the voiding process begins with relaxation of the external sphincter, followed by activation of parasympathetic efferent activity that leads to contraction of the detrusor muscle (mediated via muscarinic receptors, M\(_2\) and M\(_3\), as predominant subtypes, in the bladder) and relaxation of the smooth muscles in the bladder base and proximal urethra (mediated by the release of nitric oxide).

In BD caused by peripheral neuropathy, the affected individual usually demonstrates urinary retention. In these diseases, the nerves to the bladder are destroyed, resulting in silent, painless distension of the bladder. Similar to injury of the sacral spinal cord, the detrusor is unable to contract to empty the bladder, a condition known as detrusor areflexia. A prolonged latency of the bulbocavernosus reflex is another abnormal finding in visceral neuropathy.

**DIABETIC NEUROPATHY**

Diabetes mellitus (DM) is the most common cause of peripheral neuropathy in North America. The prevalence rate of BD increases with the duration of diabetes mellitus. For instance, the rate is around 25% after 10 years of diabetes, and >50% after 45 years of diabetes. It has been reported that 75–100% of patients with diabetic peripheral neuropathy develop diabetic cystopathy.

The cause of BD in DM is primarily peripheral and autonomic neuropathy. Animal and human studies have revealed that diabetic cystopathy develops as a result of polyneuropathy, which predominantly affects sensory and autonomic nerve fibers. The pathogenesis of diabetic neuropathy is not fully clarified. Some of the proposed pathogeneses include altered metabolism of glucose, ischemia, superoxide-induced free-radical formation, and impaired axonal transport.

The exact prevalence of voiding dysfunction caused by diabetes is, however, uncertain. BD in DM can occur in a number of ways, including diabetic cystopathy, detrusor overactivity, and urge urinary incontinence. Each form of BD in DM has been reported with variable prevalence in the literature. In earlier studies, the frequency of diabetic cystopathy varied from 25% to 80%, and the rate of detrusor overactivity ranged from 39% to 61%. The differences depend on the diagnostic methods, study criteria, and patient characteristics.

Onset of diabetic BD in most patients is insidious and often not recognized until it has reached an advanced stage. Patients often remain asymptomatic in early stages despite demonstrable bladder abnormality. Impaired bladder sensation is usually the first manifestation of lower urinary tract involvement. Micturition reflexes are delayed due to diminished bladder sensation with increases in bladder capacity and urinary retention that usually occur asymptptomatically. Patients are frequently unaware of bladder dysfunction until they have a urinary tract infection (UTI) secondary to increased residual urine volume. The common symptoms are straining, hesitation, and weakness of stream. Diabetic cystopathy is characterized by impaired sensation of bladder fullness, which leads to overstretched bladder, reduced bladder contractility, increased residual urine, and impaired uroflow.

**ELECTRODIAGNOSTIC FINDINGS**

Diabetic neuropathy is characterized by axonal degeneration, demyelination, and fiber loss. Electromyography (EMG) is usually normal but sometimes shows sphincter denervation and uninhibited sphincter relaxation. EMG of perineal muscles can be used to show denervation and detrusor-sphincter dyssynergia. Bradley et al. reported that a prolonged latency of evoked potentials in response to detrusor stimulation would be evidence of visceral neuropathy. A prolonged latency of the bulbocavernosus reflex is another abnormal finding in visceral neuropathy.
Mitsui et al. studied the relationship between abnormal nerve conduction velocity and vesicourethral dysfunction in 29 asymptomatic diabetic subjects. Nerve conduction velocities were measured in the sural sensory nerve (sensory conduction velocity, SCV) and the fibular nerve (motor conduction velocity, MCV). In 12 patients with normal SCV and MCV, voiding dysfunction was not noted. Thirteen patients with voiding dysfunction had abnormal SCV and MCV. Thus, diabetic vesicourethral dysfunction is highly correlated with abnormal nerve conduction.33

In an historical context, different diagnostic tests, such as the denervation cholinergic supersensitivity test of the bladder and urethra, have been used for evaluation of bladder function in diabetic patients. The denervation test consists of a continual reading of the intravesical pressure response to subcutaneous administration of 0.25 mg carbachol (equivalent to 2.5 mg bethanechol) after the bladder has previously been filled with 100 ml saline and allowed to accommodate. The positive test results were postulated to be related to axonopathy, which is evidence of denervation, in the neural pathway innervating the bladder.24,36 However, recent data show that urothelium afferent nerve endings and interstitial cells all express muscarinic receptors, so theoretically conditions other than “denervation” can lead to an abnormal test.8,37,38

Morita et al. reported in diabetic patients that there was a greater chance of detecting denervation supersensitivity of the urethra to an α-sympathetic agonist than of the bladder.33,39 This implies that the isolated neurogenic dysfunction of the urethra, as evidenced by denervation supersensitivity in the absence of vesical denervation supersensitivity (Vds), can cause voiding dysfunction in diabetic patients.33,39

A correlation between diabetic cystopathy and abnormal sympathetic skin response has been reported.23 Sympathetic skin responses are mediated by unmynelinated postganglionic sympathetic fibers. Abnormal sympathetic skin responses among diabetic patients would suggest that diabetic bladder dysfunction is caused by axonopathy in autonomic nerves innervating the bladder.

DIAGNOSIS

The diagnosis of diabetic cystopathy should be established by a history of neurological symptoms, neurological examination, and bladder evaluation. The evaluation of BD in DM should start with a detailed history including medication review for drugs that might impair detrusor contractility and increase urethral tone. These include calcium channel blockers, anticholinergics, α- and β-adrenergic agonists, narcotics, antidepressants, and antipsychotics. Further work-up should be done including evaluation of a patient’s voiding record, post-void residual testing, and urinalysis. Cystometric and urodynamic studies should be done to confirm the diagnosis. Vinik et al. recommended screening that includes renal function, urine residual, and voiding cystometrogram for diabetic bladder dysfunction for any diabetic patient with recurrent UTI, pyelonephritis, incontinence, or palpable bladder.30

Functional evaluation of the lower urinary tract includes cystometry, sphincter electromyography, uroflowmetry, and urethral pressure profile. In most typical cases of diabetic cystopathy, cystometry shows a long curve with lack of sensation, often until bladder capacity is reached, with a low detrusor pressure.10,25 Uroflowmetry shows low peak flow and prolonged duration of flow associated with increased residual urine.14,23 Kebapci et al. recommended urodynamic study for all type 2 DM patients at least 8–9 years after the diagnosis.27

MANAGEMENT

Patients with diabetic bladder dysfunction usually have a combination of urinary retention, overflow incontinence, and UTI. The management of lower urinary tract symptoms in DM depends on the degree of complaints and their impact on quality of life. Little research has been published to guide practice for the treatment of lower urinary tract symptoms in DM, but the important goal is to eliminate or modify risk factors that can cause worsening of DM-related nephropathy and neuropathy.40

Poor glycemic control and diabetic nephropathy can cause increased urine output, which leads to increased mean voided volume and incontinence. Optimal glycemic control should be achieved. Diet, exercise, and weight loss are encouraged in diabetic patients, but individuals who are unable to achieve or maintain optimum glucose control by diet and exercise alone should initiate oral glucose-lowering agents, insulin, or both.40

Different strategies can be applied in bladder dysfunction in DM to prevent complications and improve quality of life. Diabetic patients with reduced bladder sensation and infrequent voiding should practice timed voiding on a consistent and regular schedule (every 2–4 hours). Intermittent catheterization is often needed to achieve bladder emptying and reduce the risk of UTI with potential deterioration of renal function.

Long-term antimicrobial prophylaxis may be required for recurrent UTI. The optimal catheterization frequency is not clear and may vary from one to four times daily depending on the...
autonomic neuropathy.40 In addition, elderly diabetic patients usually have concomitant disorders, such as benign prostatic enlargement, stress incontinence, and bladder or prostate cancer or infection, which should be taken into consideration in differential diagnosis and management.40 There is no effective medication currently available to assist with bladder emptying in diabetic cystopathy, but z-blockers may be helpful in outlet obstruction from prostatic enlargement.40

**AUTONOMIC NEUROPATHY**

Autonomic neuropathies comprise a wide spectrum of syndromes and diseases that affect the autonomic nervous system. Autonomic neuropathies can be caused by hereditary or acquired diseases. The autonomic nervous system subserves numerous body functions; thus, autonomic dysfunction may manifest with various clinical presentations, including bladder dysfunction and numerous laboratory and neurophysiological abnormalities.1,42–44

Inherited autonomic neuropathies occur rarely. The most common genetic disorders presenting with autonomic dysfunction include familial amyloid polyneuropathy, hereditary sensory autonomic neuropathies, Fabry disease, and porphyrias.26,42–44

The acquired autonomic neuropathies that can be subclassified into primary and secondary disorders are much more prevalent than the inherited ones. Primary autonomic neuropathies are idiopathic and have autonomic dysfunction as a part of the disease process itself. In the secondary autonomic neuropathies, a certain cause may lead to autonomic neuropathy, but autonomic neuropathy is not a defining feature of the disease process.43,44 There are several identifiable causes of secondary acquired autonomic neuropathies, including metabolic derangements, such as DM, hepatic disease, and uremia; vitamin deficiencies, such as vitamin B12 deficiency; toxins and prescription medications, such as alcohol and chemotherapeutic medications; infectious diseases, such as Lyme disease, HIV, botulism, diphtheria, tabes dorsalis, and polyomylitis; and autoimmune conditions, such as paraneoplastic autonomic neuropathy, Lambert–Eaton myasthenic syndrome, and GBS.1,26,30,42–48

Some of the causes, such as DM, GBS, and HIV, are discussed separately in this review. Herein we emphasize the relationship between the autoimmune response of the body and the severity of autonomic neuropathy. Nicotinic acetylcholine receptors (nAChRs), particularly the α3 and the β4 subunits, are necessary for normal bladder function.49 Bladder dysfunction may be associated with neuronal nAChR antibodies.49,50 Lemon et al. developed the model of an acquired neuronal nAChR disorder and assessed its pertinence to paraneoplastic autonomic neuropathy. In that model, once rabbits were immunized with the recombinant α3 subunit, they developed profound gastrointestinal hypomotility, dilated pupils with impaired light response, and grossly distended bladders. As in patients with idiopathic and paraneoplastic autoimmune autonomic neuropathy, the severity parallels the serum levels of ganglionic nAChR autoantibody.51

Besides cystometric and urodynamic studies for the evaluation of bladder function, specific autonomic tests should be performed to assess the autonomic nervous system. Such tests include the thermoregulatory sweat test (TST), quantitative sudomotor axon reflex test (QSART), sympathetic skin response (SSR) test, and quantitative sensory testing (QST).26,52,53 A skin biopsy for a quantification of pilomotor nerves may be performed to evaluate autonomic involvement.54

**GUILLAIN–BARRÉ SYNDROME**

Guillain–Barré syndrome (GBS) is comprised of a group of acute demyelinating and axonal autoimmune polyneuropathies. It is characterized by a largely symmetrical, ascending motor paralysis with or without sensory and autonomic disturbances. Although complete recovery is possible, GBS may leave patients severely disabled.58

A range of incidence rates for autonomic dysfunction in GBS has been reported in different studies. Sakakibara et al. found BD, including urinary retention, voiding difficulties, and urinary urgency, in 7 of 28 (25%) cases in one GBS series and in 18 of 65 (27.7%) cases in another series.55,56 In other reports, micturition dysfunction was present in 11–30% of patients studied.56,57

Peripheral nerve malfunction of lumbosacral autonomic fibers, from either inflammation or immune attack on autonomic fibers, might cause either an underactive bladder (weak detrusor or detrusor hypocontractility) or bladder overactivity in GBS without central nervous system involvement. The possible mechanism for overactive bladder might be generation of abnormal (spontaneous) depolarizations in demyelinated nerve fibers and immune attack on inhibitory spinal cord interneurons, both of which cause lumbosacral autonomic hyperactivity.13,55

de Jager et al. reported a close relationship between severity of GBS and bladder dysfunction. They reviewed 63 cases of GBS patients who were intubated during the disease course and showed that 75% of them developed micturition problems.58 In addition, Sakakibara et al. stated that micturition symptoms in GBS seemed to be more common in patients with severe weakness than in those with mild weakness.55 In their study of 65
cases of GBS, 27.7% had urinary dysfunction, including urinary retention in 9.2%. Underactive detrusor, overactive detrusor, and to a lesser extent, hyperactive sphincter, were the major urodynamic abnormalities. Sakakibara et al. further reported that urinary dysfunction was clearly related to the Hughes motor grade and defecation dysfunction, and it was negatively related to serum immunoglobulin G class and antiganglioside antibody GalNAc-GD1a; there was no relationship to superficial or deep sensory defects. Therefore, they recommended checking post-void residual by ultrasound echography in GBS patients with a higher Hughes motor grade, older age, and defecation dysfunction.

Management of urinary symptoms in patients with GBS is usually supportive. Urinary symptoms usually resolve during the natural course of the disease. In some cases, α-blockers are needed to ameliorate urinary dysfunction. Intermittent self-catheterization is occasionally needed for those patients with slow and/or poor recovery.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Autonomic dysfunction in chronic inflammatory demyelinating polyneuropathy (CIDP) is not common, in contrast to GBS. In CIDP, micturition disturbance was reported in only 2% of patients in the Dyck et al. series, and in 8% in the Prineas et al. series. On the contrary, in another study, 8 of 32 (25%) CIDP patients had micturition disturbance.

The frequency of micturition disturbance may depend on the method of history-taking. Micturition symptoms were seen more commonly in severe CIDP cases presenting with severe weakness.

The major symptoms were voiding difficulty and urinary urgency, evidence of both evacuation and storage disorders in previous CIDP series. The only urodynamic data available on CIDP are the report by Sakakibara et al. of urodynamic studies in 4 symptomatic patients in whom they found disturbed bladder sensation in 2 patients and bladder areflexia in 1 patient. External sphincter electromyography showed high-amplitude and polyphasic motor unit potential changes in sphincter muscles in 1 patient, suggesting pudendal nerve dysfunction. Cystometry showed detrusor overactivity in 2 patients without evidence of central nervous system involvement that was probably related to pelvic nerve irritation or ephaptic transmission.

The management of urinary symptoms in CIDP would be the same as in GBS, as discussed earlier.

HIV-ASSOCIATED NEUROPATHY

Voiding dysfunction in acquired immune deficiency syndrome (AIDS) patients may be related to several conditions, including encephalitis, cerebral toxoplasmosis, meningitis, myelitis, polyradiculoneuritis, tumors, peripheral neuropathy, and others.

Around 9–16% patient with AIDS have peripheral nervous system dysfunction. There is some disagreement as to the overall prevalence of bladder dysfunction in HIV patients, but there are no data available describing the frequency of bladder dysfunction in HIV-related peripheral neuropathy.

Hermieu et al. studied 39 HIV-positive patients with voiding symptoms, such as straining, urinary retention, frequency, and urgency. Their urodynamic examination revealed that 56% had signs of central neurological bladder disturbances (hyperactive bladder and/or bladder sphincter dysfunction), 13% had a presumably peripheral deficit such as a hypotonic bladder, 10% had isolated urethral hypertonia, and the remainder had minor (hypersensitive bladder) or no urodynamic abnormalities.

A detailed history is necessary for precise diagnosis and choice of proper treatment. Appropriate drugs improve the condition in more than half of patients, but neurogenic voiding disturbances herald a poor prognosis. Urgency related to detrusor hyperactivity without UTI can be treated with anticholinergic medications. Low flow and straining to void in the absence of obstruction are due to impaired bladder contraction and can be treated with α-blockers and clean intermittent catheterization.

AMYLOID NEUROPATHY

Amyloid proteins are insoluble and accumulate in tissues. Primary systemic amyloidosis is characterized by the deposition of monoclonal immunoglobulin light chains (AL). In the familial form, the deposits are produced from abnormally folded transthyretin gene products (ATTR). Regardless of differences in the substance of the amyloid deposit, small-fiber neuropathy is seen in AL and ATTR amyloidosis. Amyloid neuropathies are rare, but well known.

Autonomic dysfunction in either type of amyloidosis may cause lower urinary tract dysfunction in around 30% of cases. Impairment of the lower urinary tract can manifest as urinary retention and urinary incontinence. The first urinary symptom is usually voiding difficulty. Andrade et al. assessed lower urinary dysfunction in 54 familial amyloidotic polyneuropathy patients. Initial urinary symptoms, including dysuria, incontinence, and sensitivity and contractility disturbances of the detrusor, appeared during the first 3 years of the disease in 50% of their patients. Vesicosphincter dysfunction in familial
Bladder involvement is very rarely seen in hereditary peripheral neuropathy. A few patients have been reported with the coincidence of hereditary neuropathy and bladder dysfunction. Autonomic disturbance, including bladder dysfunction, was reported as one of the major clinical signs associated with CMT secondary to the MPZ gene mutation in codon 124. Miura et al. studied a four-generation Japanese pedigree with hereditary motor and sensory neuropathy (proximal dominant form), and all affected members showed urinary dysfunction.76

CONCLUSIONS
Normal bladder function depends on the complex interaction of sensory and motor pathways. Several neurological conditions can cause BD. Diabetic neuropathy is the most common cause of peripheral neuropathy associated with BD. GBS, HIV-associated neuropathy, CIDP, and amyloid neuropathy are other major reasons for BD. The diagnosis of BD should be established by the history of neurological symptoms, neurological examination, and bladder evaluation. Management of urinary symptoms in patients with BD is usually supportive. In some cases, an α-blocker and/or cholinesterase inhibitor may be needed to improve urinary function. Intermittent self-catheterization may be needed for patients with slow and/or poor recovery.

The first two authors (A.Z.B. and B.A.) contributed equally to this study and both should be considered as first authors. A.Z.B.’s current affiliation is Neuroscience Section, Virginia Tech Carilion School of Medicine, Roanoke, VA.

REFERENCES

HEREDITARY PERIPHERAL NEUROPATHIES
Hereditary peripheral neuropathies are genetically and phenotypically heterogeneous disorders. Charcot–Marie–Tooth (CMT) disease is the most common inherited peripheral neuropathy. More than 53 genetic loci have been associated with CMT, and more than 36 causative gene defects have been identified with genetic mapping since 1982 when the first gene linkage was established.75

Amyloid polyneuropathy (FAP) occurs at an early stage of the disease even in asymptomatic patients. Retention is due to inadequate contraction of the detrusor, probably associated with non-relaxation of the internal and external sphincters. The underlying pathogenesis of these dysfunctions is thought to be damage to small nerve endings and deposition of amyloid in the detrusor.69

Ito et al. performed uro-neurological assessment in 4 patients with amyloid neuropathy. All of the patients described symptoms of lower urinary tract dysfunction and had voiding difficulties due to detrusor weakness and impaired bladder sensation. In 2 patients, cholinesterase inhibition caused urge incontinence, indicating denervation supersensitivity. The postulated underlying mechanism may be degeneration of postganglionic cholinergic and afferent somatic nerves.66,69

The consensus for management of bladder dysfunction due to amyloidosis is clean, intermittent, periodic self-catheterization, particularly when post-void residual volume is large.66,69 Because of impaired bladder sensation, scheduled catheterization should be performed in order to avoid possible injury from bladder overdistention.45 Care must be taken, however, because α-adrenergic blocking agents can exacerbate the postural hypotension which is common in these patients.66 Milnacipran, a serotonin–noradrenaline reuptake inhibitor, lacks a muscarinic receptor-blocking property,70 and therefore it is useful in the treatment of incontinence due to sphincter dysfunction with detrusor overactivity.66,70 In addition, duloxetine, a dual serotonin (5-HT)/norepinephrine reuptake inhibitor, may be used in the treatment of stress urinary incontinence.71 Duloxetine modulates lower urinary tract function centrally at the Onuf nucleus to increase activity of the pudendal nerve.72 Duloxetine facilitates sphincter activity during urine storage to maintain bladder-sphincter synergy.71,72 Tricyclic antidepressant drugs, such as imipramine and amitriptyline, have an additional use in the treatment of bladder dysfunction.73 They function to increase norepinephrine and serotonin levels and exhibit anticholinergic and direct muscle relaxant effects on the urinary bladder.73,74

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