Lower urinary tract symptoms result from either failure to store urine at low pressure with no urinary leakage or failure to void by completely emptying the bladder. These functions are two extremes of a functional continuum that is dependent on an intact and coordinated neuro-anatomic axis. Bladder emptying and urine storage involve a complex interplay of efferent and afferent signalling involving parasympathetic, sympathetic, somatic, and sensory nerves. Storage dysfunction of neurologic aetiology may result from sensitisation of afferent nerve terminals in the bladder wall or outlet, changes in the detrusor smooth muscle secondary to denervation, or damage to the central nervous system inhibitory pathways, as seen in association with neurologic disorders such as multiple sclerosis, cerebrovascular disease, Parkinson disease, brain tumours, and spinal cord injury.

Detrusor muscle contraction in the normal human bladder is mediated mainly through stimulation of muscarinic receptors. This is counterbalanced by relaxation via the sympathetic nervous system, which occurs principally via activation of adenyl cyclase with the subsequent formation of cyclic adenosine monophosphate. Whilst a significant degree of atropine resistance (defined as contraction of isolated bladder muscle in response to electrical nerve stimulation after pretreatment with atropine) is present in most animal species under normal circumstances, it is not important in the human bladder [1]. A significant degree of atropine resistance may exist in functionally abnormal bladders and has been reported in both neurogenic bladders and the aging bladder [2]. The importance of this component outside laboratory studies remains to be established [3].

In current clinical practice, anticholinergic drugs represent the first-line pharmacotherapy for both idiopathic and neurogenic detrusor overactivity (NDO) and the associated storage symptoms of overactive bladder (OAB). These drugs inhibit muscarinic receptors regardless of their anatomic location and are traditionally considered to act principally on the M3 muscarinic receptors located on the detrusor muscle. In particular, during the storage phase of the micturition cycle, one would expect minimal parasympathetic input to the lower urinary tract [4]. Conversely, it is difficult to understand how these agents, which act as competitive antagonists, could be effective during micturition when there is a massive release of acetylcholine, without resulting in urinary retention, which is uncommon at therapeutic doses as evidenced by meta-analyses of studies in both idiopathic detrusor overactivity [5] and NDO [6]. There is now experimental evidence that these drugs may act during the storage phase by decreasing the activity in afferent nerves (both C- and A-delta fibres) from the bladder [7,8]. It is notable that in the review and meta-analysis of anticholinergic use in the treatment of adult NDO, published in this edition of European Urology [6], Madhuvrata et al. conclude that the existing literature demonstrates efficacy of antimuscarinic antagonists on both symptoms and urodynamic parameters, the latter being more pronounced than seen in similar studies conducted in idiopathic OAB [5].

The review highlights the deficiencies in data relating to the use of anticholinergic therapy in patients with bladder overactivity associated with neurologic disease. Certainly more work is necessary in patients with specific neurologic lesions to ascertain how afferent and efferent innervations contribute to the effectiveness of antimuscarinic therapy. In total, 960 patients (485 men and 372 women; one study did not mention patients’ sex) from 16 randomised controlled
trials were analysed. Most of the studies in the meta-analysis assessed treatment in limited numbers of trial subjects, with only two trials reporting on >100 subjects and four studies on <20 patients. Only eight studies (n = 390 patients) contrasted anticholinergic therapy with placebo. One evaluated tolterodine 2 mg twice daily for 4 wk (n = 14); one study assessed trospium 20 mg twice daily for 3 wk (n = 61); and of the remaining trials, three were single-dose studies and three were 2-wk studies. Only one evaluated a modern delayed-release oral formulation of anticholinergic therapy; this study was of 45 mg propiverine extended release and was only reported in abstract form in 2009 [9]. Four studies reported on intravesical therapy (one study each of darifenacin and atropine and two of oxybutinin), and the remainder reported on oral therapies (three studies of tolterodine, four of propiverine, three of trospium, two of oxybutinin, and one of propantheline). Individual studies contrasted the oral administration of methantheline, flavoxate, and meladrazine; oxybutinin and propiverine; trospium and oxybutinin; propantheline and oxybutinin; and one contrasted intravesical atropine and oral oxybutinin. It is clear from this overview that the evidence base is extremely heterogeneous and, as emphasised by Madhuvrata et al, this meta-analysis has to be interpreted with caution.

There is a need for more contemporaneous study of anticholinergic therapy in this patient population. Such a study was reported at the European Association of Urology meeting in 2012. Amarenco and colleagues [10] presented the results of the solifenacin compared with placebo and oxybutynin in the treatment of subjects with neurogenic detrusor overactivity, or SONIC, urodynamic study. Patients, men and women, were aged 18–65 yr and had multiple sclerosis (MS) (Expanded Disability Status Scale ≤8) or spinal cord injury (SCI) (partial or complete lesions), with stable NDO (≥6 mo). In total, 248 patients were screened, 189 patients were randomised and received one dose or more of medication (safety population), and 176 patients were included in the full analysis set (95 MS and 81 SCI patients, in four groups: placebo (n = 43), 15 mg oxybutynin (n = 47), 5 mg solifenacin (n = 43), and 10 mg solifenacin (n = 51). The primary objective was assessment of solifenacin 10 mg efficacy compared with placebo at week 4 in changing baseline maximum cystometric capacity (millilitres) to end of treatment (calculated as the sum of the drained volume at the end of cystometry and leakage). Whilst both the lower doses of solifenacin 5 mg and oxybutynin 15 mg were associated with improvements from baseline in cystometric function, this presentation focused on the results of solifenacin 10 mg and placebo groups. The change from baseline in maximum cystometric capacity was 134.2 ml for solifenacin 10 mg (n = 51) versus 5.4 ml for placebo (n = 40; p < 0.001). Compared with placebo, solifenacin 10 mg was associated with greater improvements in bladder volume at first involuntary contraction (79.2 vs –10.1 ml; p < 0.001) and bladder volume at first leak (83.3 vs –13.2 ml; p = 0.02). Improvements in detrusor pressure at first leak (–11.7 vs 7.7 cm H2O; p = 0.01) and maximum detrusor pressure (–10.5 vs 7.5 cm H2O; p = 0.003) were also greater with solifenacin 10 mg than with placebo. Interestingly, there was no statistically significant effect with solifenacin 10 mg compared with placebo on the bladder diary parameters, mean number of catheterisations per 24 h, or the mean number of incontinence episodes per 24 h. Patients treated with solifenacin 10 mg reported significantly greater changes from baseline in score for treatment satisfaction on the visual analogue scale (VAS) than those on placebo (14.3 vs 1.3; p = 0.011). The researchers also reported statistically significant improvements in the patients’ perception in bladder treatment score with solifenacin 10 mg versus placebo (–0.6 vs –0.1; p = 0.041) at end of treatment. The incidence of treatment-emergent adverse events was low; dry mouth was more likely with solifenacin 10 mg than placebo, but the difference was not statistically significant (change in VAS score: 10.4 vs 4.4; p = 0.24). The full results of this study in a peer-reviewed paper are awaited with interest.

Bearing in mind the caveat about the heterogeneity of the published data set [5], the evidence to date supports the perception that anticholinergic agents have efficacy in the treatment of NDO. As with their use in general urologic practice, there are differences between agents with regard to their efficacy/tolerability profile [5]. Only one study [10] has evaluated sustained release formulations of antimuscarinic therapy. Furthermore, in this patient population, particularly for those using intermittent self-catheterisation, the potential for using intravesical therapy needs to be explored more fully, as the evidence relating to this method of drug application remains very limited with no adequately powered studies. Unfortunately, the relatively small number of patients with NDO as contrasted to the much larger population of patients with idiopathic detrusor overactivity and/or OAB symptoms, has led to this being a less attractive target for pharmaceutical industry-sponsored trials, hence the shortcomings of the existing literature base.

Conflicts of interest: The author has served as an advisor and researcher for Astellas Pharma Inc, Allergan Inc, Pfizer Inc, and Recordati SpA, and is an advisor to Eli Lilly and Co.

References


