

How to treat the frail elderly: The challenge of multimorbidity and polypharmacy

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Abstract

The pharmacologic management of lower urinary tract symptoms in frail older adults is complicated by two key considerations: the increased likelihood of comorbidities and the increased likelihood of polypharmacy. This brief review summarizes how these factors may impact treatment choices in this population.

In many respects, managing lower urinary tract symptoms (LUTS) in older adults is indistinguishable from the management of younger patients. There are, however, several considerations to keep in mind for older adults that may indeed impact treatment decisions. This short summary provides an overview of the implications of frailty, comorbidities and polypharmacy on the management of LUTS in older adults.

Frailty

Frailty is defined in various ways. Pathophysiologically, frailty represents a state of increased vulnerability to poor resolution of altered homeostasis after a stressor event. Clinically, frailty can be recognized by a cumulative decline in physical activity, mobility, balance, muscle strength, cognition, nutrition and endurance, with high medication use. These patients are typically homebound or institutionalized. Their prognosis is worse than non-frail older adults, with increased risk of adverse outcomes, including falls, delirium and disability. It is estimated that between 25 and 50% of people over the age of 85 can be considered frail.^{1,2}

With respect to LUTS, frailty needs to be taken into account when making management decisions, as the cause is more likely to be multifactorial than among younger and/or more robust older patients. Also, due to age-related pharmacokinetics and pharmacodynamics, as well as the increased risk of comorbidity, polypharmacy and drug-drug interactions, frail elderly patients are more susceptible to treatment-emergent side effects.

Comorbidities

Elderly patients, whether frail or not, are more likely to have chronic comorbidities. Table 1 shows several of these, with their impact on the presence and/or severity of urinary incontinence (UI).³ Patients with dementia, for example, are more than twice as likely to experience UI as those without. A history of falls in patients with dementia is associated with a further likelihood of UI due to mobility as well as functional impairment.³

Polypharmacy

With respect to medications, simply put, any medication that affects the lower urinary tract or that acts centrally has the potential to affect LUTS. Potential mechanisms include an increase in urine production (e.g., loop diuretics), interference with sphincter function (e.g., alpha-blocking agents), disruption of detrusor contractility (e.g., anticholinergic medication) and interference with cerebral control of micturition (e.g., sedative/hypnotic medication such as benzodiazepines).⁴ Drug-drug interactions may also cause pharmacokinetic or pharmacodynamic alterations, leading to unexpected toxicity or therapeutic failure.

Considerations for LUTS pharmacotherapy

There are several considerations to keep in mind when prescribing an antimuscarinic medication for LUTS in an elderly patient. Figure 1 shows a suggested algorithm, based on expert opinion, for selecting an antimuscarinic medication for older patients with LUTS, taking into account polypharmacy, frailty and concomitant conditions. In the absence of significant comorbidity and polypharmacy, any of the antimuscarinic agents can be prescribed at the discretion of the treating physician. Oxybutynin immediate-release oral preparation in doses exceeding 10-15 mg/day should be avoided as first-line treatment because of higher rates of anticholinergic side effects.⁵ Due to improved consistency in serum levels, the extended-release, once daily and transdermal formulations are associated with lower rates of anticholinergic adverse events, and are better options for the frail, elderly patient. For patients with existing constipation, the

Table 1. Comorbidities associated with bladder dysfunction

Comorbidity	Association with UI
Parkinson's disease	60% of patients have LUTS
Dementia	Odds of UI 2.3 (95% CI 1.6-3.3)
Falls and dementia	Odds of UI 4.9 (2.0-12.0)
Stroke	UI is a poor prognostic factor
Cardiovascular disease	Rates of UI increase with severity and duration of heart disease
Diabetes	80% higher risk of severe UI
Arthritis, back pain	50-90% higher risk of having UI
Obesity	Pelvic floor dysfunction 4 times more likely

UI: urinary incontinence; LUTS: lower urinary tract symptoms; CI: confidence interval.

patch or gel form of oxybutynin are preferred over other antimuscarinics, as they have the lower rates of constipation compared to all oral agents.^{6,7}

A growing body of evidence suggests that antimuscarinic agents, other than immediate-release oxybutynin at high doses, do not cause cognitive impairment in older individuals.⁸ Even in those who already have mild cognitive impairment or outright dementia, evidence indicates that antimuscarinics do not have a significant impact on memory.^{9,10} However, one must take into account comorbidities and other medications the patient may be taking. Concomitant use of cholinesterase inhibitors (e.g., donepezil, rivastigmine) and antimuscarinics, for example, may worsen physical function in elderly patients with dementia.¹¹ Caution must also be exercised among patients with cardiovascular conditions, as antimuscarinics may impact heart rate and QT interval to varying extents.^{12,13}

Importantly, the various available antimuscarinics are metabolized differently, with some agents metabolized through the hepatic cytochrome P450 system. This is particularly important to be aware of for patients taking multiple medications, as many common drugs are also inducers, inhibitors or substrates of the various isoenzymes of this system. Solifenacin and oxybutynin, for example, are metabolized through the CYP3A4 pathway, while tolterodine and darifenacin are metabolized through both CYP3A4 and CYP2D6 (Table 2).^{7,14}

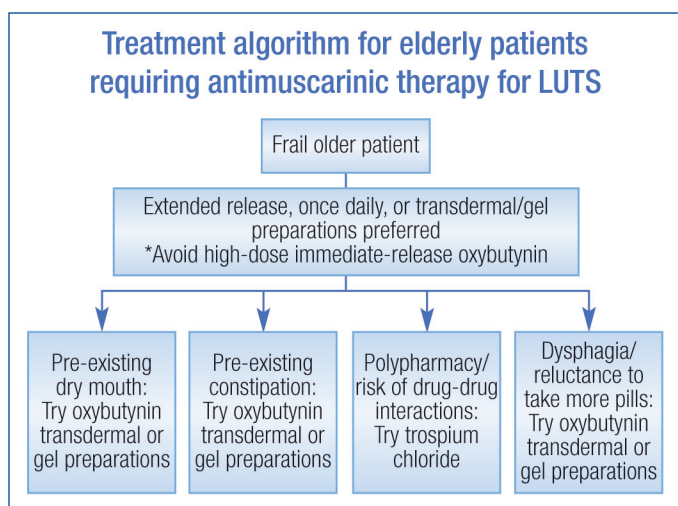


Fig. 1. Treatment algorithm for elderly patients requiring antimuscarinic therapy for lower urinary tract symptoms.

Table 2. Medications for overactive bladder: Hepatic CYP450 metabolism

Therapy	CYP450 metabolism	
	CYP2D6	CYP3A4
Tolterodine	✓	✓
Darifenacin	✓	✓
Oxybutynin	–	✓
Solifenacin	–	✓
Fesoterodine	Elimination only	Elimination only
Mirabegron	✓	✓
Trospium chloride	–	–

At the present time, there are no data available regarding the use of the beta3-adrenoceptor agonist mirabegron in specific populations of elderly or frail elderly patients with overactive bladder (OAB). It should be noted, however, that it is a substrate for both the CYP2D6 and 3A4 pathways of the cytochrome P450 system.

Conclusions

Managing LUTS in older adults involves most of the same elements as treating LUTS in younger adults. However, there is the potential for pharmacokinetic or pharmacodynamic differences in older people, particularly frail individuals. There is also an increased potential for drug-drug interactions among older patients with comorbidities treated with multiple medications. The most appropriate therapy for each patient should be customized based on individual clinical profiles.

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