



Anticholinergic drugs for overactive bladder

William Kuteesa, Fellow in Urogynaecology, and Kate H. Moore, Associate Professor, Pelvic Floor Unit, St George Hospital, Sydney

Summary

Anticholinergic drugs are first-line pharmacotherapy for overactive bladder syndrome. They block muscarinic receptors at the detrusor muscle, thus reducing bladder contractility. As no anticholinergic drugs are totally selective for the detrusor, adverse effects from muscarinic receptor blockade at other sites are common. New drugs with greater bladder selectivity and extended-release preparations are being developed to try to reduce these adverse effects. Most of the newer drugs have similar efficacy in reducing the symptoms of overactive bladder (when compared to placebo). Optimum benefit is obtained when the drugs are prescribed in conjunction with bladder retraining.

Keywords: incontinence, oxybutynin, tolterodine.

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Introduction

Overactive bladder (previously called 'unstable bladder') is a clinical symptom complex characterised by urgency (sudden and compelling desire to pass urine, which is difficult to defer), usually with frequency (more than eight voids per day) and nocturia (waking to void more than once at night). It occurs with or without urge incontinence (involuntary leakage of urine with the feeling of urgency) in the absence of infection or other irritative lesions.¹

The urodynamic diagnosis is now termed detrusor overactivity (previously called detrusor instability) because detrusor contractions are seen during filling cystometry and these are associated with the feeling of urgency.¹ There are three categories of detrusor overactivity: neuropathic (previously detrusor hyperreflexia), obstructive (commonly associated with prostatic obstruction) and idiopathic. The term overactive bladder usually refers to the idiopathic type of detrusor overactivity.

The prevalence of overactive bladder increases with advancing age and affects about 16% of adults over 40.² Of these, about 30% suffer from urge incontinence, now called 'overactive bladder wet', with profound reduction in quality of life.^{2,3} The remainder, now called 'overactive bladder dry', nevertheless

have a debilitating condition which is likely to progress to incontinence if untreated.

Management includes bladder retraining, fluid scheduling, restricted consumption of caffeine and alcohol, and avoidance of diuretic therapy. Anticholinergic (antimuscarinic) drugs are the main pharmacotherapy, but other treatments include tricyclic antidepressants and vasopressin analogues. Patients with overactive bladder 'dry' may respond more readily to bladder training without recourse to drug therapy, although this hypothesis has not been formally tested.

Most clinicians would start treatment by teaching bladder retraining. Many public health services in Australia now offer bladder retraining therapy by specialist continence advisors.* Micturition deferment techniques are taught and a 'bladder diary' gives a guide to selecting a realistic voiding interval for the patient. Prescribing anticholinergic drugs generally allows the patient to improve more rapidly, but bladder training alone is a reasonable first-line therapy.

Rationale for anticholinergic use

Detrusor muscle contractions are essential for normal micturition, but involuntary contractions produce the symptoms of overactive bladder. Contractions depend on the activation of muscarinic receptors in the bladder by acetylcholine. The M₃ muscarinic receptor-subtype is thought to be the most important in regulating detrusor contractions.

Anticholinergic drugs block muscarinic receptor activation and inhibit the spontaneous detrusor contractions found in overactive bladder. Drug efficacy is dose-dependent, but effectiveness is often limited by unwanted antimuscarinic effects in distant organs where other acetylcholine receptor-subtypes predominate (for example salivary gland M₁/M₃, gut M₂/M₃, brain M₁ and cardiac M₂). These adverse effects are also dose-dependent. They commonly include dry mouth, dry eyes, confusion, constipation, somnolence, blurred vision and increased heart rate.

There are no currently available drugs with pure selectivity for the muscarinic receptors in the detrusor. To try to improve the benefit:harm ratio a number of anticholinergics have been developed with greater selectivity for the detrusor or the M₃ receptor, or with extended release properties.

* details available from National Continence Helpline 1800 33 00 66

Do anticholinergics work?

The ability of anticholinergic drugs to reduce detrusor contractions has been well established *in vitro* and *in vivo*, however there are questions about their clinical efficacy. Anticholinergic therapy has been extensively studied in randomised placebo-controlled trials and the Cochrane Collaboration has systematically reviewed 51 studies involving 6713 patients.⁴ A striking placebo effect was observed, with 45% of those on placebo reporting cure or improvement in symptoms. (Patients in some but not all studies were given printed information about bladder training, but no formal bladder training was given.) The effect of anticholinergics was found to be a statistically significant 15% greater than placebo (equivalent to a 'number needed to treat' of seven in order to reduce leakage by one episode per 48 hours).

A problem for the review was that the studies used a wide range of outcome measures. Analysis of the two measures that were common to most randomised controlled trials revealed that anticholinergics resulted in one less micturition per 48 hours and one less incontinence episode per 48 hours.⁴ From a clinical perspective, the results seem unimpressive, but there are two reasons for this. Firstly, most studies did not include concomitant bladder training, thus they failed to reflect optimal clinical practice. Secondly, the hypotheses tested by these studies may have been inappropriate. Most did not measure treatment effect upon 'urgency', the primary symptom of overactive bladder.¹ Furthermore, the modest improvements in leakage and frequency identified in the review could have had major positive impacts on quality of life, but most studies did not include quality of life measures.

Bladder training is essential treatment for overactive bladder

Which is the most effective anticholinergic?

Uncertainty still remains about which of the anticholinergic drugs is superior in efficacy, in different patient groups (male, female, elderly) and for particular symptoms. There are also few data on the socioeconomic impact of overactive bladder symptoms or therapy.⁴

Oxybutynin

Oxybutynin is the most widely used anticholinergic for overactive bladder. Early studies showed a major clinical benefit in 60% of patients (versus 3% of those on placebo) in both objective and urodynamic assessments. Dry mouth is the most bothersome and frequent adverse effect (greater than 50%) and is associated with high discontinuation rates.⁵ The drug is comparatively inexpensive.

Propantheline

Propantheline is an old drug that is still widely used in Australia. It is a synthetic analogue of atropine that blocks muscarinic receptors at all sites, thus adverse effects can be

severe at low serum concentrations. However, propantheline is 60% of the cost of oxybutynin.

Imipramine

Imipramine is a tricyclic antidepressant with beta₃ mimetic properties that relax the dome of the detrusor, but it also has significant anticholinergic effects. Drowsiness is common, especially in the first three weeks of therapy while a steady state concentration is achieved. Imipramine may therefore be useful for treating nocturia or nocturnal enuresis.

Tolterodine

Tolterodine is an anticholinergic specifically developed to treat overactive bladder. *In vitro*, tolterodine has greater specificity for bladder tissue than for salivary glands. A meta-analysis found only four appropriate randomised controlled trials comparing tolterodine with oxybutynin.⁶ Both drugs are of similar efficacy, with oxybutynin being slightly superior on some outcomes such as incontinence episodes per 24 hours.⁶ The exact mechanism is not understood, but tolterodine halves the incidence of dry mouth compared to oxybutynin.⁶

Trospium

Trospium is a non-selective antimuscarinic drug which is frequently used in the UK as second-line therapy. It is as effective as oxybutynin, but has a lower incidence of adverse effects (similar to tolterodine).⁷ Trospium's structure limits its penetration of the blood-brain barrier and this is thought to reduce central nervous system adverse effects. This feature may be important for elderly patients.

Darifenacin

The efficacy of darifenacin, including quality of life, has been convincingly shown over placebo, but whether there is clear superiority over drugs such as tolterodine remains to be seen. Darifenacin has high M₃ receptor specificity, resulting in less impairment of cognitive or cardiac function. Some patients still develop dry mouth and constipation as M₃ receptor activity is present in the gut.

Solifenacin

Solifenacin was approved in the USA in 2004. *In vitro*, it is more selective for bladder tissue than for salivary glands. Studies suggest improvements over placebo with low rates of dry mouth (10%) and greater quality of life.⁸ A well-powered comparative randomised controlled trial⁸ found that tolterodine had a lower incidence of unwanted effects and lower discontinuation rates.

Extended-release products

Extended-release formulations of oxybutynin⁹ and tolterodine⁸ have been developed. These are thought to reduce

concentration-dependent antimuscarinic adverse events by maintaining lower and less fluctuating plasma concentrations. Once-daily administration offers greater convenience and may improve compliance. Both products seem as effective as oxybutynin, but they have a reduced frequency and severity of adverse effects.

What to prescribe

Oxybutynin should be regarded as first-line drug therapy. It fulfils criteria for cost-effectiveness, safety, efficacy, and for a significant proportion of patients, tolerability. Consideration should always be given to behavioural therapies as an adjunct, to achieve and maintain good therapeutic outcomes at the lowest drug doses.¹⁰ Patients experiencing unmanageable adverse effects from oxybutynin may benefit from changing to second-line treatments such as tolterodine. Subsequent treatment failure may warrant specialist referral.

Only two small longitudinal studies on the duration of treatment have been carried out. Those patients who require anticholinergic therapy may typically need it for at least 3–6 months.

Minimising adverse effects

In the elderly or patients with a low bodyweight, the initial oxybutynin dose should be 2.5 mg twice daily. One can increase a morning dose or add a lunchtime dose according to the severity and timing of the urge symptoms. On the other hand, if the patient has a very dry mouth in the morning, then a lower morning dose with a larger evening dose can be used. The maximum dose is 5 mg three times daily. Tolterodine is expensive and not subsidised by the Pharmaceutical Benefits Scheme so some patients may prefer to take it in the morning and use a cheaper drug at times when dry mouth may be less bothersome.

Conclusion

Anticholinergics are clinically and statistically better than placebo for overactive bladder. Most are equally effective and all have some adverse effects. This has driven the development of drugs with greater selectivity or tolerability. Until these new alternatives undergo rigorous comparative trials, oxybutynin will remain first-line in pharmacotherapy in Australia. Outcomes are improved when anticholinergics are prescribed in conjunction with bladder training.

References

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Associate Professor Moore has held consultancies with Pfizer, the manufacturer of tolterodine and darifenacin.

Self-test questions

The following statements are either true or false (answers on page 27)

7. Anticholinergic drug therapy for overactive bladder reduces the frequency of micturition by one void every two days.
8. Anticholinergic drugs with greater selectivity for M₃ muscarinic receptors have significantly greater efficacy than less selective drugs for overactive bladder.

Patient support organisation

The Continence Foundation of Australia

Website www.confound.org.au

National Continence Helpline 1800 33 00 66

Email info@continence.org.au