Clinical update
The changing face of detrusor overactivity therapy in Australia

Introduction
The overactive bladder (OAB) symptom complex affects 17% of adults over age 40, and is more common in the older person, for reasons that are not fully known.

Because Australia has a high standard of health care, more and more people are living longer. Therefore, the incidence and prevalence of this condition is likely to rise as our population ages. In contrast to stress incontinence, for which the cause is known and cure is readily available, the aetiology of detrusor overactivity remains unknown and “cure” is not yet reliably achievable. As a result, OAB will account for a relatively greater proportion of the “burden of disease” of female incontinence over the next decades.

When managing overactive bladder, first line therapy comprises bladder retraining, but this requires an intact brain/ cerebral cortex. In the elderly, this pre-requisite may not be available. Partly because of this, and partly because bladder training is often not curative even in those with an intact cerebrum, we need a range of pharmacotherapy agents.

A conundrum arises when an elderly person with OAB suffers from Alzheimer's disease and is commenced on a cholinesterase inhibitor such as donepezil hydrochloride (Aricept). In such patients, anticholinergic medications are contra-indicated, thus neuromodulation become attractive. The patient with Alzheimer's disease (or their carer) sometimes has to choose between halting the progression of the dementia, or treating the urge incontinence with anticholinergic therapy. Although this is becoming an increasingly widespread problem, this conflict was not mentioned in a very recent review of detrusor overactivity therapy in the elderly. In the following article, new pharmacotherapy agents are discussed, and neuromodulation options are considered.

New pharmacotherapy agents
Oxytrol patches were designed to deliver the widely used oral drug oxybutynin via skin absorption continuously and consistently over a 3-4 day interval. Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic M1/M3 receptors resulting in relaxation of the detrusor. Oxybutynin is metabolised primarily by the cytochrome P450 enzyme systems found in the liver and gut. One of its metabolites N-desethyloxybutynin is pharmacologically active and also causes anticholinergic side effects. The transdermal administration bypasses the first pass gut and hepatic metabolism, reducing the formation of the metabolite and hence decreasing the side effects experienced.

Clinical trials comparing oxybutynin patches with placebo show a comparable occurrence of dry mouth. Itching at the site of application is experienced by 10% to 16% of patients. The clinical efficacy of oral Oxybutynin hydrochloride (Ditropan) is similar to that of the transdermal patches.

Tolterodine (Detrusitol) (dose 2mg prescribed twice daily) was developed in the 1990s, but is still not available as a PBS prescription in Australia. Although widely available on a private script, the cost (AUD$55-80) is often prohibitive. It was the first drug designed specifically to reduce the incidence of dry mouth (about 15%) that is so common and debilitating in patients on oral oxybutynin (about 60%).

Propiverine (Detrunorm) (dose 15mg prescribed three times a day) is a non selective anticholinergic drug that also acts as a calcium channel blocker (a similar combination to the 1980s drug Terodiline that is no longer available). Dry mouth occurs in about 20% of patients but is not usually debilitating. It is widely used in the United Kingdom (UK) and is available in Europe. It is available in Australia as a private prescription on the SAS scheme.
Trospium (dose 20mg prescribed twice daily) is another non-selective anticholinergic agent, but due to structural changes has only a 4% rate of dry mouth. Also, because of its structure/metabolism it is less likely to cross the blood brain barrier and thus is less likely to cause mental confusion or other CNS side effects. It is widely used in the UK, available in Europe, and was recently approved in the United States of America (USA), but is not widely available in Australia.

Solifenacin (Vesicare) (dose 5mg or 10mg prescribed once daily) is the first M3 selective agent available in Australia. It was developed in the early 2000s, and after extensive clinical trials was released in Australia in late 2005. Dry mouth occurs in 8% of patients on the 5mg dose and 23% of those on the 10mg dose, but is generally not troublesome. A randomised placebo controlled trial revealed a “dry rate” of 50%, with significant reductions in episodes of urge incontinence, voids per day and nocturia. In a long-term, open label study of this patient group (and a second RCT cohort), 81% of patients completed 40 weeks of therapy, 5% of patients discontinued due to side effects. Whether patients with OAB should expect long term drug therapy is a separate issue, but at least this drug appeared tolerable, in contrast with six month studies of oral oxybutynin which showed a much higher dropout rate.

Darifenacin (Enablex) (dose 7.5mg or 15mg prescribed once daily) Although solifenacin is the first M3 selective anticholinergic agent to become available on prescription in Australia, darifenacin was actually developed many years before. The scientific work essential to developing this drug was carried out in the late 1990s up to 2001. Two clinical trials of darifenacin were carried out in Australia in the early 2000s. However, because of commercial decisions, the makers of darifenacin merged with the manufacturers of tolterodine, and an agreement was made to focus on the marketing of tolterodine which was in a more advanced stage of clinical trials at that time. Subsequently, the company in charge of darifenacin changed (now Novartis), and presumably in view of the tremendous success of solifenacin, the makers of darifenacin have made it available as a private prescription in Australia.

Neuromodulation Options

Electrostimulation

Traditionally, intravaginal electrostimulation is considered as a way to increase the strength of pelvic floor muscle and urethral sphincter contractions (in patients with stress incontinence). Generally, the electrostimulation is delivered at a stimulation frequency of about 30-50 Hertz, to cause a tetanic muscle contraction.

However, there is a substantial body of literature indicating that, at least under experimental conditions, electrical stimulation can be used to inhibit detrusor contractions. In this case, the electrical stimulation is applied to the afferent supply of the pudendal nerves, which is thought to provoke a reflex activation of sympathetic nerves to the detrusor that cause relaxation of the detrusor muscle contraction. The optimal stimulation

![Figure 1. Muscarinic receptor subtypes](image-url)
frequency here is 5-10 Hertz, which will stimulate the nerves, but not cause a direct muscle contraction.

Older studies showed that applying electrical stimulation to the dorsal penile nerve or to the pudendal nerve, cause relaxation of the detrusor muscle. Early clinical studies of such devices in relation to women showed promise. Brubaker and colleagues performed a sham controlled RCT involving a take-home device that was used for 20 minutes twice daily for six weeks by 33 patients with proven detrusor overactivity (DO). After treatment, half had no further evidence of DO. However, it can be seen that the stimulation needed to be provided on a regular basis, and probably for the long term in order to maintain this benefit. Hence this therapy is not widely used for DO.

**Sacral nerve stimulation**

Based on early urologic studies of patients with partial spinal cord injuries in the 1970s and 1980s, it was realised that a nerve stimulation electrode (S3 surgical implementation device) could be permanently implanted on a chosen sacral nerve root. After an initial period of use for neurologically impaired, incontinent patients, the device was later offered to patients with refractory idiopathic detrusor overactivity (IDO).

For example, a randomised controlled trial of an S3 device implantation for nerve stimulation was offered to 155 patients with refractory IDO. After randomisation, the “control group” was put on a waiting list for 6 months and given medical therapy. At recruitment, active patients underwent a preliminary insertion of the needle electrode which was taped to their skin for three days, and activated by a temporary stimulator that was worn externally. Of the 155 enrollees, 98 had a successful test stimulation and were randomised (in a 1:2 ratio). Six months after undergoing neurosurgical implantation, outcome data was available from 76 patients (34 in active stimulation, 42 in the delay group), details of the other 28 participants were not given. Of those on active stimulation, 47% were dry at 6 months on a bladder diary (no pad testing performed). On cystometry 56% were stable (compared to 16% in the control group).

In general terms, the likelihood of needing to surgically reposition or replace the stimulation device was 32.5%. Pain occurred at the neurostimulation site in 16% of patients, with pain at the electrode site in 19% and lead migration from the S3 nerve root in 7%. The rate of infection, or skin ulceration requiring explantation was 6%. There were no permanent adverse events or cases of nerve damage. The S3 implantable neurostimulator is available in a few centres in Australia, but at a cost of AUD$7,000 it is reserved for severe, “end stage” detrusor overactivity.

**TENS therapy**

Trans Cutaneous Electrical Nerve Stimulation (TENS therapy): Because implantation of a nerve stimulator at S3 was achieving promising results, the possibility that delivery of a similar current across the skin could achieve similar results was investigated. Webb and Powell reported substantial benefit when they applied TENS stimulus across the S3 dermatome (peri-anally). At cystometry, in 24 patients with refractory detrusor overactivity, 45% became stable and bladder capacity at the onset of unstable contractions was improved in the remainder. Subsequently, Hasan and colleagues in 1994 gave TENS to outpatients for 3 weeks and reported significant benefit on urodynamic parameters.

A randomised sham-controlled trial of TENS was then performed by Bower and colleagues in 1998 during cystometry.
The device was placed over the pubic bone or over the sacrum in a randomised fashion. Patients in the active group had a significant reduction in maximum detrusor pressure (p=0.008) and an increase in first desire to void (p = 0.002), with 44% of patients becoming stable, compared to 13% of those with the sham device in place (regardless of the site). Later clinical experience indicated that patients needed to use the TENS machine at least twice daily to continue benefit, so that the device is clinically cumbersome.

**SANS (Stoller Afferent Nerve Stimulator) therapy:** Acupuncture has been helpful for detrusor overactivity, when applied to known bladder points – as reported by Chang and colleagues in 1998—by increasing the levels of endogenous opioids (beta-endorphin and met-enkephalin) in the patient's cerebrospinal fluid. These substances inhibit detrusor contractions.

Therefore, the idea of applying acupuncture with an electrical stimulus to the relevant acupuncture point (the medial malleolus of the ankle) was tested. In 53 patients with refractory OAB in Seattle, SANS was applied for weekly for 12 weeks. In the 47 patients (89%) who completed the study, there was a 25% reduction in daytime voids, and 21% reduction in nocturia, with a 35% reduction in episodes of urge incontinence. A later study of acute SANS stimulation was conducted in Paris. The mean volume at first detrusor contraction was increased from 163ml to 232ml, with an increase in maximum cystometric capacity from 221ml to 277ml (p < 0.0001 for both changes).

Data regarding maximum detrusor contraction was not given. In clinical practice, the SANS device appears to have a “niche” role, especially for those suffering from nocturia.

**Magnetic field stimulation**

**The Neotonus Chair:** In early 2000s, the Neotonus chair became available. It contained a magnetic coil in the base of the chair, which produced an electric current (similar to MRI) at a frequency of 10Hz or 50Hz.

Other authors showed that the 50Hz current was effective in stress incontinence for patients who were unable to contract their pelvic floor muscle. However, the manufacturers claimed that it was useful for mixed incontinence, but data was scant. Therefore, two separate studies were undertaken among women with a sole diagnosis of IDO. The first study assessed the acute effect of magnetic stimulation (provided by Neocontrol) on detrusor function during the filling phase of standard cystometry. Multiple filling cycles were performed with stimulation at a different key moment in each cycle. This was done to establish that the device could inhibit the detrusor contraction. Subsequently, a randomised sham control trial was performed to assess clinical efficacy. A total of 20 treatments, each of 20 minutes duration, were administered over six weeks with follow-up six weeks thereafter. Half the patients received therapy from a genuine device, the others receiving fake treatment on an identical looking/sounding sham device. The sham device contained a deflector plate to degrade the magnetic field and was located in a separate room. Outcome measures included changes in a 24-hour fluid volume chart, urine loss (24 hour pad test) and quality of life instruments.

The acute chair stimulation did improve the volume at first detrusor contraction during filling, from a median value of 240ml (Interquartile range (IQR) 210–300) to 285ml (IQR 231–320), p = 0.03 and maximum detrusor pressure decreased from 40cm water (IQR 34–45) to 33cm water (IQR 25–41), p < 0.01.

The RCT was completed by 29 of 44 (66%) recruits. Of these, 15 of 29 (52%) received active treatment and 14 of 29 (48%) sham therapy. Active therapy significantly reduced the number of urge episodes per day, p < 0.01. With respect to baseline, actively treated patients experienced significant reduction in voids per day and quality of life but this trend did not reach significance when compared to the sham group. Unexpected difficulty in recruitment yielded an underpowered sample size for these outcome measures, but there was no clear picture of clinical benefit.

**Electrical stimulator implant:** Clinical trials of the surgically implantable Miniaturro device are currently ongoing in Melbourne.
and Sydney. The device differs from S3 implants in three respects. Firstly, neurosurgery is not required. Secondly, the stimulation device (a 40 mg stimulator the size of a cigarette lighter) is implanted on the inner aspect of the pubic bone. Thirdly, the stimulation electrode is implanted onto the external urethral sphincter, to provide reflex inhibitory stimuli to the detrusor muscle.

The Miniaturro device is similar to the S3 implant in that a temporary stimulation lead is placed under local anaesthetic (with an external stimulator). Only patients who respond to this therapeutic trial can undergo surgical implantation of the permanent device. The cost is not yet known in Australia, but will probably be priced in thousands rather than hundreds of dollars (similar order of magnitude to S3 implant).

The device was originally designed for women with severe painful bladder syndrome (interstitial cystitis). Early trial data indicates marked success in this difficult group, although numbers are not sufficient for publication as yet. Because many patients with refractory urge incontinence experience their urge as “painful”, and because of the success of S3 implants in refractory DO, it was thought likely that this less invasive device would also have a role to play in refractory urge incontinence. Active recruitment is ongoing.

Conclusion

As clinicians and scientists world wide realise the growing impact of DO/OAB upon the community, greater efforts to produce new drugs and new alternative therapies are occurring. Unfortunately, because we do not yet know the cause of the OAB symptom complex, a true “cure” is probably some years away.

References