

# DO NOT GO GENTLE – urinary troubles for more than the ageing

The needs of younger incontinence sufferers coupled with the ageing of the baby-boomer population portend a big boost in demand for effective and well-tolerated new medicines for lower urinary-tract dysfunction. This market is under-served today, presenting a major opportunity for drug companies. Truly effective, broadly applicable new medicines may require new thinking: that rather than leaky plumbing or blocked pipes, it may be faulty wiring that precipitates these disorders.

“Do not go gentle into that good night,” wrote Dylan Thomas. Yet for ageing baby boomers, as well as for younger women, symptoms of lower urinary-tract dysfunction (LUTD) make it difficult for an increasing number of people to “go gentle”. Based on their past behaviour, however, the vaunted baby-boomer and subsequent generations won’t give in without a fight to what have hitherto been perceived as inevitable consequences of childbirth or ageing.

The catch-all term LUTD applies to a cluster of distinguishable disorders whose definitions continue to evolve as they become better understood. While the root causes of LUTD remain obscure, the symptoms are all too familiar to sufferers:

- Urge or urgency (nagging, intense sensation that the bladder has reached its ‘failsafe’ threshold).
- Frequency of urination (eight or more times a day).

- Nocturia (sleep disturbances accompanying the need to urinate).
- In some cases, obstruction of urine flow.
- In others, urinary incontinence.
- Urogenital or pelvic pain.

*(Note: Some may suggest that LUTD as a cluster term should encompass male erectile dysfunction and sexual dysfunction. In this review we are excluding discussion of disorders associated with sexual function, although the anatomical proximity and co-morbidity ought to be noted by the reader.)*

## Disorders affecting urination

Constituent LUT disorders, whose prevalences appear in Table 1, are distinguished by symptomatology and often gender:

**Stress urinary incontinence (SUI):** inability to prevent leakage of urine during activities that increase abdominal pressure (eg, athletics, sneezing or lifting).

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**Table 1:** Estimated prevalence of lower urinary tract dysfunction in 2001 (in millions)<sup>1,2</sup>

Disease condition	Worldwide <sup>§</sup>	US
Stress Urinary Incontinence	64.6	24.2
Urge Urinary Incontinence <sup>#</sup>	20.2	7.2
Mixed Urinary Incontinence <sup>#</sup>	28.7	10.5
Benign Prostatic Hyperplasia/LUTS <sup>¶</sup>	52.3	17.4

<sup>#</sup> Overactive bladder = UUI + MUI + Dry OAB (prevalence data not available); total OAB prevalence may exceed 70 million worldwide. <sup>§</sup> Worldwide denotes the 7 major pharmaceutical markets (USA, Jap, Fr, Ger, It, Sp, UK).

<sup>¶</sup> BPH data are from 2000 estimates.

SUI overwhelmingly strikes women, generally of childbearing age, and is believed to result from weakening, by pregnancy and childbirth, of urine-impeding structures at the bladder base.

**Urge urinary incontinence (UUI):** Episodes of leakage driven by bladder muscle (detrusor) contraction, against a background of urgency, frequency and nocturia.

**Mixed urinary incontinence (MUI):** Any combination of SUI and UUI.

**Overactive bladder (OAB) syndrome:** inclusive term that encompasses not only UUI and MUI, but also ‘dry’ OAB: the urge, urinary frequency and nocturia common to UUI and MUI, but absent the leakage. The etiology of OAB is uncertain, but may involve gradual erosion of inhibitory voluntary neural circuitry, unmasking an innate involuntary reflex.

**Benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS):** in men, urinary storage difficulties typical of OAB plus obstruction of urinary flow, coincident with enlargement of prostatic mass.

**Neurogenic bladder:** this term refers to a catastrophic loss of bladder control in patients with spinal cord injury, stroke, multiple sclerosis or Parkinson’s disease.

The relationship between urinary incontinence and overactive bladder is clarified in **Figure 1**.

While severe obstruction due to BPH can cause serious kidney damage, LUTD is seldom acutely life-threatening yet quality-of-life impact is often severe. In contrast, SUI substantially restricts the activity range of a younger population that strongly wishes to remain very active. The OAB patient is always in fear of a sudden, significant loss of urine, or sudden urge to urinate, or both. The costs of all these conditions can include sleep loss, social and psychological stigma, and the need to limit activities such as going out to the movies or even swinging a golf club.

## A growing unmet need

Several factors stand to drive demand for LUTD therapeutics in the near and intermediate future:

- In the context of OAB and BPH, it is significant that on January 1, 2006, the first of the vaunted baby-boomer generation, the swollen demographic cohort born in developed countries between 1946 and 1964, turns 60.
- Not only are the numbers of people reaching 60 growing, but so are their life expectancies.
- When compared with their parents, baby-boomers and generations beyond are thought of as richer, better educated, more assertive, active and politicised, and perhaps quicker to visit a doctor’s office.
- The last five to eight years have seen a great increase in direct-to-physician and then direct-to-patient marketing by drug companies. The Pharmacia (Pfizer) ‘Gotta Go Gotta Go’ advertising for Detrol® has become familiar to US audiences. While this treatment is for OAB, younger female patients with SUI remain unsatisfied.
- Primary-care physicians are ever more familiar with LUTD. Meanwhile, a new breed of sub-specialists is emerging that is tuned in to the neurology of the urinary tract.
- The practice of urology is becoming more oriented toward treatment with medicines.

These factors may lead to more public dialogue of such urological themes. As the Viagra® example has shown, once a popular taboo topic is broached, silence quickly yields to frank candour. Can one envision knots of ageing baby-boomers congregating in supermarket aisles to noisily discuss the relative merits of competing brands of designer absorbent products?

But no pad or incontinence brief will ever substitute for effective, well-tolerated medicines. And this large and growing market is poorly served by currently available treatment options. There is, to

date, no approved drug for SUI. The most commonly prescribed agents for OAB are only weakly effective, producing a 20-30% reduction in urination frequency. In practice, this might mean a decrease from 13 down to 10 times per day. In all instances, side-effects and less-than-sterling patient compliance are issues.

Herein lies a huge opportunity for drug-makers. In contrast to, say, cholesterol reduction or inflammatory pain relief, the LUTD arena is underdeveloped. There is much room for new, effective drugs with decent side-effect profiles. Of course, any drug developed to treat a widely prevalent disorder that is not life-threatening must be exquisitely safe and, to ensure compliance, extremely well-tolerated. This clearly poses a challenge as the few validated targets for LUTD tend to abound in all sorts of tissues and cells besides the ones at which therapy is directed. It may be hoped that a better understanding of the anatomy and physiology of LUTD will lead to better, more carefully targeted drugs with fewer side-effects and increased efficacy.

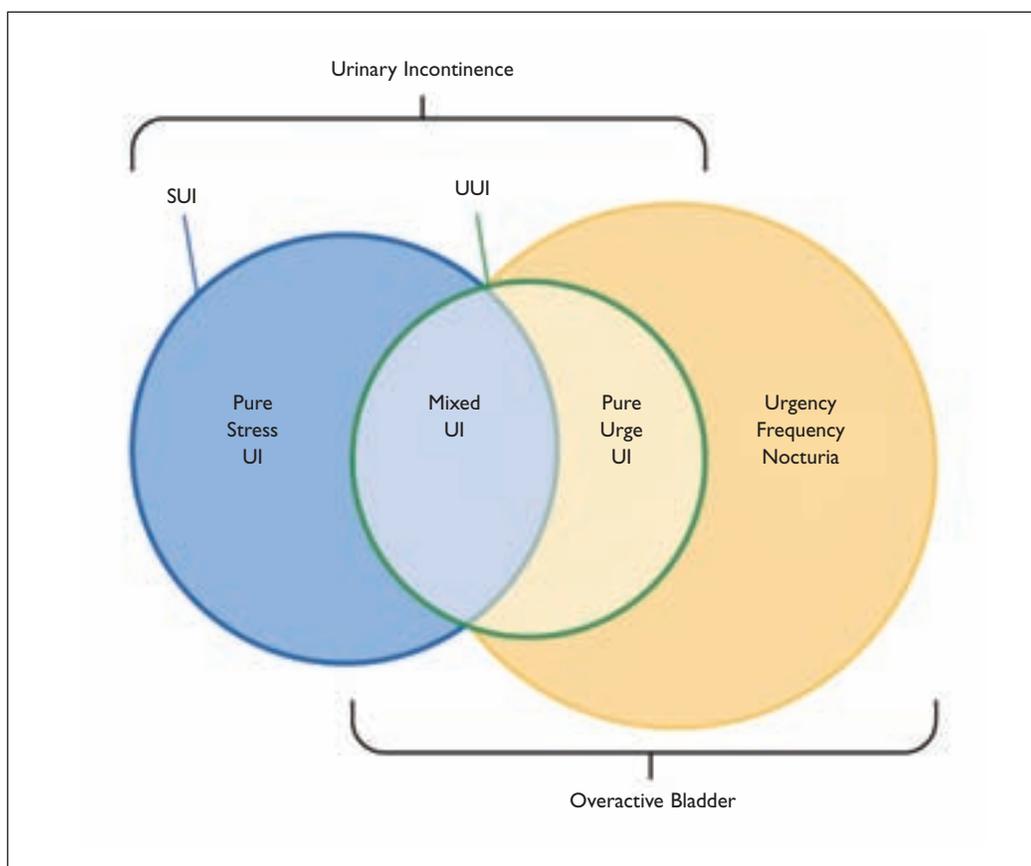
A significant challenge to researchers in the LUTD field is that model systems currently employed in preclinical development are more

akin to neurogenic bladder or acute inflammatory insult than to the far more common conditions characterised by gradual loss of bladder function. Unquestionably, the advent and validation of better animal models will both accelerate drug development and, potentially, result in better therapeutics.

**Existing drugs**

The market for LUTD drugs has grown rapidly, and this promises to continue. Total annual LUTD-related pharmaceutical sales today are in the \$4 billion range, up five- to 10-fold from a decade ago; 10 years from now, they may exceed \$10-15 billion. The leading medicines for the treatment of LUTD are shown in **Table 2A**.

Virtually none of that money is spent on SUI. Despite off-label use of indirect sympathomimetics (sold as nasal decongestants) convincing data have not warranted their approval for this indication. Whether or not their side-effect profile (mild cardiovascular and other, more serious problems) precludes their use is uncertain. Typically, SUI patients are offered pelvic floor, or Kegel, exercises. A small percentage, albeit a significant number, opt for surgery.



**Figure 1**  
Understanding symptom overlap in LUT conditions

**Table 2A:** Leading medicines in lower urinary tract dysfunction

Drug name	Mechanism	US launch	Primary indication	Company
tolterodine ER/Detrol LA	antimuscarinic (non-selective)	2001	OAB	Pharmacia/Pfizer
tolterodine IR/Detrol	antimuscarinic (non-selective)	1998	OAB	Pharmacia/Pfizer
oxybutynin/Ditropan XL	antimuscarinic (non-selective)	1999	OAB	J & J
tamsulosin/Flomax	$\alpha_1$ -adrenoceptor antagonist	1997	BPH/LUTS	Yamanouchi/BI
doxazosin/Cardura	$\alpha_1$ -adrenoceptor antagonist	1991	BPH/LUTS	Pfizer
alfuzosin/Xatral	$\alpha_1$ -adrenoceptor antagonist	- (Eur 1988)	BPH/LUTS	Sanofi-Synthelabo
finasteride/Proscar	5 $\alpha$ -reductase inhibitor (selective)	1992	BPH/LUTS	Merck

**Table 2B:** Promising compounds in development (P11-recent launch)

Drug name	Mechanism	Phase (in US)	Primary indication	Company
Oxytrol	oxybutynin transdermal patch	L-2003	OAB	Watson
Tropium Chloride	antimuscarinic (non-selective)	Prereg	OAB	Indevus
Solifenacin Succinate	antimuscarinic (M3-selective)	Prereg	OAB	Yamanouchi
Darifenacin	antimuscarinic (M3-selective)	Prereg	OAB	Novartis
(S)-Oxybutynin	antimuscarinic (non-selective)	III	OAB	Sepracor
AZD-0947	K <sub>ATP</sub> -channel agonist	II	OAB	AstraZeneca
KRP-197	antimuscarinic (non-selective)	II	OAB	Kyorin/Ono
Fesoterodine	antimuscarinic (non-selective)	II	OAB	Schwarz
HCT-1026	NO-donating NSAID	II	OAB	NicOx
Rec-15/3079	5-HT <sub>1A</sub> receptor antagonist	II	OAB	Recordati/Pharmacia
KW-7158	K <sub>Ca</sub> -channel agonist (afferent)	II	OAB	Kyowa Hakko
Dutasteride	5 $\alpha$ -reductase inhibitor (non-selective)	L-2003	BPH/LUTS	GlaxoSmithKline
Silodosin	$\alpha_{1A}$ -adrenoceptor antagonist	III	BPH/LUTS	Daiichi/Kissei
AIO-8507L	$\alpha_{1A}$ -adrenoceptor antagonist	II	BPH/LUTS	Ono
RBx-2258	$\alpha_{1AD}$ -adrenoceptor antagonist	II	BPH/LUTS	Ranbaxy
Duloxetine Hydrochloride	monoamine reuptake inhibitor (SNRI)	Prereg	SUI	Lilly/Boehringer Ingelheim
R-450 (ROI 151240)	$\alpha_{1A}$ -adrenoceptor partial agonist	II	SUI	Roche/Chugai

Only 10 years ago, sales of drugs for OAB ran at ~\$50 million annually; now the figure is ~\$1.5 billion. The leading drugs for OAB today are antimuscarinics, which target acetylcholine receptors regulating smooth-muscle tone. The market leader, Pharmacia/Pfizer's tolterodine (Detrol®), is now available as a long-acting formulation (Detrol LA®; also Pharmacia/Pfizer) and has weathered the strong challenge of extended release versions of an older anti-muscarinic, oxybutynin (Ditropan XL®, Johnson & Johnson).

All these agents are non-selective: they target the five muscarinic receptors equally. At effective doses, non-selective anti-muscarinics cause dry

mouth, eyes, and skin, as well as cognitive impairment and constipation – both of special concern in elderly patients. The sustained-release formulations stabilise plasma concentrations and thus reduce side-effects, but at the expense of efficacy. Trospium, an anti-muscarinic compound that does not penetrate the central nervous system (but carries all the peripheral side-effect drawbacks), is marketed successfully in Europe by Madaus and is in Phase III testing, under license to Indevus Pharmaceuticals, in the United States.

Annual sales of BPH/LUTS therapeutics have grown from \$200-300 million a decade ago to more than \$2 billion today. Two classes of drugs are in

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use. For treatment of urinary obstruction, and some storage symptoms, the mainstays are  $\alpha_1$ -adrenoceptor blockers. These agents relax the prostate and bladder outlet, allowing easier emptying. They cannot be used at higher doses that might improve efficacy as they induce orthostatic hypotension, (a potentially dangerous posture-change-driven drop in blood pressure), as well as asthenia (mental lethargy) and altered ejaculatory function.

The current market leader is Flomax<sup>®</sup> (tamsulosin, Yamanouchi). As with the anti-muscarinics, flattened peak-to-trough plasma concentration makes it better tolerated than past candidates, but symptom improvement regarding urinary flow and storage symptom score is modest. Normal rates of urinary flow are 20-25ml/sec; an impaired flow rate may be 10ml/sec, which the drug might boost to perhaps 13ml/sec.

Merck's Proscar<sup>®</sup> (finasteride) and GSK's recently launched, more potent agent, Avodart<sup>®</sup> (dutasteride), are both 5-alpha-reductase inhibitors. These drugs reduce prostate size by blocking conversion of testosterone to dihydrotestosterone, and have been directed at BPH. Unfortunately, prostate size reduction doesn't correlate well with relief from symptoms except if the gland is very large, and even then it takes months to see much improvement. Sexual dysfunction (particularly a drop in libido) is a side-effect. These agents tend to be co-administered with other drugs. Their market size is fairly small, though recent findings regarding surgery delay and reduced cancer risk, and marketing by GSK, may lead to growth.

### The clinical pipeline

Table 2B lists promising compounds in development for LUTD (Phase II – launch). The first agent likely to be approved for SUI – Lilly's duloxetine – reduced incontinence episodes in Phase III studies, and Lilly recently received conditional approvability from the FDA. Duloxetine may be available in 2004-5 for SUI and marketed perhaps under the brand name Yentreve – a brand name reported by the investment community that Lilly has not yet publicly confirmed. While the drug's mechanism for improving continence is not unequivocally established, there is intriguing evidence that it involves enhanced control at the CNS level over the external sphincter that surrounds the urethra. This is an exciting and innovative approach for incontinence therapy and response will be eagerly followed.

As an SNRi (serotonin/noradrenaline reuptake inhibitor), duloxetine is a member of the same

mechanistic class of drugs as the older tricyclic antidepressants, which have long been known for utility in urology. Indeed, Lilly is preparing to launch duloxetine, pending final regulatory approval, under the brand name Cymbalta<sup>®</sup>, for depression. This raises some issues: what patient population would be ideally suited for this drug? Are there drug-drug interactions that physicians need to be concerned about? Will the side-effect profile be sufficiently well-tolerated? Nausea and insomnia in clinical trial subjects were significant with a discontinuation rate of 17-30%?<sup>3,4</sup>

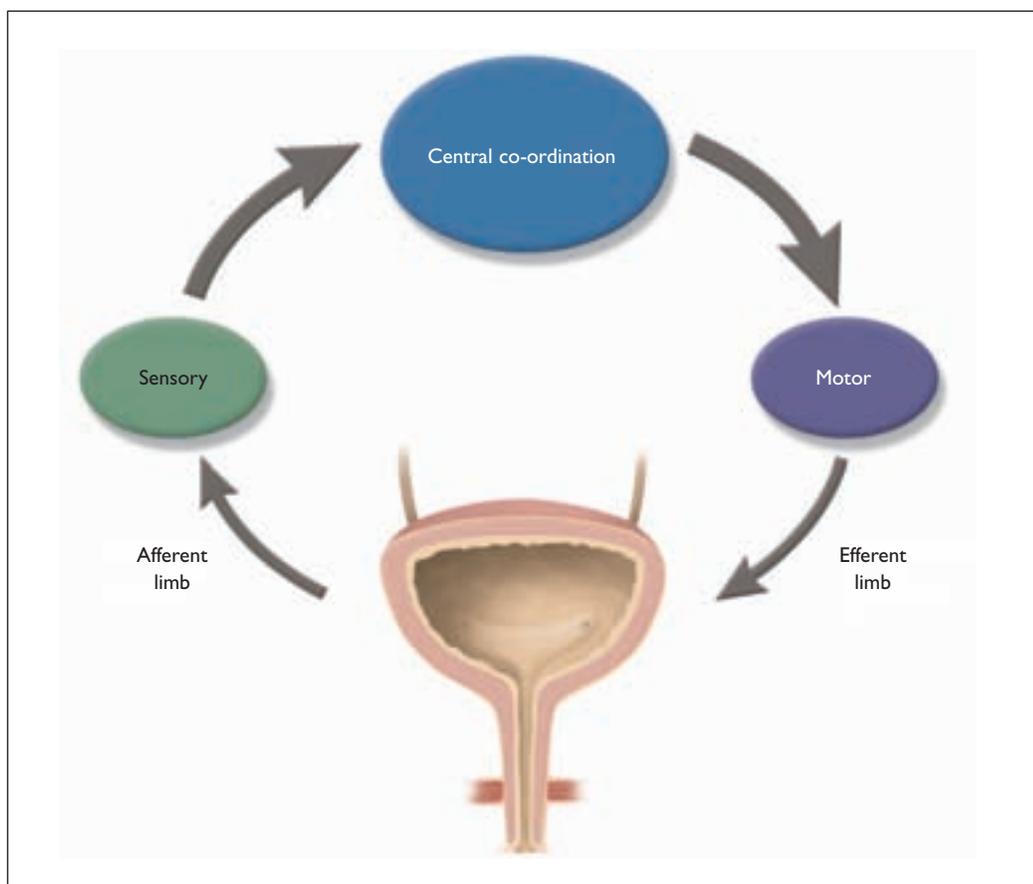
Roche is in Phase II with R450, a novel  $\alpha_{1A/1L}$  adrenoceptor partial agonist, for SUI. This drug appears to increase smooth-muscle tone at the neck of the bladder and urethra without significant effect on blood pressure<sup>5,6</sup>, a side-effect that has been of concern in past trials of full  $\alpha_1$ -adrenoceptor agonists.

The reigning theme in current drug development for OAB (and BPH) has been receptor-subtype selectivity. Whereas all approved anti-muscarinics are non-selective, newer, subtype-selective compounds are advancing through late-stage clinical trials. Five subtypes of muscarinic receptor have been identified. Novartis's darifenacin and Yamanouchi's solifenacin, for which NDAs have been submitted, are selective for M3 receptors, assumed to mediate the excitability of bladder smooth muscle. According to published data, improved efficacy has yet to be significantly demonstrated, side-effects such as dry mouth persist<sup>7</sup>, and constipation may worsen with use of these drugs<sup>8</sup>. It remains to be established whether this efficacy to side-effects ratio will offer a next-generation advantage.

M2 receptors may also be involved in smooth muscle compliance, making them a potential target, but, in addition, they mediate vagal slowing of heartbeat. Blocking M2 without risking heart-rate elevation is a challenge. Another challenge: both M2 and M3 receptors are involved in gastrointestinal secretion and transit.

In a similar vein, selective  $\alpha_1$ -adrenoceptor antagonists are being explored for BPH/LUTS. Of the three subtypes – A, B, and D – the A subtype is prominent in urinary-outlet tissues. Despite this, the efficacy of  $\alpha_{1A}$ -adrenoceptor antagonists has been disappointing, according to a number of companies and as published by Roche<sup>9</sup>. Tamsulosin, a nominally non-selective drug has a slight A/D preference over B, and Ranbaxy has licensed a purportedly  $\alpha_{1AD}$ -adrenoceptor-selective compound to Schwartz Pharmaceuticals. This agent may have reached Phase II testing, but no

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**Figure 2**  
Plumbing to wiring

data have been published yet. Abbott had taken a similar approach, namely ABT-980 (or fiduxosin), into Phase II, but then discontinued its Phase III trial. Whether  $\alpha_{1AD}$  antagonism or some other combination is the right mechanism remains to be determined.

In each case (BPH, OAB), efforts toward targeting single receptor subtypes ( $\alpha_{1A/1L}$ -adrenoceptor, M3-receptor) may turn out to be overly specific. Currently, non-selective agents remain as the market leaders in each disease. The attractiveness of proven targets dictates that someone will finally prosper with a truly differentiating agent from each class; however, such an agent will unlikely be pharmacologically specific for a single subtype. It will be a complex and time-consuming process to identify the optimal profile. Nonetheless, the progress that is being made in teasing out the functions and pharmacological characteristics of receptor subtypes offers great promise for future drug development. Indeed, when the receptors in question play such universally important roles in physiology as muscarinic or adrenergic receptors, LUTD-driven efforts to distinguish among receptor subtypes is bound to yield serendipitous synergies

concerning applications of these discoveries across broad ranges of indications. The Princes of Serendip are always waiting in the wings for their random appearances, yet we must be both patient and tenacious.

### Plumbing to wiring and the reflex bladder

Understanding the integrated circuitry controlling LUT function is critical for successful discovery of superior medicines (Figure 2). Some researchers have advanced the prospect that as we age, our voluntary inhibitory circuitry, which overrides a more primitive, innate spinal reflex, begins to erode, and that this erosion may play a role even in cases of urinary disorder where no obvious nerve damage is evident.

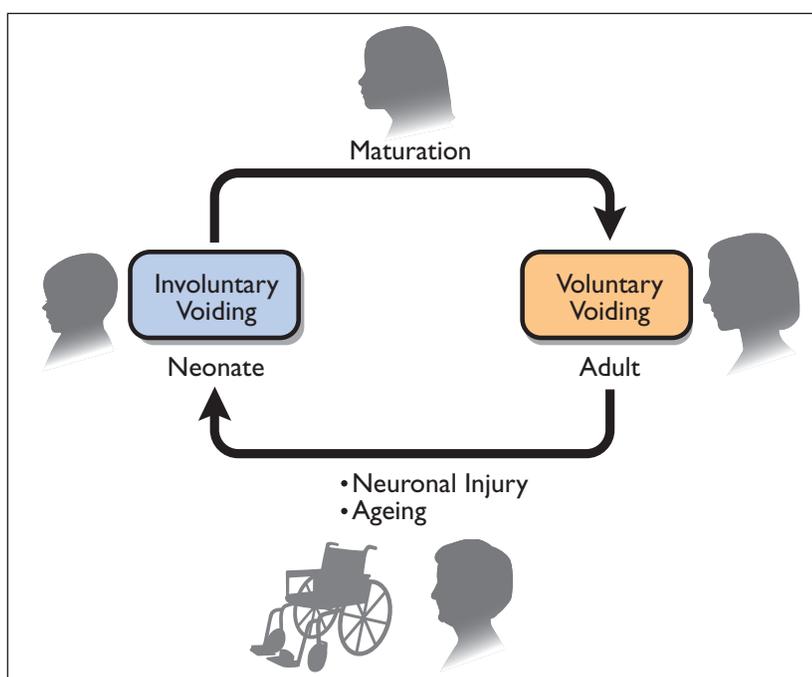
It is known that as the bladder fills and its wall stretches, urothelial cells release substances that trigger neuronal sensors (including c-fibres, unmyelinated neurons associated with dull, aching sensations). C-fibres carry signals to structures in the spinal cord that activate various segmental reflexes to regulate the urinary-tract tissue responses. Overlying and – in a healthy person –

overriding this reflex bladder (see Figure 3) is a voluntary control system. Here, so-called A $\delta$ -fibres play a major role, impacting with second-order neurons that send signals up to the brain. This circuitry is laid down early in life through a learning process during which young children gradually gain control over urination.

In neurogenic-bladder patients, a rapid deterioration of this descending inhibitory control occurs, ‘unmasking’ the c-fibre reflex beneath. Work with patients with extreme bladder conditions has demonstrated the importance of the c-fibre pathway in the diseased state. Both capsaicin, isolated from hot peppers, and resiniferatoxin, another natural plant product, can cause chronic desensitisation of c-fibres. These agents cannot be introduced orally, but are infused directly into the bladder, often under local anaesthetic, to remain there for 30-60 minutes. The c-fibre desensitisation thus induced may last for weeks or months, with notable improvement in symptom management.

The long-term future of therapeutics in the OAB/LUTD area may be greatly influenced by agents that can successfully mimic these toxins. It has been hypothesised that the typical LUTD patient has experienced a gradual deterioration in central inhibitory control – as, perhaps, we all have – and that gradual loss of central inhibition of the reflex bladder leads to symptoms of OAB. Can we target those fibres and reduce their heightened activity by introducing agents orally?

**Figure 3**  
The reflex bladder



### The road ahead

Recent findings suggest that LUTD patients are most bothered not just by incontinence but by urgency – interestingly, the major symptom that is most prevalent across all LUTD categories and the least well met by current therapeutics. At the same time, there is a growing recognition that these constituent disorders may share commonalities, including sensory-nerve involvement. It has been shown, for example, that in BPH patients who have chronic obstruction, there is an increase in nerve growth factor generation within the bladder, and that this causes an increase in c-fibre innervation.

Several novel projects reportedly target c-fibre pathways. P2X3 receptors may prove to be an ideal target. They are almost exclusively found on c-fibres, which are limited in function to transmitting sensations of pain and discomfort in response to noxious or inflammatory circumstances. P2X3 receptors may be important in generating the sensation of the filling bladder. A University of Maryland group has found that bladder epithelial cells cultured from patients with BPH and interstitial cystitis (a more extreme sensory disease of the bladder) release more ATP (a factor that triggers P2X3 receptor activation) at lower levels of stretch and pressure than cells from normal tissue. Roche scientists have created gene-deleted mice lacking expression of P2X3 receptors. These mice appeared to live a normal life but exhibited longer between-micturition intervals than control mice<sup>10</sup>. The pioneer of the reflex-bladder concept, William de Groat of the University of Pittsburgh, has also demonstrated success with a novel P2X3 antagonist in an animal model of bladder dysfunction<sup>11</sup>.

Early-stage efforts are under way in related areas. The action of capsaicin and resiniferatoxin are mediated through TRPV channels, also heavily expressed on c-fibres. An oral agent that harmlessly mimics the toxin action would certainly be worth consideration. In addition, receptors for the many prostanoids (eg, PGE<sub>2</sub> and PGI<sub>2</sub>), and sensory neuropeptides (eg, NK1, NK2, CGRP) are found on c-fibres. Not surprisingly, several companies are currently working with novel chemicals that block these receptors and may have potential in management of LUTD symptoms, with urgency as the key.

Potassium channels, or K-channels, are found on every cell of the body. Some work on K-channel agonists is under way, in the hope of relaxing smooth muscle surrounding the organs of urine storage and transport. But achieving K-channel selectivity is difficult, and these agents have been

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## Selected points of neurological intervention in the lower urinary tract

Urine is generated more or less constantly by the kidneys, and then carried via small tubes called ureters to the bladder, an organ of urine storage, for eventual escort to the outside world through another tube, the urethra. Smooth-muscle 'valves' at both the ureter-bladder junction and the base of the bladder (called the bladder neck) operate under the involuntary control of the autonomic nervous system. Also surrounding the urethra is a mostly voluntary sphincter that allows delay or suspension of voiding.

The innermost wall or lining of the bladder, also lining the ureter and urethra, is called the urinary epithelium or 'urothelium'. In addition to serving as a barrier between urine and the surrounding thick coating of smooth muscle of the bladder, the urothelium may actually be part of the primary sensory apparatus that detects bladder filling. As the bladder reaches a certain pressure threshold, nerve pathways are activated; at a higher threshold, conscious awareness of the filling bladder sets in. The difference between a normal person and person with OAB is the amount of time between knowing one's bladder is filling and the urge to void immediately. In the incontinent person, that latency can be very short.

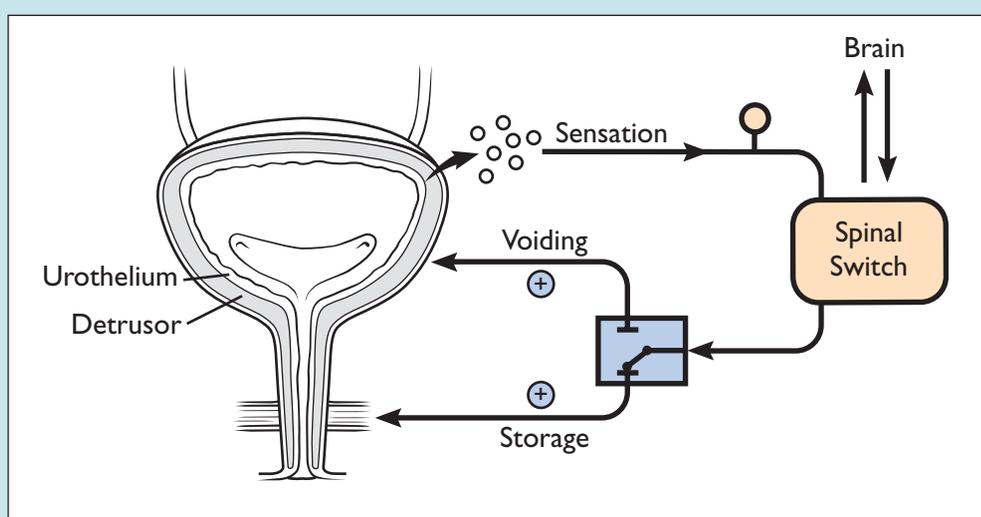


Figure 4: Wired: urinary control circuit

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largely disappointing as their impact on the target tissue has been inseparable from their cardiovascular effects. However, Kyowa-Hakko is in Phase II with an agonist for a neuronal K-channel agonist that renders c-fibres less excitable. It remains for fully randomised controlled trials to demonstrate actual symptom relief.

That said, the numerous angles from which drug developers are approaching the summit of reflex-bladder control, and the broad potential for medications modulating reflex-bladder activity to diminish or eliminate some of the most distressing symptoms of disorders across the entire LUTD spectrum, heralds the possibility of nothing less than a revolution in treatment.

That term 'revolution' has not lost its romantic

appeal for the baby-boomers. Despite their transition to middle age, and – soon enough – beyond, they have not evinced an inclination to “go gentle into that good night”. Similarly a generation of younger women is not likely to be satisfied going gently with their activities. Better treatments – in the face of previously mentioned factors aligned to swell demand for LUTD therapies in the coming years – will make for an even bigger market than the one already projected. **DDW**

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