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Oxybutynin

A Review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability

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Synopsis

Oxybutynin possesses anticholinergic and spasmolytic properties, which together form the basis for its use as a therapeutic option in patients with overactive detrusor function – either idiopathic detrusor instability (DI) or detrusor hyperreflexia. Of the symptoms of detrusor overactivity, urge incontinence is often the most distressing to the patient. Urge incontinence and other subjective parameters (urinary frequency, urgency) improve in tandem with objective (cystometric) measures (maximum detrusor pressure during filling, volume at first desire to void, maximum bladder capacity) in ambulatory, including elderly, patients treated with oxybutynin. However, on the basis of results of limited investigations, the drug appears ineffective in elderly institutionalised individuals. Relative to other anticholinergic drugs, oxybutynin appears at least as effective as propantheline and similar in efficacy to propiverine in small trials, although these results are not definitive. Further investigation of intravesical oxybutynin may lead to this route becoming an option in patients with pre-existing catheters.

Adverse effects – dry mouth, constipation, blurred vision – related to the anticholinergic activity of oxybutynin occur frequently and can be sufficiently troublesome to necessitate treatment discontinuation in up to 25% of patients, depending on the dosage. Increases in residual urine volume suggesting urinary retention (undesirable in patients with idiopathic DI), also can develop in some oxybutynin recipients.

In summary, oxybutynin is one of the few drugs proven to be beneficial in some patients with overactive detrusor function. Despite the occurrence of unwanted anticholinergic effects in many patients, and apparent lack of efficacy in the elderly institutionalised population, oxybutynin should be considered for the drug of first choice in patients with detrusor overactivity, including the elderly ambulatory population, when pharmacological therapy is indicated.

Pharmacodynamic Properties

The majority of the beneficial and unwanted effects of oxybutynin in patients with detrusor instability (DI) stem from its anticholinergic properties. Oxybutynin competitively binds to parasympathetic muscarinic receptors, with a higher affinity for brain (M_1) than for cardiac (M_2) or ileal\bladder receptors (M_3). In addition, it antagonises detrusor contractions *in vitro* and *in vivo*. Compared with atropine, its affinity for muscarinic receptors is 10 times less in the brain and between 5 and 27 times lower in the detrusor muscle.

These anticholinergic effects of oxybutynin, together with its spasmolytic activity, are responsible for the relaxant effects of the drug on the detrusor muscle of the urinary bladder (thus reducing undesirable spontaneous contractions). The net result, as shown in both animals and humans (see Therapeutic Use, below) is a reduction in maximum detrusor pressure during filling and increases in bladder volume and capacity, but with a propensity for increases in residual urine volume. The contribution, if any, of local anaesthetic properties to the mechanism of action of the drug remains speculative.

Pharmacokinetic Properties

Wide interindividual variation in pharmacokinetic parameters is evident following oral administration of oxybutynin. The pharmacokinetic profile of the drug does not appear to be altered in healthy elderly individuals compared with young volunteers. However, the terminal plasma elimination half-life was prolonged from 2 to 3 hours in healthy elderly individuals to about 5 hours in 'frail' elderly individuals and its systemic bioavailability increased. The presence of food also

increases the bioavailability of oxybutynin and slightly delays its rate of absorption. Hepatic biotransformation of oxybutynin yields the active metabolite *N*-desethyl-oxybutynin in addition to its most abundant but inactive metabolite, phenylcyclohexylglycolic acid. Active metabolites of oxybutynin may be responsible for much of the pharmacological activity of the drug.

Therapeutic Use

Oxybutynin alleviates subjective manifestations of idiopathic DI and detrusor hyperreflexia, including the distressing symptom of urge incontinence, and corrects abnormal objective measures. Subjective improvement in noncomparative trials was rated 'excellent or good' in 55 to 70% of patients receiving oxybutynin for up to 2 years. While this finding gives some preliminary indication of efficacy, placebo-controlled trials are vital to establish the benefit of a treatment in DI, as patients with this condition exhibit a high placebo response. As demonstrated by several such investigations in ambulatory patients, oxybutynin decreases urinary frequency, urgency and episodes of urge incontinence, in addition to increasing bladder volume at first desire to void, enhancing maximum bladder capacity and reducing maximum detrusor pressure during filling.

However, oxybutynin appears to have varying degrees of success in alleviating nocturia, and potentially detrimental increases in residual urine volume have been documented with its use. Moreover, as with other pharmacotherapy, cure is elusive. Furthermore, in contrast to unselected populations, elderly institutionalised patients have generally failed to improve during oxybutynin therapy, although patient numbers have been small. Elderly but ambulatory individuals experienced a modest subjective improvement with oxybutynin in one placebo-controlled trial, but urge incontinence was relieved to a similar extent by placebo and oxybutynin.

On the basis of limited comparisons with other anticholinergic drugs, oxybutynin appears at least as effective as propantheline and similar to propiverine in idiopathic DI. This benefit may be offset somewhat by the increases in residual urine volume which are associated with oxybutynin but apparently not with propantheline. However, urge incontinence was relieved in significantly more oxybutynin than propantheline recipients (58 *vs* 45%, $p < 0.05$) in the largest placebo-controlled trial, conducted in 154 patients. Some evidence suggests better results with oxybutynin than with propantheline in patients with detrusor hyperreflexia rather than idiopathic DI. Interestingly, intravesical administration of oxybutynin has shown promise in individuals with detrusor hyperreflexia: this route may become an option in individuals with pre-existing or intermittent catheters, and those unresponsive to or intolerant of oral therapy.

Tolerability

Atropine-like symptoms are frequent during oral oxybutynin therapy. Dry mouth develops in at least 50% of oxybutynin recipients, constipation in about 15%, drowsiness in about 12% and blurred vision in approximately 5%. Discomfort has been severe enough to warrant treatment discontinuation in approximately 7 to 27% of patients given oxybutynin in clinical trials. Reflux oesophagitis has been reported infrequently during oxybutynin treatment and no serious cardiac effects have been linked to its use. Intravesical oxybutynin appears to cause few systemic adverse events.

Oxybutynin may be less well tolerated than propantheline, as shown in the largest comparative trial, although smaller studies have demonstrated similar tolerability profiles for the 2 drugs, and in one study patients were more willing

to tolerate the unwanted effects of oxybutynin than those of propantheline. Whether increasing age influences the severity and incidence of unwanted effects, particularly in institutionalised patients, has not been examined specifically.

Dosage and Administration

The recommended oral dosage of oxybutynin is 5mg 2 to 3 times daily, up to a maximum of 5mg 4 times daily. The dose should be titrated to maximise response and minimise adverse effects. However, a lower starting dose of 3 or 5mg twice daily is recommended in the elderly, titrated as necessary, and clinical experience has suggested that a dosage of 2.5mg 2 or 3 times daily may be a suitable starting dosage in elderly and nonelderly adults. The drug is contraindicated in patients with conditions which may be aggravated by its anticholinergic activity. Drowsiness or blurred vision may reduce patients' ability to perform tasks requiring mental alertness.

Oxybutynin is a tertiary amine ester (fig. 1) possessing anticholinergic (antimuscarinic), spasmolytic and local anaesthetic properties. It has been used extensively to treat patients with urinary frequency, urgency, nocturia and urge incontinence arising from overactive detrusor function, whether the origin is neuropathic (detrusor hyperreflexia), arises from other sources (detrusor instability) or is idiopathic. This review evaluates its therapeutic efficacy in such patients in general and in the elderly in particular.

1. Overview of Detrusor Instability

1.1 Pathophysiology and Aetiology

The bladder is innervated by the parasympathetic, sympathetic and sensory nervous systems. Muscarinic cholinergic innervation predominates in the smooth muscle of the bladder (the detrusor), whereas the trigone and urethra (bladder neck) are controlled principally by sympathetic α-adrenergic receptors. During micturition, the detrusor muscle contracts in response to parasympathetic nerve-released acetylcholine, which stimulates muscarinic receptors. Simultaneously, reflex inhibition of the somatic motor innervation leads to relaxation of the external urethral sphincter. The internal sphincter of the bladder neck and proximal urethra also relaxes, and urine is voided.[1-4]

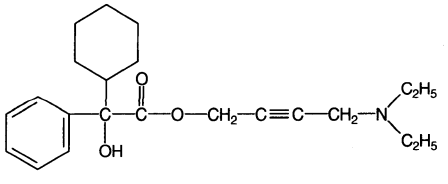

Fig. 1. Structural formula of oxybutynin.

In patients with overactive detrusor function, the detrusor muscle of the bladder contracts spontaneously or can be made to contract during the filling phase while the individual is trying to inhibit micturition.[1,5,6] This overactivity may lead to a variety of symptoms including:

- urinary urgency (the sensation of impending voiding)
- daytime and nocturnal urinary frequency (bladder emptying before bladder is full; prompted by urgency)
- urge incontinence, defined as the involuntary loss of urine associated with a strong desire to void.[5-8]

Urgency is classified into 2 types: motor urgency arises from overactive detrusor function, whereas sensory urgency is associated with a hypersensitive bladder in the absence of detrusor overactivity.[5,6,9] Urge incontinence is perhaps the most upsetting consequence of detrusor overactivity, although it does not develop universally in patients with this condition. Distal sphincter mechanisms may be weak in some, but by no means all, patients with this symptom.[8]

Symptomatic definitions allow the clinician to distinguish between urge incontinence (arising as

a result of motor or sensory urgency) and other forms of urinary incontinence, such as genuine stress incontinence.[5,10] However, cystometric tests are required to establish whether urge incontinence arises from detrusor overactivity (motor urgency) or detrusor hypersensitivity (sensory urgency). Once it has been determined that a patient's incontinence probably arises from detrusor overactivity, neurological, cytological and other tests can be used to determine the cause of the instability and treatment instigated. This may include behavioural therapy, pharmacological treatment or surgery (see also section 7). In men with overactive detrusor function, outflow obstruction resulting from benign prostatic hypertrophy or prostate cancer should be eliminated or treated before instigating pharmacological therapy, as drugs such as oxybutynin may precipitate urinary retention (see section 6).[8]

There are several known causes of overactive detrusor function (table I). The term 'detrusor hyperreflexia' is used to describe overactivity resulting from a neurological disorder, whereas detrusor instability (DI) describes overactivity of non-neuropathic or unknown origin.[5] In the elderly, as in younger patients, one or more factors may contribute to DI. However, in the majority of cases the cause of DI is unknown.[6,9] The high placebo response in patients with DI (section 4.3) has prompted some investigators to seek a psychological basis for the problem (reviewed by Moore and Sutherst[11]). However, a recent study by these authors in 53 postmenopausal women found no correlation between placebo response and psychoneurotic history.[11]

Possible mechanisms for idiopathic DI include loss of central (supraspinal) control of the detrusor muscle (i.e. failure to maintain learned techniques for adequate voluntary bladder control) and loss of peripheral control (i.e. increases in cholinergic and/or α-adrenergic activity), although the latter is favoured.[7,8] Another postulated mechanism is a reduction in the functional motor innervation of the bladder, causing the detrusor to become unstable.[12]

Table I. Causes of overactive detrusor function[4,10]

Neurological	**Pharmacological**
Cerebrovascular disease	Parasympathomimetics
Multiple sclerosis	Diuretics
Parkinson's disease	Sedative hypnotics
Senile dementia	
Tumours	**Outflow obstruction**
	Benign prostatic hypertrophy
Local	(males)
Cystitis (including	
inflammatory, infectious, and	**Other**
interstitial)	Restricted mobility
Urethritis	Stool impaction
Bladder stone	Excessive urine production
Bladder tumour	
	Psychosomatic
Surgery	
Bladder augmentation	**Idiopathic**
Bladder replacement	

1.2 Epidemiology

Estimates of the prevalence of DI in the general adult population range from 8 to 50%,[10,13] but it is generally accepted to be approximately 10%.[6,10] The prevalence of DI increases with increasing age, approaching 40% in individuals over the age of 50 years and rising to as high as 60 to 80% in institutionalised incontinent patients.[10,14] In the latter group, its prevalence has also been linked to loss of mobility and severity of mental impairment.[14] As seen in table I, neurological causes of DI include such age-related conditions as senile dementia and Parkinson's disease.

In addition to being associated with increasing age, urge incontinence occurs more frequently in women than in men. It has been reported that, although the prevalence of incontinence is similar in elderly institutionalised men and women,[14] between 10 and 25% of noninstitutionalised women experience urge incontinence, compared with <7% of men.[4,13,15] This means that, next to genuine stress incontinence, urge incontinence arising from DI is the second most common cause of female urinary incontinence.[7] The reasons for this gender difference are not clear, but both childbirth and menopausal status have been implicated.[13,15,16]

Urge incontinence, then, is a major problem in terms of its high prevalence, particularly among

Table II. *In vitro* evidence for anticholinergic (antimuscarinic) and spasmolytic effects of oxybutynin on animal isolated detrusor muscle or whole bladder

Animal model	Effect
Anticholinergic (antimuscarinic) effects	
Dog[18] and guinea-pig[19] detrusor	Competitively inhibited binding of the specific muscarinic radioligand ^{3}H-quinuclidinyl benzilate to muscarinic receptor sites
Guinea-pig[19,20] and mini-pig[21] detrusor	Competitively antagonised carbachol-induced contractions
Rabbit whole bladder[22]	Suppressed bethanechol-induced contractions
Guinea-pig detrusor[23]	Inhibited electrically stimulated contractions
Guinea-pig detrusor[20]	Inhibited acetylcholine-induced turnover of phosphoinositide
Spasmolytic effects	
Rabbit detrusor[24]	Reduced the amplitude of spontaneous phasic contractions
Guinea-pig detrusor[20]	Reduced contractile response to potassium chloride
Guinea-pig detrusor[23]	Reduced electrically stimulated contractions
Rabbit whole bladder[22]	Reduced electrically stimulated contractions

the elderly, and its effects on the individual's quality of life. The condition has considerable emotional and social consequences, especially in women.[13,15,17] It has been estimated that two-thirds of women wear some protection (i.e. a pad) if incontinence occurs at least weekly. Half of incontinent patients may limit their daily activities because of embarrassment or worry about social situations,[13] and some may also alter their lifestyles, including sexual activities and choice of clothing.[15]

2. Pharmacodynamic Properties

Among the pharmacological options for the treatment of overactive detrusor function are anticholinergic drugs such as oxybutynin, which are proposed to override the excess cholinergic activity postulated to contribute to idiopathic DI (section 1.1). Despite the availability of oxybutynin for almost 20 years in some countries, its pharmacodynamic properties have not been comprehensively studied. Although oxybutynin is known to have mixed anticholinergic and spasmolytic effects, and possibly local anaesthetic properties, the mechanisms by which it exerts some of these effects have yet to be fully elucidated. Most studies have, of necessity, been conducted *in vitro*, measuring receptor binding and the effects of oxybutynin on the contractile responses of animal or human detrusor and other smooth muscle to stimulation by direct electrical means or by parasympathomimetic agents.

Human urodynamic studies have generally been performed as part of clinical trials which evaluated both objective and subjective measures of the effects of oxybutynin on DI. Consequently, data on the effects of oxybutynin on human urodynamics are included in section 4.

2.1 Effects on Muscarinic Cholinergic Receptors

Oxybutynin antagonises acetylcholine-induced stimulation of postganglionic parasympathetic muscarinic receptor sites. Evidence for this activity comes from *in vitro* data obtained using isolated detrusor or intact bladder preparations from several animal species. In these studies, micromolar concentrations of oxybutynin competitively antagonised detrusor contractions elicited by muscarinic agents or electrical stimulation of parasympathetic pathways (table II).

The antagonist activity of oxybutynin at muscarinic receptors of the detrusor has been variously reported to be 5,[10,25] 9[21] or 27[18] times lower than that of atropine. Similar data have been reported using *in vitro* preparations of guinea-pig ileum, where oxybutynin has exhibited competitive antagonism of acetylcholine-induced[23] and

carbachol-induced[20] contractions. In rat brain, *in vitro* affinity of oxybutynin for muscarinic receptors was approximately 10 times lower than that of atropine.[26]

Several studies have investigated the selectivity of oxybutynin for muscarinic receptors at different tissue sites. Subclasses of muscarinic receptors, designated M_1, M_2 and, more recently, M_3, M_4 and M_5, have been proposed, depending on the affinity of selective muscarinic receptor antagonists for these sites[27] or evaluation of mRNA sequences.[28] However, several tissue sites appear to possess more than one muscarinic receptor subclass, and the true number and characteristics of these subclasses have yet to be determined.[19] Radioligand binding studies in various animal tissues have shown that oxybutynin has a higher affinity for muscarinic receptors of the cerebral cortex and parotid gland (M_1 receptors) than those of the heart (M_2 receptors) or the smooth muscle of the ileum or bladder (M_3 receptors).[19,27,29] In an *in vitro* study of human detrusor, Yamaguchi et al.[28] reported that this tissue possessed both M_2 and M_3 receptors.

Data from studies of *in vitro* preparations of human tissues support these findings in animals. In human detrusor muscle, radioligand binding studies using the specific muscarinic radioligand ^{3}H-quinuclidinyl benzilate have found the inhibition constant (K_i) of oxybutynin to be approximately 3 to 5 nmol/L, compared with 0.2 to 0.9 nmol/L for atropine and 1.4 μmol/L for carbachol.[30,31] In comparison, both oxybutynin and atropine had significantly lower K_i values in human parotid gland (1.3 and 0.7 nmol/L, respectively), indicating a higher affinity for this tissue site, as reported in animal studies.[30]

2.2 Effects on Detrusor and Other Smooth Muscle

Oxybutynin is a musculotropic agent with a direct-acting relaxant effect on the smooth muscle of the urinary bladder, gastrointestinal system and uterus.[25,32] Various *in vitro* animal studies using isolated detrusor or intact bladder preparations have provided evidence for this activity (table II). In these studies, oxybutynin reduced both spontaneous contractions of the detrusor and contractions evoked by electrical stimulation or potassium chloride. Similar results have been reported using guinea-pig ileum,[20] taenia caeci and ureter,[23] and the smooth muscle of rabbit renal pelvis.[24]

The spasmolytic effects of the drug *in vitro* are approximately 500 times weaker than its anticholinergic effects.[20] In a rabbit whole bladder preparation, stimulation by direct electrical means or by the parasympathomimetic agent bethanechol were used to elicit an equivalent contractile response. Oxybutynin at a concentration of 100 μmol/L inhibited the bethanechol-induced response by 95% and the direct electrically induced response by 64%.[22]

It has been suggested that the direct smooth muscle relaxant effect of oxybutynin is mediated via calcium antagonism. Data from some *in vitro* animal studies support this view, as Ca^{++}- and K^+-induced contractions of guinea-pig ileal and detrusor muscle[20] and ureter and taenia caeci muscle[23] are antagonised by oxybutynin. However, Malkowicz et al.[33] found no evidence that this mechanism of action was involved in the muscle relaxant effect of oxybutynin on isolated rabbit detrusor muscle.

2.3 Effects on Urodynamic Parameters

Several urodynamic parameters have been monitored in *in vivo* animal studies to assess the effects of oxybutynin. These include cystometric measurements of bladder capacity, intravesical pressures during the collecting and emptying phases, and micturition threshold pressure and volume. Oxybutynin administered intravenously, subcutaneously or intravesically has been demonstrated to have a number of beneficial urodynamic effects, such as reducing maximum intravesical pressure during both the emptying and filling phases, and increasing bladder threshold volume and bladder capacity (table III).

In patients with overactive detrusor function, additional urodynamic parameters have been eval-

Table III. *In vivo* urodynamic effects on animal bladder of oxybutynin administered intravenously, subcutaneously or intravesically

Animal model	Effect
Anaesthetised guinea-pig,[20,27] mini-pig[21] and rat[34]	Dose-dependently reduced maximum intravesical pressure during the collecting phase
Anaesthetised guinea-pig[35]	Dose-dependently reduced maximum intravesical pressure in response to pelvic nerve stimulation
Decerebrate dog[36]	Reduced maximum intravesical pressure during the emptying phase Dose-dependently increased bladder threshold volume during the collecting phase
Rat[34]	Dose-dependently increased bladder capacity

uated, including bladder volume at different degrees of desire to void. Results similar to those obtained in animal studies have been reported in patients with detrusor hyperreflexia (section 4).

Oxybutynin has also been shown to improve urodynamic parameters in both animals and humans with bladders constructed from intestinal segments. In a dog model, oral or intravesical administration of oxybutynin reduced mean bladder pressure and increased bladder capacity compared with baseline values, although statistically different changes occurred only after intravesical administration. In 2 patients with caecal or ileocaecal urinary diversions, intravesical administration of oxybutynin 10mg in 50ml normal saline over 30 minutes reduced bladder pressure by 12 and 38%, respectively, compared with baseline values. In addition, bladder capacity was increased by 9% in 1 patient and contractile activity reduced in the other patient.[37]

2.4 Local Anaesthetic Effect

In molecular structure (fig. 1), oxybutynin resembles those amines with a local anaesthetic effect, such as lidocaine (lignocaine), and is purported to share this property.[6,32] *In vivo* animal data have suggested that oxybutynin has twice the anaesthetic potency of lidocaine when administered intradermally.[20] However, the contribution of any local anaesthetic effect of oxybutynin to its effects on detrusor activity in patients has not been determined.

3. Pharmacokinetic Properties

There are few published data available on the pharmacokinetics of orally administered oxybutynin in elderly volunteers and patients. Consequently, pharmacokinetic data obtained from young adult volunteers have been included in this section for supplementation and comparison. Only one study has investigated the pharmacokinetics of the intravesically administered drug. The following data relate to the oral formulation, unless otherwise stated.

All populations studied exhibited large interindividual variation in pharmacokinetic parameters, particularly in the maximum plasma concentration attained (C_{max}) and the area under the plasma concentration-time curve (AUC).[38,39] No gender differences in these parameters were apparent in young healthy volunteers, and given the wide interindividual differences in both young and elderly populations, gender did not appear to have a major influence on the pharmacokinetic profile of oxybutynin in elderly patients.[38]

Hughes et al.[38] reported that the pharmacokinetic profile of a single 5mg oral dose of oxybutynin was similar in both 'healthy and active' elderly patients with DI (mean age 76 years, n = 10) and young adult volunteers (mean age 29 years, n = 8). In both populations, a C_{max} of approximately 15 μg/L was achieved in less than 1 hour (table IV). In another study in which 18 young healthy adult volunteers (age range 19 to 38 years) received the same dose of oxybutynin, the mean C_{max} achieved was somewhat lower (8.2 μg/L), but the time taken to reach C_{max} (t_{max}) was similar (approximately 0.8h).[39]

The study by Hughes et al.[38] also included a group of elderly patients with DI (mean age 79 years, n = 10) who were described as 'frail'. These patients were less mobile and had a greater dependence on others compared with the otherwise 'healthy and active' elderly patients. Several differences were found between the pharmacokinetic profile of oxybutynin in the 'frail' elderly and its profile in the young volunteers and healthy elderly. In particular, in the 'frail' elderly, values for C_{max} and AUC were significantly higher compared with those of the young volunteers (table IV).

A comparison of pharmacokinetic parameters after oral and intravesical administration of 5mg oxybutynin in 5 patients with detrusor hyperreflexia (age and condition not stated) demonstrated C_{max} values of 21 and 14 μg/L, respectively, with corresponding t_{max} values of 1 hour and 3 hours.[40] Apart from the protracted time to reach C_{max} after intravesical administration, other values were within the range of those reported in other studies.

The presence of food is reported to cause a slight delay in oxybutynin absorption (values not stated) in healthy volunteers (age not stated).[41] The absolute systemic bioavailability of oxybutynin (1.2% in young adult volunteers[39]) is also increased (to 25%), in the presence of food,[41] and in the 'frail' elderly, although values were not stated.[38]

Oxybutynin is metabolised in the liver.[42] The major metabolite, phenylcyclohexylglycolic acid, is pharmacologically inactive. However, the main active metabolite of oxybutynin, *N*-desethyl-oxybutynin, has pharmacological activity similar to that of the parent compound,[38] and radioreceptor assay studies have found that more than 90% of detectable biological activity is attributable to active metabolites.[26] These data suggest that much of the pharmacological activity of oxybutynin is exerted by this active metabolite. However, the pharmacological profiles of *N*-desethyl-oxybutynin and other active metabolites have not been adequately characterised.

Elimination of oxybutynin appears to be biphasic. Single-dose studies in both healthy young volunteers and healthy elderly patients have reported the terminal plasma elimination half-life ($t_{1/2\beta}$) to be approximately 2.2h.[38,39] However, $t_{1/2\beta}$ was prolonged in 'frail' elderly patients (4.6h) compared with values in young volunteers (2h) and the healthy elderly (2.3h) [table IV].

Repeated dose studies with oxybutynin have been conducted in young healthy volunteers, and in both healthy and 'frail' elderly patients with DI. Repeated administration of oxybutynin to both young healthy volunteers and healthy elderly patients did not affect its pharmacokinetic profile at steady state. Furthermore, no evidence of drug accumulation in plasma was found in a total of 31 healthy elderly patients with DI (age range 70 to

Table IV. Summary of mean pharmacokinetic parameters of oxybutynin after administration of single oral 5mg doses to healthy young adult volunteers and single and repeated 5mg doses to elderly patients with urge incontinence and detrusor instability[38]

Parameter	Single dose			Multiple dose	
	healthy young adult volunteers (n = 8)	healthy elderly (n = 10)[a]	frail elderly (n = 10)[b]	healthy elderly (n = 10) [dose 5mg tid]	frail elderly (n = 10) [dose 5mg bid]
C_{max} (μg/L)	13.4	16.7	32.0†	18.1	37.3**
t_{max} (h)	0.76	0.69	0.60	0.65	0.56
$t_{1/2\beta}$ (h)	2.0	2.3	4.6†*	3.1	5.4
AUC (μg/L • h)	21.4	31.8	48.4†	36.9	103.6*

a Otherwise healthy, active elderly patients, mean age 76 years (range 67 to 84 years).

b Elderly patients with a lack of mobility and a greater dependence on others than healthy elderly patients, mean age 79 years (range 73 to 87 years).

Abbreviations and symbols: AUC = area under the plasma concentration-time curve; bid = twice daily; C_{max} = peak plasma concentration; tid = 3 times daily; t_{max} = time to C_{max}; $t_{1/2\beta}$ = terminal elimination half-life. Statistically significant differences † $p < 0.05$ (frail elderly *vs* young); * $p < 0.02$ (frail elderly *vs* elderly); ** $p < 0.005$ (frail elderly *vs* elderly).

94 years) receiving oral oxybutynin 2.5 or 5mg 3 times daily orally for up to 2 weeks.[38,42] However, Hughes et al.[38] reported a significant increase in C_{max} in 'frail' elderly patients receiving oxybutynin 5mg twice daily, to approximately twice that achieved in healthy elderly patients receiving oxybutynin 5mg 3 times daily. This was accompanied by a prolongation of $t_{1/2\beta}$, and a consequent significant increase in AUC (table IV). Thus, the bioavailability of oxybutynin was greater in 'frail' than in healthy elderly patients. These data suggest that a lower dosage of oxybutynin should be given to elderly patients who are less mobile.[38]

4. Therapeutic Use in Detrusor Instability

4.1 Clinical Trial Methodology and Outcome Measures

Clinical investigations, whether noncomparative or comparative, have assessed the effect of oxybutynin on several or all of the common manifestations of detrusor instability, including urinary frequency, urgency, nocturia and urge incontinence. Visual analogue or linear analogue scales were often used by patients to assess symptoms, but methods of presenting trial results lacked uniformity, and subjective ratings such as 'cure' or 'marked improvement' were generally not defined. Cystometric or urodynamic evaluations (volume at first desire to void; maximum bladder capacity; maximum detrusor pressure during filling) undertaken in all comparative trials provided objective measures of efficacy. Residual urine volume was also measured to determine whether reduced contractility also predisposed patients to urinary retention and its attendant undesirable effects. Most trials excluded patients with genuine stress incontinence, cystitis and urinary tract infections. A criterion for inclusion in some protocols was the presence of involuntary detrusor contractions > 15cm H_2O or, less commonly, > 30cm H_2O. Only 1 trial[43] stated that it included some patients who had received previous drug treatment.

For the most part, comparisons of oxybutynin with other drugs are few, include small patient numbers and have used disparate subjective measures of efficacy. Trials comparing oxybutynin with placebo are also small in size and diverse in outcome measures, but virtually all comparative studies were randomised, double-blind and usually crossover in design. Generally, the duration of treatment with oxybutynin was 1 to 6 weeks, and washout periods in crossover protocols varied from 6 days to 4 weeks. Fixed dosage regimens were used in most instances, although titration of oxybutynin dosage is preferred clinically, especially to minimise adverse effects which may limit therapy (section 5).

While several trials were conducted specifically in elderly patients (> 65 years), some excluded patients older than 75 years and still others provided inadequate descriptions of the proportion of elderly patients involved.

4.2 Noncomparative Studies

Because of the high placebo response rate (section 4.3) among patients with DI, noncomparative trials contribute little to the quantification of relative efficacy for potential treatments. However, they give some preliminary indication of subjective efficacy and may aid in identifying subgroups of potential responders.

In various trials of 25 or more participants, the improvement in urinary frequency, urgency or urge incontinence was considered to be 'excellent or good' in about 55 to 70% of patients with DI who received oxybutynin in dosages of 2.5 to 15mg daily for up to 2 years.[44-48] No clear dose-response relationship was evident from these studies, but response was independent of age and tended to be better in previously untreated than previously treated patients in a retrospective review,[49] although in a small trial[50] 20 of 21 patients unresponsive to previous drug therapies (flavoxate, diazepam) improved after treatment with oxybutynin (10 to 15mg daily for 2 months). Interestingly, among 58 elderly patients (mean age 79 years), those with predominantly nocturnal incontinence or poor bladder filling sensation responded

best.[51] These results, however, are not substantiated in controlled trials (sections 4.3 and 4.4).

4.3 Comparisons with Placebo

Table V illustrates that, despite a measurable placebo response, oxybutynin 9 to 20 mg/day improves subjective parameters (urinary frequency, urgency and urge incontinence) and cystometric measurements to a greater extent than placebo in ambulatory patients. Bladder volume at first desire to void increased by about 70 to 80ml with oxybutynin versus about 10 to 25ml with placebo, maximum detrusor pressure during filling decreased by 17 to 23cm H_2O versus a change of –13 to +1cm H_2O, and maximum cystometric or bladder capacity expanded by 60 to 104ml versus a range of –14 to +7ml for placebo.

Moore et al.[53] recorded 'cure' or 'marked improvement' in urgency and urge incontinence in 60% of 49 women during oxybutynin treatment versus 2% during the placebo phase; this reflected significant increases in volume at first desire to void and bladder capacity, and a decrease in maximum detrusor pressure during filling in the oxybutynin phase relative to placebo (table V). 'Stable' bladder was documented in 22 to 62% of oxy-

Table V. Comparative efficacy of oxybutynin (O) and placebo (P) in patients with detrusor instability; all trials were randomised, double-blind and crossover in design, except where noted

Reference	No. of evaluable patients (mean age)	Dosage (duration)	Subjective parameters (change from baseline)			Objective parameters (change from baseline)			Overall results
			frequency	urgency	UI	VFD (ml)	MDP (cm H_2O)	MBC (ml)	
Collas et al.[52]a	28 (82y[b])	O 2.5mg bid (6w)	–27 (at 2w)*		O ≡ P				O ≥ P
	29	P (6w)	–6 (at 2w)						
Moore et al.[53]	49 (46.2y)[c]	O 3mg tid (nd)	–35%	60%[d]		+70*	–17*	+104*	O > P
		P (nd)	–9%	2%[d]		+8	+1	+7	
Ouslander et al.[54]e	113	O 2.5mg tid then 5mg tid (10d)			–6%[f]				O ≡ P
		P (10d)			–3%[f]				
Riva & Casolati[43]	24 (51.5y)[g]	O 5mg tid (20d)	–30%*†	61%*†[h]	76%*†[h]	+69*†			O > P
		P (20d)	–12%	43%[h]	43%†[h]	+19			
Tapp et al.[55]	21(61y)[c]	O 5mg qid (14d)		–34*[i]	–40*[i]	+80	–23*	+60	O > P
		P (14d)		–7[i]	–25[i]	+26	–13	–14	
Zorzitto et al.[56]	18 (73.9y)	O 5mg bid (8d)			18[j]				O ≡ P
		P (8d)			18[j]				

a Abstract of a parallel group trial. Patients also received bladder retraining.

b For both drug and placebo groups combined.

c Women only.

d Percentage of patients with cure or marked improvement in urgency and urge incontinence.

e Abstract only. Patient population comprised those who had a poor response to a regimen of prompted voiding alone. This regimen was continued throughout the trial.

f Difference from baseline in percentage of episodes of wetness.

g Included 5 patients with urge incontinence associated with sensory urgency.

h Percentage of patients in whom symptom was absent or weak.

i Visual analogue scale used.

j Expressed as number of toileting intervals with at least 1 'incontinent event'/number of observations. Patients were institutionalised and toileting took place at 10 scheduled times each day.

Abbreviations and symbols: bid = twice daily; d = days; MBC = maximum bladder capacity; MDP = maximum detrusor pressure during filling; nd = no data; qid = 4 times daily; tid = 3 times daily; UI = urge incontinence; VFD = volume at first desire to void; w = weeks; y = years; * $p < 0.05$ *vs* placebo; † $p < 0.05$ *vs* baseline; ≥ indicates tendency for better effect; > indicates significantly better ($p < 0.05$); ≡ indicates equivalent effect.

butynin recipients versus 5 to 42% of placebo recipients.[53,55] Few investigators have distinguished 'cure' from other ratings. In 1 of these trials, 38% of 24 patients were considered 'cured' with oxybutynin; of these, 3 resumed therapy during follow-up.[43]

Nocturia appears to respond as well to placebo as to oxybutynin. In the few patients who complained of nocturia at baseline in various trials, there were conflicting results. This symptom either resolved in all patients (4 of 4) regardless of which treatment was used,[43] was decreased to a similar, unspecified, extent by both oxybutynin and placebo,[52] or was significantly reduced compared with baseline (using a visual analogue scale) in patients receiving oxybutynin (change from baseline of −15.7; $p < 0.05$) but not placebo (change from baseline −7.0).[55]

In contrast to its effects in younger and/or ambulatory patients, oxybutynin tended to be ineffective in elderly institutionalised patients. A regimen of prompted voiding combined with oxybutynin (2.5 to 5mg 3 times daily for 10 days) did not reduce episodes of incontinence to any clinically relevant degree compared with placebo in 57 such patients (mean age 86 years) who had responded poorly to a regimen of prompted voiding alone.[54] Similarly, oxybutynin (5mg twice daily for 8 days) did not differ from placebo in 18 elderly institutionalised patients (mean age 74 years).[56]

The small sample sizes and short treatment durations may have obscured any possible differences between treatments in these trials, or it may be that difficulties inherent in treating institutionalised and often bedridden patients are contributory. Indeed, some benefit for oxybutynin over placebo was evident in a larger series of 57 elderly (mean age 82 years) but ambulatory patients.[52] In patients receiving oxybutynin (2.5mg twice daily) in addition to bladder retraining for 6 weeks, urinary frequency was decreased significantly during the last 2 weeks of therapy with oxybutynin but not placebo (table V). After an initial 2 weeks' therapy, more oxybutynin recipients (86%) than placebo patients (55%) considered treatment beneficial. This difference was not, however, significant at study end (79 *vs* 55%) and changes in episodes of nocturia and incontinence were similar in both groups. Nonetheless, these results indicate a small subjective benefit for oxybutynin compared with placebo when given to ambulatory elderly patients for up to 6 weeks.

During oxybutynin, but not placebo, therapy mean residual urine volumes increased by up to 75ml, suggesting a degree of urinary retention.[53,55,56] However, differences versus placebo were not universally significant.[53] Tapp et al.[55] noted that residual volumes were abnormal (increase of > 100ml) in 7 of 21 patients; increases tended to occur in older patients and those with longer voiding times.

4.4 Comparisons with Other Anticholinergic Therapies

On the basis of limited investigations, oxybutynin appears to be at least as effective as propantheline and similar to propiverine in patients with overactive detrusor function (table VI). The largest trial, a 4-week investigation in 154 patients with idiopathic DI or detrusor hyperreflexia,[59] demonstrated greater benefits with oxybutynin 5mg 3 times daily than with placebo, as measured by urinary frequency, volume at first desire to void and maximum cystometric capacity (fig. 2), and a tendency for a better effect than with propantheline 15mg 3 times daily (table VI). Symptoms of urge incontinence were improved more often with oxybutynin (58% of patients) than with propantheline (45%) or placebo (43%). These data are supported by the results of a study in patients with detrusor hyperreflexia subsequent to multiple sclerosis.[57] Oxybutynin 5mg 3 times daily (n = 19) was considered superior to propantheline 15mg in the same regimen (n = 15) after 6 to 8 weeks' administration (table VI).

In contrast, in 23 women with idiopathic DI maximum bladder capacity was the only parameter to show greater improvement with oxybutynin than with propantheline given in titrated dosages for 4 weeks. No other significant differences were dis-

Table VI. Comparative efficacy of oxybutynin (O) and other anticholinergic drugs in patients with detrusor instability (DI) or detrusor hyperreflexia

Reference	No. of evaluable patients (mean age)	Study design (duration)	Dosage	Subjective parameters (change from baseline)		Objective parameters (change from baseline)			Overall results
				frequency (F) or urgency (U)	UI	VFD (ml)	MDP (cm H_2O)	MBC (ml)	
Gajewski & Awad[57]	19 (nd)[a]	r,pl (6-8w)	O 5mg tid	F: −1.3†[b] U: −0.8†[b]	−1†[b]		−14	+144‡	O > PR
	15 (nd)[a]		PR 15mg tid	F: −0.6[b] U: −0.5[b]	−0.5[b]		−0.6	+35	
Holmes et al.[58]	20F (42.4y)[c]	r,co,sb (4w)	O 5mg tid[d]	F: −18%†	−22†[e]	+81†	−15†	+128‡†	O ≡ PR
			PR 15mg tid[d]	F: 0.1%	+12[e]	+66	−9†	+61	
Thüroff et al.[59]	59 (48y)[f]	r,pl,db,pc, mc (4w)	O 5mg tid	F: −1.8*[g]	58%*‡[g]	+51*		+80*	O ≥ PR
	48 (51y)[f]		PR 15mg tid	F: −0.9[g]	45%[h]	+11		+49	
	47 (52y)[f]		P tid	F: −0.3[g]	43%[h]	−10		+23	
Wehnert & Sage[60]	10 (nd)	r,co,pc (3w)	O 5mg tid	U: 67%[h]			−25	+65	O ≡ PP
			PP 15mg tid	U: 63%[h]			−19	+118†	
			P tid	U: 48%[h]			−24	+69	

a All patients had detrusor hyperreflexia.

b Mean improvement in grades of symptoms.

c Women only.

d Starting dosage; dose titrated according to response/adverse effects.

e Linear analogue scale used.

f Patients with either idiopathic DI or detrusor hyperreflexia.

g Expressed as change in 24-hour voiding frequency.

h Percentage improvement from baseline.

Abbreviations and symbols: co = crossover; db = double-blind; MBC = maximum bladder capacity; mc = multicentre; MDP = maximum detrusor pressure during filling; nd = no data; P = placebo; pc = placebo controlled; pl = parallel; PP = propiverine; PR = propantheline; r = randomised; sb = single-blind; tid = 3 times daily; UI = urge incontinence; VFD = volume at first desire to void; w = weeks; y = years; * $p < 0.05$ *vs* placebo; † $p < 0.05$ *vs* baseline; ‡ $p < 0.05$ *vs* active comparator; > indicates better effect ($p < 0.05$); ≥ indicates tendency for better effect; ≡ indicates equivalent effect.

cerned between the 2 drugs, although results were consistently better numerically with oxybutynin.[58] This was also the case in a small crossover trial in 10 patients that found oxybutynin to be similar to propiverine in measures of urinary urgency, maximum detrusor pressure during filling and maximum cystometric capacity[60] (table VI).

The placebo response was high (subjective symptom improvement of about 45%) in trials that included a placebo arm.[59,60] In keeping with findings presented in section 4.3, there were conflicting results regarding the ability of oxybutynin and propantheline to alleviate nocturia. One study reported that both treatments reduced the incidence of nocturia to a similar degree,[58] whereas another reported a significant decrease from pretreatment values in symptom grade with oxybutynin (1.0, $p < 0.05$) but not propantheline (0.6).[57]

During oxybutynin therapy, residual urine volume either remained unchanged[58] or increased significantly compared with propantheline,[59] whereas the latter drug either had no effect[58] or slightly decreased[59] this parameter. These findings tend to support those of placebo-controlled trials discussed in section 4.3, indicating that oxybutynin ameliorates symptoms of detrusor overactivity but at the cost of an increase in residual urine volume. However, Thüroff et al.[59] reported that this increase primarily occurred in patients with detrusor hyperreflexia, in whom pharmacological relaxation of the bladder is often accompanied by intermittent or indwelling catheterisa-

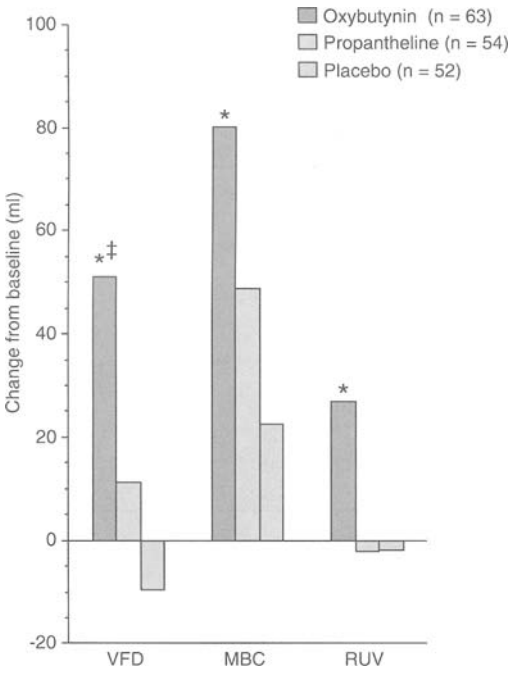

Fig. 2. Cystometric changes in patients (aged 16 to 83 years) with detrusor instability treated with oxybutynin 5mg 3 times daily, propantheline 15mg 3 times daily or placebo for 4 weeks.[59] *Abbreviations and symbols:* MBC = maximum bladder capacity; RUV = residual urine volume; VFD = volume at first desire to void; * $p \leq 0.05$ *vs* placebo; ‡ $p \leq 0.05$ *vs* propantheline.

tion.[59,61] Thus, an increase in residual urine volume would not necessarily be a cause for concern in these patients.

4.5 Intravesical Administration

Intravesical administration of oxybutynin has been investigated as a means of decreasing anticholinergic adverse effects while maintaining clinical efficacy. A 5mg tablet is crushed and dissolved in 30ml distilled water; the solution (sometimes warmed to prevent reflex bladder contractions) is then instilled via an intravesical catheter. This method is usually considered an option only in patients with detrusor hyperreflexia caused by spinal cord injury or diseases such as myelodysplasia and multiple sclerosis, in whom indwelling or intermittent catheters are commonly pre-existent. About 55 to 90% of such patients improved subjectively after instillation of oxybutynin 5mg as single[61,62] or multiple[63-66] 5mg doses in small noncomparative trials. Objective parameters also showed a tendency to improve, with bladder capacity and compliance increasing, and peak intravesical pressure, urinary frequency and nocturia decreasing, in comparison with baseline values.[61-63,65,66]

In the only randomised, double-blind, placebo-controlled study of patients with urge incontinence as a result of DI, 20mg oxybutynin administered intravesically over a period of 10 days significantly improved several urodynamic parameters compared with placebo ($p \leq 0.05$) [n = 39]. However, this study was reported in abstract form only, and no further details were available.[67]

Instillation of oxybutynin 5mg 2 to 3 times daily for an unspecified period produced improvement in 55% of 33 participants unresponsive to or intolerant of other drug therapy, about half of whom had DI and the remainder detrusor hyperreflexia.[64] Use of protective urinary pads decreased from 3.7 to 1.2 pads/day, and 9 patients achieved normal bladder control. The authors recommended oxybutynin as an option in these difficult-to-treat individuals who would be likely to require surgery otherwise.

5. Tolerability

Adverse effects related to oxybutynin are primarily anticholinergic in nature and are, at least in part, dose-related. Atropine-like symptoms – mostly dry mouth, blurred vision and constipation – occur frequently and may be severe enough to necessitate treatment discontinuation. On retrospective analysis, about 50% of 271 oxybutynin recipients (dosage range 2.5mg twice daily to 5mg 3 times daily) of mean age 53 years experienced dry mouth and 15% reported constipation.[68] These findings agree with those of the Centres Régionaux de Pharmacovigilance and Laboratoire Debat in France, which collated data on adverse effects attributable to oxybutynin (dosage not stated) over a 5-year period in 115 adults of mean age 60 years.[69] Approximately half of the adverse

effects resembled atropine overdosage and included mydriasis, dry mouth, facial flush, auditory and visual hallucinations, agitation, confusion, delirium and nightmares. Miscellaneous skin reactions (rash, oedema, urticaria, photosensitivity) developed in 33 patients and erythema multiforme in 2. 'Allergies' have been reported by other authors.[43]

A similar review in 180 patients in the UK[70] revealed an incidence of 76% for any adverse effect associated with oxybutynin (dosage up to 5mg 3 times daily, reduced in the elderly). Dry mouth, dysphagia and stomal ulcers were most prevalent, occurring in 144 patients (80%), followed by gastrointestinal discomforts such as diarrhoea, constipation, distension and nausea (13%), CNS effects (headache, dizziness or drowsiness; 11%) and visual disturbances (dry eyes and blurred vision; 5.5%) [fig. 3]. 23% of patients were intolerant of their symptoms and discontinued therapy.

This treatment withdrawal rate falls in the range of ≤ 27% reported among oxybutynin recipients in placebo-controlled trials (section 4.3). The highest withdrawal rate (27%) was recorded among a series of postmenopausal women treated with the highest recommended dosage of oxybutynin (5mg 4 times daily) of whom 26 of 31 complained of severe dry mouth.[55] However, in the largest of the placebo-controlled studies (in which patients received oxybutynin 3mg 3 times daily), adverse effects were experienced by up to 88% of 53 women, but led to only 7.5% withdrawing from therapy.[53] The most common unwanted symptoms were dry mouth (88% for oxybutynin *vs* 33% for placebo), stomal ulcers (16 *vs* 0%), constipation (12.5 *vs* 0%) and drowsiness (12.5 *vs* 7%).

Subsequent to a report of reflux oesophagitis in a woman with cerebral palsy treated with oxybutynin (dosage not stated),[71] other authors have reported this effect (14 of 271 patients [5%] in 1 series).[68] Pseudo-obstruction developed in a patient with Parkinson's disease who had received oxybutynin plus the tricyclic antidepressant lofepramine.[72]

Oxybutynin may be less well tolerated than propantheline. In the largest and best designed trial, the incidence for oxybutynin of 63% (n = 63) for unwanted effects, mainly dry mouth and gastric upset, was significantly greater than the rate of 44% for propantheline (n = 54) and 33% for placebo (n = 52). Nonetheless, withdrawal rates were low (2 patients with oxybutynin, 3 with propantheline).[59] Furthermore, the possible better efficacy of oxybutynin compared with propantheline in some patients may offset this disadvantage in tolerability: in 1 trial[58] patients were more

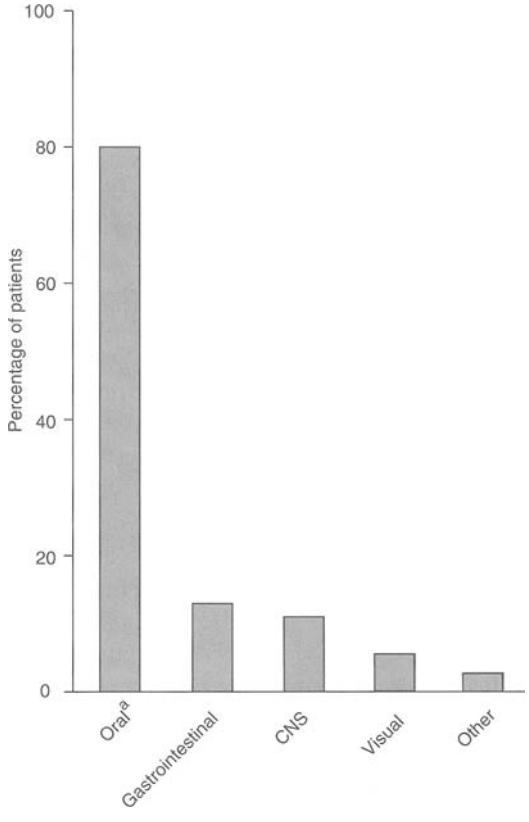

Fig. 3. Incidence of adverse effects reported in 180 patients with detrusor instability during therapy with oxybutynin (up to 5mg 3 times daily) for periods of 1 day to 3 years. Analysis was retrospective and examined a 5-year period of oxybutynin use (1982-1987) in the UK.[70] a = Dry mouth, dysphagia, stomal ulcers.

amenable to tolerating adverse effects with oxybutynin than with propantheline in exchange for perceived improvement in incontinence symptoms with the former. Smaller investigations using the same dosages have found similar adverse effect profiles for the 2 drugs. Discontinuation rates were 21% for oxybutynin versus 27% for propantheline in 34 patients with hyperreflexia,[57] and both drugs were considered to have similar tolerability profiles in another 23 individuals.[58]

It is difficult to ascertain whether increasing age has any bearing on the tolerability of oxybutynin. None of the subjective adverse effects reported by elderly institutionalised patients or nursing staff in a small trial of 15 individuals required treatment withdrawal.[73] The incidence of adverse effects during treatment with oxybutynin 5 or 10mg daily was similar to that of placebo in 57 ambulant elderly patients[52] and in 24 geriatric institutionalised patients.[56] However, oxybutynin was ineffective at this latter dosage, the washout period was short (6 days), as was treatment duration (8 days), and 42% of the population were 'confused or unreliable' at least some of the time.[56]

The worldwide withdrawal of the mixed anticholinergic/calcium antagonist terodiline, because of its association with episodes of QTc interval prolongation and supraventricular arrhythmias, has prompted examination of the cardiac effects of oxybutynin in patients with DI. Treatment with oxybutynin 2.5 to 10mg daily for 4 weeks did not influence heart rate or QTc dispersion and did not significantly prolong the QTc interval in 21 elderly individuals (mean 75 years), 15 of whom had concomitant vascular disease.[74] Although the results of this small noncomparative trial cannot be considered definitive, they nonetheless add weight to evidence from clinical trials discussed in section 4 demonstrating a general lack of cardiac effects with oxybutynin. Tachycardia has been reported in 4 of 30 oxybutynin-treated patients[43] and 'heart disturbance' in 1 of 63;[59] however, no attempt was made to determine causality to the drug.

There have been variable reports of adverse effects in patients treated with intravesical oxybutynin in small clinical trials. Only one study has reported systemic antimuscarinic adverse effects (dry mouth, flushing),[66] and these and other adverse effects (recurrent urinary infections, inconvenience of catheterisation) led to over 50% of patients discontinuing treatment. However, 11 of the 18 patients were children, who may have been less tolerant of the procedure than adults. Two studies reported an inability to retain the solution intravesically in about 20% of patients,[62,64] whereas others reported no adverse effects associated with this procedure.[63,75]

6. Dosage and Administration

The recommended initial oral dosage of oxybutynin is 5mg 2 to 3 times daily.[76-78] Dosage should be titrated, to a maximum of 5mg 4 times daily, to optimise response and minimise adverse effects. However, in the elderly, a lower starting dose of 3 or 5mg twice daily has been recommended,[77,78] and clinical experience has led some clinicians to suggest a starting dose of 2.5mg twice or 3 times daily for all adult patients, with titration as necessary.[10,68] Intravesical instillation of oxybutynin as a crushed 5mg tablet has been effective in small clinical trials (section 4.5).

Oxybutynin is contraindicated in patients with conditions which may be aggravated by its predominantly anticholinergic activity. These include untreated angle closure glaucoma or untreated narrow anterior chamber angles, obstruction of the bowel, bladder outflow obstruction (precipitation of urinary retention may occur), intestinal atony, severe ulcerative colitis and myasthenia gravis.

As with other anticholinergic drugs, use of oxybutynin may worsen symptoms of hyperthyroidism, prostatic hypertrophy, cardiac arrhythmias and coronary artery disease, and may aggravate hiatus hernia associated with reflux oesophagitis. Patients should be warned that drowsiness or blurred vision may reduce their ability to perform tasks requiring mental alertness.

Treatment of oxybutynin overdosage is symptomatic. A woman who had ingested 100mg of oxy-

butynin recovered fully after symptomatic treatment.[79]

7. Place of Oxybutynin in Therapy

As an individual's age increases, so does the likelihood of developing DI. Depending on the severity of DI and motivation of the patient, approaches to its management and treatment are varied (table VII). Because behavioural training actively involves patients in their own therapy and is devoid of adverse effects, it is the preferred first strategy. Behavioural training may be followed by, or in some cases combined with, drug therapy. Surgical or other invasive strategies are usually reserved as a final recourse for refractory patients.[6,7]

The most common form of behavioural training is bladder drill. Its aim is to gradually prolong the interval between voids by encouraging the patient to consciously delay micturition, despite urge, according to a set pattern over time.[6] A subjective response rate of 85% and an objective rate of 50% have been quoted for this therapy,[8] which is particularly suitable for patients with minor urodynamic abnormalities and symptoms (e.g. urinary frequency, urgency).[8] Other strategies such as biofeedback and acupuncture may also be attempted, although estimates of their efficacy are imprecise.[6-8]

Disadvantages of behavioural therapy are that the patient must be cognisant, highly motivated and cooperative, and that training is generally time-consuming for both the patient and the clinician. Moreover, bladder drill is of limited success in incontinent patients who do not have sufficient control of voiding to undertake the procedure.[6-8,10] Given these constraints, behavioural training is often impractical in the elderly, particularly those with impaired cognition.

Pharmacological therapy can thus be considered an option under these circumstances. Unfortunately, among the diversity of drug treatments (table VII) investigated for their potential to overcome overactive detrusor function, few have well-documented efficacy. Tolerability concerns may also restrict their use: cardiac arrhythmias may render older tricyclic antidepressants unsuitable in elderly patients, while orthostatic hypotension can be problematic with α_1-adrenoceptor antagonists. Anticholinergic agents have thus found greatest use to date, despite a high incidence of atropine-like adverse effects. Their position has gained even greater prominence in the wake of the worldwide withdrawal of the mixed anticholinergic/calcium antagonist terodiline, because of the development of serious ventricular arrhythmias in some patients.

Oxybutynin, which has now been in clinical use for almost 2 decades in some countries, is considered by some clinicians to be the drug of choice at present.[15] It possesses mixed spasmolytic and anticholinergic (antimuscarinic) activity. These prop-

Table VII. Options in the treatment of idiopathic detrusor instability or detrusor hyperreflexia[6-9,80]

Behavioural	Pharmacological	Surgical/other
Bladder drill	Anticholinergics (e.g. propantheline;	Intravaginal or intrarectal electrical stimulation
Biofeedback	emepronium) + spasmolytic properties (e.g.	Denervation by subtrigonal phenol injection
Acupuncture	**oxybutynin**; dicyclomine)	Augmentation cystoplasty ('clam' cystoplasty)
Hypnosis	Tricyclic antidepressants (e.g. imipramine)	Bladder transection
Reduced fluid intake (i.e. tea,	Smooth muscle relaxants (e.g. flavoxate;	Ileocaecal urinary diversions
coffee, alcohol, citrus juice)	baclofen, diazepam)	Autoaugmentation
	Potential options	
	β_2-Adrenoceptor agonists (e.g. terbutaline; clenbuterol)	
	Calcium antagonists	
	α_1-Adrenoceptor antagonists (e.g. prazosin)	
	Prostaglandin synthetase inhibitors (e.g. indomethacin; flurbiprofen)	

erties are responsible for its ability to improve cystometric and subjective parameters, thus restoring a measure of bladder control in some patients. Disparities in outcome measures and trial methodologies have hampered efforts to quantify the response to oxybutynin or to gauge its efficacy relative to other options. Nonetheless, in ambulatory individuals, including elderly patients, oxybutynin is usually superior to placebo and, in limited investigations, appears at least as beneficial as propantheline and similar to propiverine. Urge incontinence was alleviated in more patients treated with oxybutynin than with propantheline in the largest trial. Conversely, elderly institutionalised participants in small trials have responded poorly to oxybutynin and the susceptibility of nocturia to the drug has not been demonstrated conclusively. Cure has not been commonly reported with oxybutynin or, indeed, with any drug therapy.[8] Results of clinical trials comparing oxybutynin with darifenacin, a new selective muscarinic antagonist, are awaited with interest.

The success of intravesically administered oxybutynin in preliminary investigations suggests this approach as an option in patients with pre-existing or intermittent catheters, especially if the underlying pathology is neurological, or in patients intolerant of oral therapy. In patients previously uncatheterised but who may be candidates for this route of administration, the clinician and patient must weigh the therapeutic benefit against the discomfort of catheterisation and the potential risk of urinary tract infection.

As mentioned previously, the high incidence of unpleasant atropine-like adverse effects is the major drawback to the use of oxybutynin and other anticholinergic agents. Dry mouth is the most common effect, reported in at least half of oxybutynin recipients, constipation is experienced by about 15% and blurred vision, while less frequent, can limit patients' daily activities. In reality this may not be problematic because DI and urge incontinence undergo spontaneous remissions/exacerbations and thus treatment may be needed only for short periods.[7] Nonetheless, some data have shown that up to one-quarter of patients discontinue oxybutynin therapy because of intolerable adverse effects. Attempts to address this problem include recommendations for dosage reductions and development of an as-yet unavailable modified-release formulation.[1]

In summary, effective pharmacological options to treat patients with idiopathic DI or detrusor hyperreflexia are few and are far from ideal. Despite its profile of often poorly tolerated anticholinergic adverse effects and apparent lack of efficacy in elderly institutionalised patients, oxybutynin should be considered for the drug of first choice in treating ambulatory, including elderly, individuals with detrusor overactivity, when drug therapy is appropriate.

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