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Comparative Tolerability of Drug Therapies Used to Treat Incontinence and Enuresis

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Contents

Abstract

Drug therapy for incontinence and enuresis has met with varying degrees of success. Currently, there is no medication available that specifically targets the lower urinary tract without having untoward effects elsewhere in the body. Patients with urge incontinence are the most difficult group to treat. The agents most commonly used to treat urge incontinence, i.e. anticholinergics, musculotropics and tricyclic antidepressants, are limited in their effectiveness and have anticholinergic adverse effects. Other medications with theoretical treatment potential such as nonsteroidal anti-inflammatory drugs and calcium antagonists require more in depth clinical study before widespread use is appropriate. Although estrogen is well tolerated, its role in the treatment of incontinence in postmenopausal women may be limited.

Medical treatment for stress incontinence is most successful in patients with a mild condition. Drugs with α-adrenergic activity alone or in combination with

estrogen in postmenopausal women, are fairly effective and demonstrate few adverse effects at doses used to treat stress incontinence. Enuresis pharmacotherapy consists mainly of desmopressin and tricyclic antidepressants. Adverse effects are minimal with the doses commonly used. While the majority of patients improve with therapy, a significant portion relapse after treatment is terminated.

Tolerability of a particular therapy depends on the effectiveness and adverse effects of the agent, the severity of incontinence and the general health of the patient. In general, patients are willing to accept a greater degree of inconvenience if a drug produces the desired effect. However, individualisation of therapy should be used to maximise compliance and outcome. Blinded, dose-titration studies are needed to better determine doses for optimum tolerability. Research into drugs specifically targeting the lower urinary tract may lead to more effective and well tolerated therapy for incontinence and enuresis.

Urinary incontinence is involuntary loss of urine and is a social and hygienic problem.[1] It affects some 13 million people in the US alone and is associated with direct and indirect costs of about $16 billion per year.[2] Appropriate management, including medical therapy, can significantly reduce cost and morbidity. Pharmacological therapy for urinary incontinence and enuresis has enjoyed varying degrees of success. However, to date there is no group of medications which can consistently treat incontinence and enuresis without producing annoying adverse effects. In particular, there is a lack of bladder-specific anticholinergic medications for patients with urge incontinence. Depending on the general health of the patient, adverse drug reactions may present absolute contraindications to a specific therapy. Patient satisfaction with a particular therapy may be greatly influenced by these adverse effects as the patient weighs the beneficial effects of a drug against the associated unpleasant effects. Tolerability of drug therapy depends on many factors including bioavailability, selectivity of response, effective half life, preexisting medical conditions and patient enthusiasm toward treatment regimen.

The importance of the placebo effect, which can be almost 50%, must be considered when evaluating drug therapy.[3] In order to allow for the placebo effect, the scope of this review is restricted to placebo controlled trials or direct comparison studies between drugs for which placebo controlled trials are available (table I). Peer reviewed articles, published in English, representing designed studies with defined outcome variables and adverse effect data were extracted from the medical literature by systematic review of the MEDLINE database from 1966. The US Department of Health and Human Services' Agency for Healthcare Policy and Research (AHCPR) Urinary Incontinence In Adults Guideline Panel's 1996 clinical practice guideline update for the treatment of urinary incontinence provided a reference standard for the drugs evaluated.

1. The Medical Basis of Drug Therapy for Incontinence

The lower urinary tract is under the control of both the sympathetic and parasympathetic nervous systems. The parasympathetic system stimulates contraction of the detrusor while inhibiting urethral smooth muscle contraction. Conversely, the sympathetic system relaxes the detrusor through ß-adrenergic activity, and contracts the bladder neck by stimulation of α-adrenergic receptors. The process of micturition is under control of the parasympathetic system, and is caused by contraction of the detrusor, inhibition of sympathetic action on the bladder base and urethra and inhibition of somatic nerves to the striated urogenital sphincter. Urine storage is primarily a function of the sympathetic system which inhibits parasympathetic activity on the lower urinary tract. α- and ß-adrener-

gic receptors increase urethral tone and relax the detrusor, respectively, while stimulation of somatic nerves to the striated urogenital sphincter further raises outlet resistance.[30]

Urge incontinence refers to involuntary loss of urine associated with a strong urge to void. Urinary urgency may be categorised into sensory urgency which is associated with hypersensitive bladder states or motor urgency which is associated with detrusor overactivity. According to the International Continence Society,[1] detrusor instability is a condition in which the detrusor is objectively shown to contract despite the patient's efforts to inhibit micturition. Motor overactivity of the detrusor in the presence of identifiable, pertinent neurological disease is known as detrusor hyperreflexia. When there is simultaneous detrusor contraction and involuntary urethral contraction, detrusor-sphincter-dyssynergia is said to exist.

The term stress incontinence may refer to a symptom, sign or condition. It can be the patient's statement of loss of urine with physical exertion or the observation of urinary loss coincident with physical exertion. It can be associated with an anatomic defect caused by either loss of support of the urethrovesical junction, or intrinsic sphincteric deficiency resulting in loss of urethral resistance irrespective of bladder neck support. Genuine stress incontinence is the condition in which involuntary urine loss occurs when intravesical pressure exceeds maximum urethral pressure in the absence of detrusor activity.

Enuresis refers to involuntary urinary loss, regardless of the aetiology, beyond the age of toilet training. Diurnal enuresis may be caused by constitutional factors such as dementia, but can also be caused by sphincteric insufficiency. Nocturnal enuresis may be associated with detrusor instability, but detrusor instability is not necessarily associated with nocturnal enuresis. Primary nocturnal enuresis comprises 75 to 90% of all cases with the remaining considered secondary, usually to some disruptive life event.[31]

2. Drugs Used to Treat Urge Incontinence

Drug therapy for urge incontinence is directed toward interfering with the contractile activity of the bladder at various levels. This may involve blocking the activity of acetylcholine, direct suppression of smooth muscle, inhibiting CNS mechanisms or regulating substances such calcium and prostaglandins believed to help modulate bladder contractility. The most effective medications generally carry significant anticholinergic adverse effects which can greatly affect their tolerability.

2.1 Anticholinergics

2.1.1 Propantheline

Propantheline is a synthetic analogue of atropine with pure anticholinergic properties. No drug approximates the effects of atropine on the bladder *in vitro* better than propantheline, although its CNS effects are less marked.[32] It is widely regarded as the benchmark by which other anticholinergic agents used to treat urological conditions are compared.[33] Like other quaternary ammonium compounds it has a low bioavailability and absorption varies greatly with the individual.[34]

In a single-blind, placebo controlled study in elderly institutionalised patients with urge incontinence, treatment with propantheline was initiated at a dosage of 15mg 4 times daily.[4] Those patients whose incontinence did not respond to propantheline or placebo (30 of 34 patients) were treated with propantheline 30mg 4 times daily. The incidence of adverse events (primarily anticholinergic) for both 15 and 30mg 4 times daily dosages was 53% while the incidence of adverse events with placebo were 39 and 23%, respectively. Treatment with propantheline 30mg 4 times daily was only 17% more effective than placebo. Ultimately, 11% of patients receiving propantheline 30mg 4 times daily level withdrew from the study because of severe adverse events (ileus, nausea/vomiting, urinary retention and syncope) compared with 3% who withdrew because of adverse events with placebo. The authors terminated the study early be-

Table I. Blinded, controlled trials of drug therapy for urinary incontinence

Drug/reference	Dosage	n	Mean age (ys)	Study length (wks)	Response[a]	Adverse effects[a]	Withdrawals because of adverse effects (%)
Propantheline							
Zorzitto et al.[4]	15-30mg qid	34	74	3	No	Yes	11
Holmes et al.[5]	30mg tid[b]	23	42	8	No[c]	Yes[c]	9
Thuroff et al.[6]	15mg tid[b]	169	49	4	No[d]	Yes	6
Penthienate							
Coombes and Millard[7]	5mg tid	20	64	8	Yes[e]	Yes	5
Scopolamine							
Muskat et al.[8]	1.25mg q3d transdermal	20	52	2	Yes	Yes	0
Oxybutynin							
Tapp et al.[9]	5mg qid	37	61	6	Yes	Yes	27
Moore et al.[10]	3mg tid	53	46	12	Yes	Yes	7
Nilsson et al.[11]	10mg qd controlled release	17	46	16	No[f]	No[f]	0
Enzelsberger et al.[12]	20mg qd intravesical	20	60	4	Yes	No	0
Trospium chloride							
Stohrer et al.[13]	20mg bid	61	NA	3	Yes	No	0
Madersbacher et al.[14]	20mg bid[b]	64	32	2	No[g]	No[b]	6
Tolterodine							
Jonas et al.[15]	1-2mg bid	242	57	4	Yes	No	5
Imipramine							
Castleden et al.[16]	50mg hs[h]	33	73	12	No	Yes	5
Doxepin							
Lose et al.[17]	50-75mg hs	20	53	8	Yes	Yes	0
Flurbiprofen							
Cardozo et al.[18]	50mg bid	30	49	5	Yes	No	0
Flunarizine							
Palmer et al.[19]	20mg qd	14	51	4	Yes	Yes[i]	0
Phenylpropanolamine (norephedrine; PPA)							
Lehtonen et al.[20]	50mg bid	43	50	2	Yes	No	0
Colleste et al.[21]	50mg bid	24	47	4	Yes	No	0
Fosseberg et al.[22]	50mg bid	20	53	4	Yes	Yes	5
Norepinephrine (noradrenaline)							
Ek et al.[23]	100mg bid	25	54	4	Yes	No	8
Estrogen							
Walter et al.[24]	1mg estradiol + 1mg estriol qd	29	56	16	Yes[j]	No	0
Samsioe et al.[25]	3mg estriol qd	31	70	12	Yes[k]	No	0

Table I. Contd

Drug/reference	Dosage	n	Mean age (ys)	Study length (wks)	Response[a]	Adverse effects[a]	Withdrawals because of adverse effects (%)
Cardozo et al.[26]	3mg estriol qd	56	59	12	No	No	0
Wilson et al.[27]	3mg estriol qd	36	57	12	No	No	0
Estrogen and PPA							
Walter et al.[28]	4mg estriol + PPA 50mg bid	29	61	16	No	No	0
Hilton et al.[29]	1.25mg conjugated estrogens qd + 50mg PPA bid	60	56	4	Yes	No	3

a Significant compared with placebo.

b Comparison with oxybutynin 5mg tid.

c Significant over pretreatment levels, not significant versus oxybutynin.

d Significant for oxybutynin versus propantheline and placebo.

e Significant versus propantheline also.

f Comparison with oxybutynin 5mg bid.

g Not significant versus oxybutynin.

h Approximate average dose.

i Adverse effect of oedema occurred with long term use with 10mg qd.

j No significant effect on urethral pressure.

k Not significant in patients with stress incontinence.

bid = twice daily; **hs =** at night; **n =** number of patients; **NA =** not available; **q3d =** every 3 days; **qd =** once daily; **qid =** 4 times daily; **tid =** 3 times daily.

cause of occurrence of these adverse events in light of their finding of a modest clinical improvement.

Caution and individual dose titration should be used when propantheline is given to older patients who may be more susceptible to adverse effects of the agent.

In a single-blind, crossover, patient-controlled variable dose comparison with oxybutynin, the mean tolerated dosage of propantheline was 90 mg/day (range 45 to 145 mg/day) given in 3 divided doses while that of oxybutynin was 15 mg/day (range 7.5 to 30 mg/day).[5] Subjective improvement occurred in 11/23 patients receiving propantheline and 14/23 receiving oxybutynin and both drugs demonstrated some objective improvement. For propantheline, the only adverse event that statistically significantly more patients experienced during treatment than before treatment was blurred vision. There was no difference in adverse event severity between propantheline and oxybutynin as measured by linear analogue scale. Three patients withdrew from the study. Two patients were unable to tolerate either drug while 1 patient experienced optic disc cupping while receiving oxybutynin.

Another comparison study found propantheline to have no more significant adverse events that placebo, but also to be no more effective than placebo.[6] A double-blind, placebo controlled, crossover trial was conducted using propantheline 15mg 3 times daily and oxybutynin 5mg 3 times daily. Adverse events were reported by 44% of the patients taking propantheline versus 33% taking placebo and 66% taking oxybutynin. Only 6% of patients withdrew from the study because of anticholinergic adverse effects in the propantheline arm versus 3% for oxybutynin and none for placebo. Dry mouth was the most often cited ad-

verse event (cited by 31% of propantheline recipients, 48% of oxybutynin recipients and 12% of placebo recipients). The authors actively asked the study participants to report adverse events which may account for the small number of study participants discontinuing treatment despite the fairly high incidence of adverse events. The overall subjective grade of improvement (0 to 100%) was higher for oxybutynin (58%) than either propantheline (45%) or placebo (43%).

2.1.2 Penthienate

Penthienate is a quaternary ammonium compound available in the UK and it has recently been studied as an alternative to propantheline in the treatment of urge incontinence.

In a randomised, placebo-controlled, crossover trial, penthienate 5mg 3 times daily was found to be subjectively and objectively superior to placebo and propantheline 15mg 3 times daily.[7] All of the patients receiving penthienate complained of dry mouth, compared with 55% of patients receiving placebo and 60% of the patients receiving penthienate were willing to repeat treatment, compared with 25% of patients receiving placebo. In a comparison with propantheline, both drugs demonstrated cystometric improvements, although penthienate was superior.[7] Penthienate had significantly higher scores for efficacy than propantheline (83 versus 38%, respectively) but was also associated with more mouth dryness (73 versus 55%, respectively). The number of patients willing to repeat treatment with penthienate or propantheline was nearly equal (52 versus 48%, respectively). This may reflect the fact that although patients felt that penthienate caused more severe dry mouth they were willing to repeat treatment because they felt that it was more efficacious.

2.1.3 Scopolamine

Scopolamine is a belladonna alkaloid used mainly in the treatment of motion sickness and sialorrhoea. The agent causes significant anticholinergic adverse effects when taken orally or systemically. Transdermal delivery systems have been developed in an effort to circumvent these adverse effects.

A randomised, placebo-controlled, parallel study was carried out in 20 patients with detrusor instability to evaluate the potential benefit of transdermal scopolamine.[8] Treatment consisted of a patch containing 1.25mg scopolamine or placebo applied to the skin every 3 days. The scopolamine group demonstrated significant symptomatic and cystometric improvement. 70% felt improved with treatment (5/10 patients felt that the improvement was significant and 2/10 felt it was moderate) versus 20% with placebo (1/10 significant and 1/10 moderate). Dry mouth was experienced by 60% of the treatment group and 20% of the placebo group experienced dizziness and 1 placebo recipient reported blurred vision. No patient withdrew from the trial because of adverse events. Further study may be indicated to evaluate transdermal scopolamine in the treatment of incontinence.

2.1.4 Terodiline

Terodiline is an anticholinergic agent with calcium antagonist, local anaesthetic and direct muscle relaxant properties which showed promise in the treatment of urge incontinence.[35] It has proven to be well tolerated and efficacious in the treatment of urge incontinence.[36] Unfortunately, serious cardiac arrhythmias have been associated with terodiline and it has been withdrawn from the market in Europe and clinical trials have been suspended in the US.[2]

2.2 Musculotropics

2.2.1 Oxybutynin

Oxybutynin is a tertiary amine with anticholinergic, direct muscle relaxant and local anaesthetic properties.[37] Oxybutynin and propantheline are the most widely studied drugs used in the treatment of urge incontinence. The efficacy of oxybutynin has been well documented and traditionally has demonstrated the best objective improvements in the treatment of detrusor instability.[2] However, its effectiveness comes at a price of significant adverse effects.

In a double-blind, crossover study at a dose of 5mg 4 times daily, 10 of 31 patients withdrew from the study because of drug adverse events, primarily

dry mouth and blurred vision.[9] Of the 29 patients complaining of dry mouth with oxybutynin, 26 rated it as severe. Six months after the trial, only 7 of 16 patients contacted were still taking oxybutynin and all had self-reduced the dosage to 3 to 5mg 3 times daily. Oxybutynin was effective in producing a stable cystometrogram in 62% of patients versus 42% for placebo.

In another double-blind study of oxybutynin 3mg 3 times daily, involving 53 women with detrusor instability, the rate of withdrawal from treatment was only 7.5%.[10] Dry mouth was the most common adverse event occurring in 88% of patients taking oxybutynin (compared with 33% taking placebo) and was the reason cited for withdrawing from the study in the 4 patients who withdrew. The dry mouth experienced by the oxybutynin group was significantly more severe than that experienced by the placebo group based on a visual analogue score. Other complaints occurring to a greater degree with oxybutynin than placebo were mouth ulcers and constipation. Oxybutynin cured or improved symptoms of detrusor instability in 60% of patients versus 2.3% for placebo. The authors felt that the greater benefit and fewer adverse events seen in this study were because of the lower 3mg 3 times daily dosage.

Efforts to minimise adverse effects have led to alternative forms of administration for oxybutynin. A once daily 10mg sustained release formulation of oxybutynin was compared with 5mg conventional tablets twice daily in a double-blind, placebo-controlled, crossover trial in 17 women with urge incontinence.[11] There was no difference in efficacy or serum drug concentrations between the 2 forms. The most common adverse effect was dry mouth in 69 and 82% of patients in the sustained release and conventional tablet groups, respectively. There was no difference between groups in the number of patients reporting adverse effects (14/16 controlled release, 17/17 conventional) and no patient withdrew from the study because of adverse effects. 17% of patients characterised adverse effects as severe with the 10mg sustained release dose compared with 14% with conventional tablets. This study found no differences in tolerability between the sustained release form and the conventional tablet. These results are not unexpected in light of a recent study which showed oxybutynin and its chief metabolite *N*-desethyloxybutynin have similar antimuscarinic effect and the same binding characteristics in human detrusor and parotid gland tissue.[38]

Local application has been used in an attempt to decrease the adverse effects associated with oxybutynin without sacrificing effectiveness. A randomised, double-blind, placebo-controlled study of intravesical oxybutynin showed this route of administration to be effective with negligible adverse effects.[12] 52 patients with detrusor hyperreflexia secondary to spinal cord injury were treated with oxybutynin 20mg in 40ml saline or placebo on a daily basis for 12 days. Three to 5 days were required to show an effect and 82% of treatment patients had a stable detrusor on cystometrogram versus 0% with placebo. The only adverse effect was dizziness in 3 patients receiving oxybutynin which was relieved immediately by eating. No oxybutynin patients withdrew from the study, but 6 left in the placebo group because of lack of effect. In selected patient groups, intravesical application of oxybutynin appears to be an appealing alternative to oral therapy.

2.2.2 Trospium Chloride

Trospium chloride is a quaternary ammonium derivative with anticholinergic and direct muscle relaxant activities which is available in Europe.[13] It has been proven effective in a double-blind, placebo-controlled study involving 61 patients with spinal injury and detrusor hyperreflexia. At a dosage of 20mg twice daily, significant improvements in cystometric parameters occurred with trospium chloride while spontaneously reported adverse events were less with the agent than with placebo (4 versus 18%). No patient withdrew from the study because of adverse events, but 9% of the placebo group stopped because of lack of effect. In a double-blind comparison with oxybutynin 5mg 3 times daily, trospium chloride 20mg twice daily was judged to be equal to oxybutynin with regards

to improvement in objective and subjective parameters with fewer severe adverse events.[14] Anticholinergic adverse events occurred in 56% of patients receiving trospium chloride and 54% of patients receiving oxybutynin. Only 4% of patients in the trospium group rated their dry mouth as severe compared to 23% in the oxybutynin group and withdrawal from the study because of adverse events occurred more frequently with oxybutynin (16%) than with trospium chloride (6%). Furthermore, patients taking oxybutynin withdrew from the study earlier (mean 7.1 days) than the trospium chloride group (mean 14.3 days).

2.2.3 Tolterodine

Tolterodine is a novel muscarinic antagonist recently developed specifically for the treatment of urge incontinence. It is somewhat bladder selective and has been shown to reduce bladder pressure at doses lower than those affecting salivation. Phase I studies determined that clinical doses of less than 6.4mg were needed to avoid urinary retention.[39] A review of phase II data involving 319 patients recommended a dosage of 1 or 2mg twice daily for optimum tolerability and efficacy.[40] Patients were randomised to receive tolterodine 0.5, 1, 2, 4mg or placebo twice daily. There was no higher rate of withdrawal from the study because of adverse events with any dose of tolterodine than with placebo (8%). The major adverse event reported by all patients in the study was dry mouth of mild to moderate intensity. Patients taking tolterodine 0.5 and 1mg twice daily experienced dry mouth at a rate no different from that seen with placebo (7, 13 and 13%, respectively), while patients taking tolterodine 2 and 4mg twice daily experienced dry mouth at a rate of 26 and 36%, respectively. However, patients taking tolterodine 4mg twice daily experienced increased post void residuals and patients experienced urinary retention.

A recent double-blind, parallel study in 242 patients confirmed the safety and efficacy of tolterodine.[15] Patients were randomised to receive either tolterodine 1mg, 2mg or placebo twice daily for 4 weeks. There were statistically significant improvements in cystometric parameters for both treatment groups. However, only patients in the tolterodine 2mg twice daily group experienced significant changes in maximum cystometric capacity. There was no difference in reported adverse events between the placebo, tolterodine 1mg and 2mg groups (39, 32 and 32%, respectively). Dry mouth was the most common complaint (10% of the tolterodine 2mg, 8% of the 1mg and 2% of the placebo groups) and was of mild to moderate intensity. Other adverse events were accommodation problems, constipation and headache. Although 10 patients withdrew from the study because of adverse events, there was no difference between active treatment and placebo groups (4% of patients receiving tolterodine 1mg, 3% of patients receiving tolterodine 2mg and 7% of patients receiving placebo).

2.2.4 Dicycloverine (Dicyclomine)

Dicycloverine (dicyclomine) is a synthetic antimuscarinic with direct smooth muscle relaxant effects. It is primarily used to treat gastrointestinal hypermotility disorders and is fairly well tolerated, its adverse effects being mainly anticholinergic in nature.[33] No suitable, large, controlled studies are available for dicycloverine in the treatment of urge incontinence. A pilot, double-blind, crossover study found that dicycloverine 30mg 3 times daily was well tolerated, but dicycloverine relieved the symptoms of urge incontinence no better than placebo.[41] Adverse effects were stated as minor and no patients withdrew from the study because of adverse effects attributable to dicycloverine. More definitive studies need to be performed in order to adequately evaluate the utility of this drug in the treatment of urge incontinence.

2.2.5 Flavoxate

Flavoxate is a tertiary amine with smooth muscle relaxant and mild anticholinergic properties. It is well tolerated with a generally lower incidence of anticholinergic adverse effects than other anticholinergic agents.[42] Numerous uncontrolled studies have suggested a possible role for this drug in the treatment of urge incontinence. However, randomised, controlled studies have shown it to be of no more benefit than placebo.[2]

2.3 Tricyclic Antidepressants

2.3.1 Imipramine

All tricyclic antidepressants act with central and peripheral anticholinergic effects, reuptake blocking effects at synaptic terminals of noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5-HT) and have centrally active sedative effects to varying degrees. Imipramine has prominent systemic anticholinergic effects, but relatively weak antimuscarinic effects on the bladder.[43] Although imipramine is an α_1-receptor antagonist, sustained use results in an α_1 stimulation effect because of desensitisation of α_2-receptors which causes urethral constriction.[44]

In an attempt to differentiate between voiding habit training alone and the effect of imipramine, a double-blind, dose titration study of elderly patients with detrusor instability was initiated.[16] Patients began treatment with imipramine 25mg at night and increased the dosage monthly until continence was achieved, no further benefit could be realised or adverse effects became prohibitive. The average dosage tolerated was 54 mg/day (range 25 to 100 mg/day). Common adverse effects reported were dry mouth and constipation. One patient became confused while receiving imipramine 25mg at night and only 1 patient withdrew from the study because of adverse effects. Although 14/19 patients receiving imipramine and 6/14 receiving placebo become continent, this was not statistically significant. Likewise, there was no significant improvement in cystometric findings with imipramine. The authors felt the role of voiding habit training was confirmed by the study.

2.3.2 Doxepin

Doxepin is a tricyclic antidepressant similar to imipramine, but with more sedating effects and a longer time of onset of effect when used for depression.[45] In a double-blind, crossover study, a group of 19 women with detrusor instability were treated with doxepin at a dosage of 50mg at night.[17] Patients whose detrusor instability did not respond to treatment and who did not experience adverse effects were given an additional 25mg every morning. Patients taking doxepin showed a significant improvement in nocturnal symptoms and maximum capacity. Fourteen patients preferred treatment with doxepin, 2 preferred treatment with placebo and 3 with neither. Adverse events were experienced by 73% of patients receiving doxepin versus 15% receiving placebo. The most common adverse events were fatigue and dry mouth (combined incidence 42%). The adverse events were well tolerated and no patient withdrew from the study because of adverse events.

2.4 Nonsteroidal Anti-inflammatory Drugs

2.4.1 Flurbiprofen

It has been postulated that nonsteroidal anti-inflammatory drugs (NSAIDs) could be effective in the treatment of urge incontinence via interference with prostaglandin mediated bladder contractions. Flurbiprofen is a propionic acid derivative anti-inflammatory agent related to ibuprofen. In a placebo-controlled, crossover study of 30 women with detrusor instability oral flurbiprofen 50mg 3 times daily produced significant cystometric and symptomatic improvements.[18] However, significantly more adverse events were experienced by patients receiving flurbiprofen (43%) than by patients receiving placebo (17%). No patient withdrew from the study or reduced the dosage because of adverse events, and 63% of all patients wished to continue treatment after the trial. Additional controlled studies are needed to assess the potential of NSAIDs in the treatment of urge incontinence.

2.5 Calcium Antagonists

2.5.1 Flunarizine

Flunarizine is a calcium antagonist which has a direct smooth muscle relaxant effect and a mild antihistaminic effect, but little cardiac activity. In a placebo controlled trial, 14 patients with detrusor instability were treated with flunarizine 20 mg/day.[19] Flunarizine treatment was associated with a subjective improvement in 11 of the 14 patients and objective improvement was seen in 4 of the 14 patients. Aside from the occurrence of atonic bladder in 1 patient, no major adverse effects were

reported and no patient withdrew from the trial because of adverse effects. During a subsequent long term follow up of the trial, 1 patient receiving flunarizine 10 mg/day developed peripheral oedema, that in the absence of another obvious cause was assumed to be caused by the drug. Although *in vitro* studies have demonstrated the potential of calcium antagonists for the treatment of urge incontinence, large, adequately controlled clinical studies are lacking.[46]

3. Drugs Used to Treat Stress Incontinence

The aetiology of stress incontinence is such that surgery is the primary treatment in the majority of cases. There is a role for medical therapy, especially in less severe cases and the medically infirm patient. The rationale for pharmacological treatment of stress incontinence is based on selection of agents that affect α-adrenergic receptors in the bladder base, bladder neck, proximal urethra and pelvic floor musculature at the bladder outlet. Strategies are designed to increase bladder outlet resistance by stimulation of α-adrenergic activity, suppression of ß-adrenergic activity so that α-adrenergic effects predominate, and estrogen supplementation for direct effect on urethral mucosa and periurethral tissues.

3.1 Adrenergic Agents

3.1.1 Phenylpropanolamine (Norephedrine)

The moderate efficacy and good tolerability of phenylpropanolamine (norephedrine) for the treatment of stress incontinence has been proven in controlled studies. A double-blind, placebo-controlled study of 43 women with mild to moderate stress incontinence demonstrated significant symptomatic and cystometric improvements in patients treated with phenylpropanolamine 50mg twice daily.[20] Clinical improvement was reported in 15 of 21 patients receiving phenylpropanolamine versus 8 of 22 patients receiving placebo. Adverse events were reported in 23% of treatment recipients and 19% of placebo recipients. The most common adverse event reported was dry mouth, which was experienced by 14% of patients receiving phenylpropanolamine and no patient withdrew from the study because of adverse events.

Using a double-blind, crossover schedule, a study in 24 women with mild to moderate stress incontinence who were treated with phenylpropanolamine 50mg twice daily yielded similar results.[21] A significant effect over placebo was found by subjective and objective measure. Patient preference for treatment reported that 58% of patients preferred phenylpropanolamine, with 95% of these having a good or moderately good effect, 17% preferred placebo and 25% had no treatment preference. Adverse events were reported by 12% of patients in both the phenylpropanolamine and placebo groups. No patients experienced severe adverse events and patients with drew from the study because of adverse events. Serum phenylpropanolamine concentrations did not correlate with either objective or subjective treatment response or adverse events.

A double-blind, crossover study of 23 women showed improvement in subjective and objective parameters with phenylpropanolamine 50mg twice daily.[22] Subjective improvement occurred in 60% of patients with phenylpropanolamine and 15% with placebo although no patients became continent. Subjective assessment of improvement decreased with increasing degree of stress incontinence. A phenylpropanolamine serum concentration of 150 ng/ml seemed necessary for objective effect but did not correlate with increases in urethral pressure. Adverse events occurred in 3/20 patients receiving phenylpropanolamine and these included insomnia, restlessness and pruritus. There were no reported adverse events with placebo and no patients withdrew from the study because of adverse events.

Norepinephrine has also been shown to be effective and well tolerated in the treatment of stress urinary incontinence.[23] An oral dose of 100mg twice daily was given to 25 women with stress incontinence in a double-blind, crossover study. Subjective improvement occurred in 12/22 patients receiving norepinephrine and 1/22 receiving pla-

cebo, while 9/22 did not respond to either treatment. Of the 12 patients improved with treatment, only 2 became continent. There were fewer leakage episodes with norepinephrine but this was not significant over placebo. Adverse events occurred in 20% of patients including insomnia and urinary hesitancy. There was no significant increase in blood pressure associated with treatment and only 1 patient withdrew from the study because of stimulant effects.

4. Drugs Used to Treat Both Stress and Urge Incontinence

4.1 Adrenergic Agents

4.1.1 Phenylpropanolamine

Although phenylpropanolamine is primarily used to treat stress incontinence, it has theoretical application in the treatment of urge incontinence due its $ß_2$-agonist activity. Although a recent double-blind, crossover study involving 10 children with myelodysplasia and detrusor hyperactivity found that phenylpropanolamine 100 to 200 mg/day (2.1 to 3.7 mg/kg) was well tolerated, it was not effective.[47] A moderate to good effect was reported by half the patients while the remaining patients reported no effect. Adverse events including fatigue, sleep disturbances and mood changes occurred in 50% of patients while they were receiving phenylpropanolamine. The authors felt the small objective effect noted was not sufficient to recommend use of this agent for urge incontinence except in select cases.

4.2 Estrogen

Estrogen has been used for decades in the treatment of both urge incontinence and stress incontinence, but role of estrogen as a stand-alone treatment for incontinence has yet to be defined. In an effort to assimilate available data, a meta-analysis was carried out in 1994 which showed an overall significant effect of estrogen therapy on subjective improvement for patients with incontinence.[48] However, evidence for objective effect was less convincing.

A double-blind study of postmenopausal patients with sensory urgency found a significant improvement in the symptoms of frequency, urgency and urge incontinence with a combination of estradiol 2 mg/day and estriol 1 mg/day.[24] Of patients taking estrogen, 63% experienced resolution of their sensory urgency compared to 10% of patients receiving placebo. There was no objective improvement in urethral closure pressure. The treatment group had significantly higher serum estrogen levels and estrogen related changes in vaginal tissues. However, there were no adverse effects or significant changes in serum lipid levels.

A double-blind, crossover study involving 34 women aged 70 years or older found estrogen to be well tolerated.[25] At a daily oral estriol dose of 3mg only 4 patients complained of mastodynia and uterine bleeding while no adverse events were reported with placebo. There were no significant adverse events mentioned and no patients withdrew from the study because of adverse events. In the study, 6/8 patients with mixed stress and urge incontinence, 8/12 patients with urge incontinence and 0/11 patients with stress incontinence experienced significant resolution of their symptoms compared with placebo. The authors suggested that the older age of the study group and that the estrogen was given as a single dose may have contributed to adverse events.

Estriol was further studied in a double-blind, placebo-controlled, randomised study involving 56 healthy postmenopausal women with urge incontinence.[26] Oral estriol 3 mg/day was administered with no reported adverse events. Estriol demonstrated a significant increase in volume at the first desire to void and a decrease in detrusor pressure at maximum cystometric capacity. However, there was no difference between estriol and placebo at relieving urge incontinence–related symptoms.

Oral piperazine estrone was well tolerated in a double-blind trial of 36 postmenopausal women with stress incontinence, but failed to demonstrate a significant effect.[27] Treatment consisted of piperazine estrone 3mg given orally at bed time. Of

patients taking piperazine estrone 11/16 reported an improvement in stress incontinent symptoms versus 10/18 patients who received placebo, and no significant objective change was noted with piperazine estrone. Adverse events were generally mild (mastalgia, nausea, etc) and were not significantly increased with piperazine estrone treatment. No patients withdrew from the study because of treatment adverse events.

4.3 Estrogen with α-Adrenergic Agonists

4.3.1 Phenylpropanolamine

Oral estriol and phenylpropanolamine were used in a randomised, double-blind study for stress incontinence in postmenopausal women.[28] 28 patients were given phenylpropanolamine 50mg twice daily and oral estriol 4 mg/day. Both agents, alone and in combination, were significantly preferred over placebo, with 14/15 patients preferring phenylpropanolamine, 9/12 preferring estriol, 10/14 preferred estriol and phenylpropanolamine to estriol alone. No patients withdrew from the study because of medication related adverse events and the incidence of adverse effects related to the active treatment was not different than the incidence for placebo.

Another study compared oral estrogen to vaginal estrogen alone and in combination with phenylpropanolamine in 60 postmenopausal women.[29] Conjugated estrogens 1.25 mg/day were given either orally or vaginally, alone and in combination with phenylpropanolamine 50mg twice daily. Patients receiving oral estrogen were the only group with a significant increase in adverse events over placebo, while those receiving vaginal estrogen enjoyed the greatest therapeutic benefit. The improved benefit with fewer adverse events for vaginal compared with oral estrogen supports the role of local estrogen therapy.

5. Drugs Used to Treat Enuresis

Treatment for enuresis can be either behavioural or medical. Enuresis alarms offer improvement or cure for nearly 80% of patients undertaking this therapy. This relatively inexpensive treatment consists of use of a moisture sensor that is connected to an audio alarm which trains the patient to awaken when they have the urge to urinate. Patients usually do not experience large reductions in effectiveness after treatment is discontinued as do those using drug therapy. However, success using alarm therapy requires motivation and persistence.[49] Strategies in the medical treatment of enuresis are directed toward reduction of urine volume, reduction of bladder contractility, or increasing outlet resistance. The most widely studied and prescribed drugs for enuresis are desmopressin, a synthetic analogue of vasopressin, and tricyclic antidepressants.

5.1 Desmopressin

Desmopressin is the newest drug to be used in the treatment of enuresis. It is generally administered as a nasal spray and optimal efficacy is usually achieved at 20 to 40 μg/day with response rates of 70 to 80% during treatment.[31] A review of the adverse effects of desmopressin used to treat enuresis found adverse effects in, at most, 31/717 patients (4.3%).[50] The majority of these adverse effects were mild and related to local nasal irritation. Dosages employed ranged from 10 to 80 μg/day intranasally, with 10 to 40 μg/day dosages used in children. Six patients receiving desmopressin experienced hyponatraemic seizures; 5 the patients were receiving treatment with desmopressin 20 μg/day or less, and 1 was receiving a dosage of 80 μg/day. All patients recovered fully. Most seizures occurred between 3 and 45 days of treatment, but 1 seizure occurred after 180 days of treatment.

Adverse effect data from double-blind, placebo-controlled studies in 276 patients found that, overall, desmopressin, at dosages of 20 to 40 μg/day, was associated with no more adverse events than placebo.[51] Nasal complaints tended to be the most common adverse event in patients receiving desmopressin.

Oral desmopressin has been available for the treatment of diabetes insipidus and recently has been evaluated for the treatment of enuresis. A preliminary, double-blind, dose titration, crossover

study of oral desmopressin found no difference in adverse event incidence or efficacy between desmopressin 200μg orally and 20μg nasally.[52] The incidence of adverse event was no different between either treatment group and placebo and no serious adverse effects were reported. Nasal discomfort occurred in 2/29 and epistaxis occurred in 3/29 patients receiving nasal desmopressin. About 80% of patients showed improvement with oral desmopressin with 40% demonstrating a greater than 50% improvement over pretreatment levels. Response to nasal desmopressin was 93% with 50% having at least a 50% improvement. Placebo resulted in response rate of 27 with 20% having at least a 50% improvement. The same authors found equal effectiveness between 200 and 400 μg/day orally, and less effect on electrolytes and weight gain with 200μg in an open dose response study.[52]

Oral desmopressin was further evaluated in a comprehensive study and only minor adverse effects were reported.[53] The trial was a multiple stage trial that included a single-blind dose response portion, a double-blind efficacy portion and 2 open long term treatment arms. 25 patients (age range 11 to 21 years) participated in the trial. Using the lowest dose that produced a 50% decrease in enuresis, optimal dosages were 200 μg/day for 5 patients and 400 μg/day for 19; the remaining patient withdrew from the study for reasons that were unrelated to the study. Patients continued these doses in the double-blind and long term portions of the study. The most common adverse events that occurred were headaches and abdominal pain and these were experienced by 5 and 6 patients, respectively. The symptoms disappeared during treatment. There was a total bodyweight gain of 5% throughout the study, but no evidence of water retention or elevated mean blood pressure for the group. Serum electrolytes levels remained within normal range. There was a 70 and 76% response rate for the 2 long term arms. These decreased to 50 and 44% during post-treatment periods. Four patients withdrew prior to the long term periods (1 with the first, 3 with the second) because of lack of effect.

In a recent, double-blind placebo controlled study, no significant differences in efficacy or adverse effects were found between oral desmopressin at 200 and 400 μg/day and nasal desmopressin 20 μg/day.[54] Drug-related adverse effects were reported by 6/203 patients. One patient taking nasal desmopressin 20 μg/day reported dizziness and 1 taking oral desmopressin 200 μg/day reported oedema. Both experienced mood changes in the form of aggression and nervousness which necessitated withdrawal from the study. One patient reported headache while taking oral desmopressin 400 μg/day. There were no episodes of hyponatraemia or water retention. Oral desmopressin was rated as having excellent efficacy and tolerability by 70 and 96% of patients, respectively. Four patients taking oral desmopressin 200 μg/day withdrew from the study because of lack of effect as did 1 patient taking oral desmopressin 400 μg/day.

5.2 Tricyclic Antidepressants

Tricyclic antidepressants, imipramine in particular, have been long-standing treatments for nocturnal enuresis. It is unclear by what mechanism imipramine is effective in enuresis, but anticholinergic activity, alterations of sleep patterns and an increase in antidiuretic hormone secretion have been suggested.[55] The medication is fairly well tolerated at the dose of 25 to 75 mg taken at night doses that is used to treat enuresis. Common adverse effects include anxiety, personality changes, decreased appetite and insomnia; severe adverse effects are rare. However, imipramine is generally not given to children under 6 years old because of the potential for toxicity.[31] Overdose of tricyclic antidepressants classically results in coma, seizures and cardiac disturbances; the later are treated with physostigmine.[44] It is unclear whether serum concentrations of imipramine need to be monitored, but recent data from a placebo-controlled study suggests a moderate correlation between higher serum concentrations and efficacy.[56]

A review of double-blind, placebo-controlled studies has shown a short term success rate with imipramine of 50%, dropping to 25% after therapy

Table II. Dosages for optimum tolerability in the treatment of incontinence and enuresis and associated adverse effects

Drug	Dosage	Adverse effects
Anticholinergics and musculotropics		
Propantheline[4-6]	15mg tid-qid up to 30mg tid	Dry mouth, oral ulcers, blurred vision, dry skin, constipation, somnolence, confusion, urinary retention
Penthienate[7]	5mg tid	
Scopolamine[8]	1.5mg q3d transdermal	
Oxybutynin[5,6,9-11,38]	3-5mg tid	
Trospium chloride[13,14]	20mg bid	
Tolterodine[15]	1-2mg bid	
Tricyclic antidepressants		
Imipramine[16,58,59]	50-75mg qd hs adults, 25mg hs children	Dry mouth, fatigue, dizziness, blurred vision, nausea, constipation, ileus, confusion, somnolence
Doxepin[17]	50mg hs	
Nonsteroidal anti-inflammatory drugs		
Flurbiprofen[18]	50mg tid	Indigestion, nausea, constipation, rectal burning, dizziness
Indomethacin[61]	50mg hs PR	
Calcium antagonists		
Flunarizine[19]	20mg qd	Drowsiness, hypotonic bladder, oedema
Adrenergic agonists		
Phenylpropanolamine (norephidrine)/norepinephrine (noradrenaline)[20-23]	50-100mg bid	Insomnia, restlessness, nervousness, dry mouth, urinary hesitancy
Estrogens		
Estradiol[24]	1mg qd PO	Breast tenderness, uterine bleeding, nausea
Conjugated estrogens[29]	1.25mg qd PO or PV	
Estriol[25,26,56]	3mg qd PO or 1 mg qd PV	
Estrone[27]	3mg qd PO	
Vasopressin analogues		
Desmopressin[50-55]	20-40mg qd nasal or 200-400mg qd PO	Rhinitis, epistaxis, abdominal pain, hyponatraemia, seizures, oedema, headache

bid = twice daily; **hs =** at night; **PO =** orally; **PR =** rectally; **PV =** vaginally; **q3d =** every 3 days; **qd =** once daily; **qid =** 4 times daily; **tid =** 3 times daily.

is discontinued.[57] In a recent, double-blind, placebo-controlled study in children comparing imipramine with mianserin, a tetracyclic antidepressant that lacks anticholinergic activity, no adverse effects were reported in patients receiving imipramine at a dose of 25mg at night.[58] 80 children with enuresis, aged 5 to 13 years old, were treated with imipramine 25mg, mianserin 10mg at night or placebo over a 3 month period. Definite improvement occurred in 72% of patients taking imipramine versus 38% with mianserin and placebo. Only 57% of patients taking imipramine, 37% of patients taking placebo and 38% of patients taking mianserin retained a definite improvement 2 months after cessation of treatment. No adverse effects, either emotional or physical occurred during the treatment period and compliance was excellent.

A double-blind, placebo-controlled, study in patients with psychiatric disorders taking imipramine, nortriptyline or desipramine at a dose of 75mg at night found them to be well tolerated with a low incidence of adverse events.[59] 212 adults with various mental disorders were treated over a 4 month period to evaluate the efficacy of tricyclic antidepressants in the treatment of nocturnal enuresis. Adverse events reported were few relative to

the number of treatment days. The most common adverse events were restlessness, excitement, and gastrointestinal symptoms (nausea, vomiting and diarrhoea). Most of the adverse events reported as severe were associated with placebo and only occurred in isolated instances. However, 1 serious adverse event (paralytic ileus) occurred in the active medication group. Even though treatment resulted in a statistically significant drug effect in several groups, the actual average improvement in dry nights was small. The greatest response to treatment occurred in patients who had a higher baseline number of dry nights while those with no dry nights at baseline tended to show no improvement.

5.3 Miscellaneous Agents to Treat Enuresis

5.3.1 Oxybutynin

The role of musculotropic therapy in the treatment of enuresis is unclear. Early studies of propantheline and oxybutynin appeared to support a role for anticholinergic therapy in nocturnal enuresis.[31] However, a double-blind study of oxybutynin found that there was no significant difference in treatment between oxybutynin taken with the evening meal and placebo.[60] Of the of 41 patients in the trial (mean age 10 years), 1 withdrew from the study because of adverse events while receiving oxybutynin 10mg. Mild adverse events (abdominal discomfort, fatigue, dizziness, headache and dry mouth) occurred in 5 of 30 patients who completed the study. The low incidence of adverse events in this group is may be due in part to decreased absorption of oxybutynin when taken with food.[33]

5.3.2 Indomethacin

NSAIDs are postulated to possibly be of benefit in treating enuresis by inhibiting prostaglandin mediated bladder contractions. Indomethacin is a methylated indole derivative which has potent prostaglandin synthesis inhibiting properties.[44] Indomethacin was used to treat enuresis in a 30 day, double-blind, crossover study in children.[61] 19 children aged 6 to 15 years were given indomethacin 50 mg suppositories or placebo nightly. Adverse events such as headache, dizziness, heartburn, vomiting and rectal burning were noted, but no patients withdrew from the study. Satisfactory response was noted in 14/19 patients receiving indomethacin. The same author found encouraging results with diclofenac in an earlier double-blind study.[62] Additional study of NSAIDs is needed to further define their possible role in the treatment of enuresis.

6. Conclusion

Therapy for urge incontinence continues to be unsatisfying in light of the lack of bladder-specific medications. Drugs with primarily anticholinergic activity continue to provide the mainstay of therapy for this condition. Their effectiveness is limited by untoward effects, particularly dry mouth. Tolerability of a particular therapy is dependent on the patient's overall health, severity of incontinence and effectiveness of the medication (table II). Patients are often willing to endure unpleasant effects if they are not severe and the medication is effective.

Medical treatment of stress incontinence also continues to be unsatisfying in view of the limited effectiveness of available drugs. While adverse effects are usually minor, patients with less severe stress incontinence appear to obtain improved results.

The most effective long term treatment for nocturnal enuresis is behaviour modification. Medical therapies can produce similar improvement rates, with a low degree of adverse effects. However, relapse of symptoms after treatment has been discontinued is a problem.

Individualisation of therapy is necessary to maximise compliance and efficacy when treating incontinence. Daily dosages that promote maximum tolerability may not coincide with dosages required for maximum effect. Continued research into agents acting specifically at the level of the bladder, as well as blinded dose-titration trials of existing drugs are necessary to improve tolerability of medical therapy.

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