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Pharmacotherapy for Overactive Bladder: Oxybutynin vs. Tolterodine

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Overactive bladder (OAB) is defined as urinary urgency and frequency, with or without urge incontinence and involuntary loss of urine.¹ More than 17 million people in the United States are affected with urinary incontinence and it is estimated that 7% to 33% of women and 40% to 80% of men have overactive bladder as the predominant type of urinary incontinence.^{2, 3} Types of urinary incontinence include stress, urge, mixed, overflow, and functional incontinence. OAB has been used to describe urge incontinence in clinical trials.⁴ The cost of treating urinary incontinence in 1995 was estimated at \$30 billion in the elderly, and this cost is only expected to increase as our population ages.⁵

While the exact pathophysiology underlying OAB is unclear, it may involve involuntary detrusor contractions, involuntary sphincter relaxation or detrusor hyperactivity with impaired bladder contractility.⁶ Upon patient complaint of urinary incontinence, a thorough history and physical should be conducted in order to determine which type of incontinence is present and to rule-out any underlying conditions. OAB should be suspected when a patient complains of dysuria, nocturia, more than 8 micturitions per 24 hours and often leaks after a preceding urge to void. In contrast, stress incontinence is the involuntary loss of urine during an increase of intra-abdominal pressure from activities such as laughing, coughing, sneezing, or exercising. Diagnostic tests such as measuring post-void residual urine volume, filling cystometry for urge incontinence, and uroflowmetry for obstructive bladder can help categorizing the specific type of urinary incontinence. Treatment begins with using one of a number of different modalities tailored to the diagnosed type of urinary incontinence.^{4,6,7}

Lifestyle modification and behavioral therapy is recommended first line for OAB.⁶ This begins with avoiding or limiting foods and medications that can exacerbate symptoms. Alcohol, caffeine, diuretics, narcotics, antidepressants and antihistamines can all exacerbate OAB. Various behavioral techniques (e.g. 'Kegel' exercises, bladder training and biofeedback) that aim at strengthening or retaining the bladder can reduce and adequately control symptoms in mild cases of OAB.⁸

Drug therapy can be considered for patients who have persistent symptoms despite behavioral therapy. Anticholinergic drugs are recommended as first line, with oxybutynin being the drug of choice.⁶ Older pharmacological agents such as propantheline, dicyclomine, and tricyclic antidepressants, like imipramine, have been used but have become alternatives due to poor patient tolerability and lack of strong evidence from clinical trials.^{6,7} Oxybutynin XL (Ditropan XL®), the once-daily formulation of oxybutynin, tolterodine (Detrol®) and its once-daily formulation, tolterodine LA (Detrol LA®) are also indicated for treatment of OAB.

Comparative clinical trials have not shown a statistically significant difference in efficacy between oxybutynin and tolterodine, even among the elderly.^{3, 9-12} Efficacy measurements are mostly subjective, based on micturition diary recordings and are reported in clinical trials as mean number of urge incontinence episodes per 24 hours or per week, mean number of micturitions per 24 hours and mean volume voided per micturition. High placebo response rate was noted across studies, 39-47% of placebo recipients perceived symptom improvement compared to

49-50% of oxybutynin recipients and 50-52% of tolterodine recipients. The high placebo response rate was thought to be due to the benefits of maintaining micturition diaries.^{9,10} Furthermore, in some clinical trials, there was no statistically significant difference in reduction of number of incontinence episodes per 24 hours between tolterodine and placebo.^{9,13,14}

The incidence of adverse effects is dose-related for both oxybutynin and tolterodine.^{12,14,15} Dry mouth is the most common side effect, occurring in 50% of tolterodine-treated patients, in 86% of oxybutynin treated patients and 21% of placebo treated patients.⁹ Although reduced, the incidence of dry mouth in tolterodine treated patients is still greater than that of placebo group. Due to its ability to cross the blood-brain barrier, oxybutynin has been associated with cognitive impairment in older adults.¹⁴ Although tolterodine is about 30 times less lipophilic than oxybutynin, indicating that it may not penetrate as easily into the central nervous system, headache, dizziness, and fatigue have been reported with tolterodine. In addition, clinical trials have shown no significant difference in CNS effects between oxybutynin and tolterodine in immediate- or controlled-release formulations.^{9-14, 16-20}

Oxybutynin XL has not demonstrated increased tolerability with respect to dry mouth compared to immediate release oxybutynin in clinical trials.¹⁸ Birns et al¹⁹ compared the efficacy of oxybutynin XL 10 mg once daily with oxybutynin 5 mg twice daily in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. There was no statistically significant difference between oxybutynin XL and oxybutynin in efficacy as measured by daytime continence (53% versus 58%) or in occurrence of individual side effects (55% versus 67%).

Van Kerrebroeck et al.²⁰ found the mean reduction in urge incontinence episodes per week from baseline were 11.8, 10.6 and 6.9 for tolterodine LA, tolterodine and placebo, respectively in a 12-week treatment study of OAB. There was no statistically significant difference between the extended-release or immediate-release formulation of tolterodine. The total rate of dry mouth was 23%, 30%, and 8% for tolterodine LA, tolterodine, and placebo, respectively. Oxybutynin XL and tolterodine LA may offer the convenience of once-daily dosing; however, this has not been shown to improve patient compliance. Therefore, without clinical superiority in efficacy or safety and with their higher costs, oxybutynin XL and tolterodine LA are not recommended first line therapy for OAB at this time.

A combination of behavioral therapy and drug therapy has been shown to be more effective than either drug or behavioral therapy alone. In an extension of a randomized trial involving 35 patients not satisfied with single treatment alone, patients were offered combination of drug and behavioral modification therapy. For patients who had already experienced a 57% reduction in incontinence episodes per week with behavioral therapy alone, they experienced a further reduction of 31% when oxybutynin was added. In patients who first started on oxybutynin, a further reduction of incontinence episodes was observed when behavioral therapy was added, increasing their percentage of time continent from 72.7% to 84.3%.²¹

TABLE 1 - SUMMARY OF RANDOMIZED CONTROLLED CLINICAL TRIALS

Study & Design	Treatment	Efficacy Endpoint Mean reduction from baseline (percent reduction from baseline)	Absolute treatment difference between active and placebo:	Incidence of dry mouth
Abrams et al ⁹ RCT, 293 patients, 12 weeks	Tol 2 mg bid Oxy 5 mg tid Pla	1) Micturitions/24 hrs Tol: 2.7 # (21%) Oxy: 2.3 (19.5%) Pla: 1.6 (10.5%)	Tol: 1.1 micturition Oxy: 0.7 micturition	Tol 50%
		2) Incontinence Episodes/24 hrs Tol: 1.3 (47%) Oxy: 1.7 # (71%) Pla: 0.9 (19%)	Tol: 0.4 episode Oxy: 0.8 episode	Oxy 86%
		3) Subject perceived symptom improvement Tol: 50% Oxy: 49% Pla: 47%		Pla 21%
Millard et al ¹³ RCT, 316 patients, 12 weeks	Tol 1 mg bid Tol 2 mg bid Pla	1) Micturitions/24 hrs Tol 1 mg: 2.3 # (20%) Tol 2 mg: 2.3 # (20.5%) Pla: 1.4 (12.4%)	Tol 1 mg or 2 mg: 0.9 micturition	Tol 1 mg 24%
		2) Incontinence Episodes/24 hrs Tol 1 mg: 1.7 (43%) Tol 2 mg: 1.7 (47%) Pla: 1.3 (37%)	Tol 1 mg or 2 mg: 0.4 episode	Tol 2 mg 39%
		3) Subject perceived symptom improvement Tol 1 mg: 41% Tol 2 mg: 59% Pla: 38%		Pla 13%

RCT = Randomized Controlled Trial, Tol = Tolterodine, Oxy = Oxybutynin, Pla = Placebo, # = statistical result over placebo

SUMMARY

Treating OAB involves appropriate screening procedures and a step-wise treatment approach. Lifestyle modification and behavioral therapy remain first line given their efficacy, tolerability, and low cost. Pharmacological agents may be considered as adjuncts to behavioral therapy for patients who are still severely symptomatic despite lifestyle modification and behavioral therapy. Clinical studies have shown that drug therapy provides small reduction in reducing urinary incontinence symptoms. Therefore, because of the associated high placebo effect, the high adverse effect profile and the high cost, drug therapy should be initiated judiciously in all patients, especially in the elderly and in patients with significant co-morbidities.⁷ When drug therapy is initiated, re-evaluation for clinical improvement is needed after 12 weeks and periodically thereafter to justify the need for continuation of therapy.

Without clinical trials to show clear clinical efficacy and safety superiority of any pharmacological agent, oxybutynin, in its generic form, is considered the most favorable agent due to its lower cost. (see Table 2) Other drugs currently under study aim to deliver increased selectivity for receptors in the bladder with decreased anticholinergic side effects. Alternative routes of administration, such as transdermal patch delivery of oxybutynin, are being tested in clinical trials. Oxybutynin patch has shown comparable efficacy to oral oxybutynin and comparable incidence of systemic side effects to placebo.²² Finding the right treatment for a specific patient may involve employing several methods and a detailed education plan. Helping a patient regain control over bladder function is an essential part in preserving his or her health.

TABLE 2 – COST COMPARISONS

DRUG	USUAL DOSE	COST PER MONTH*
Oxybutynin	5 mg bid-tid (max 20 mg/day)	\$8 - \$15
Oxybutynin XL (Ditropan XL®)	5-15 mg qd (max 30 mg/day)	\$70 - \$168
Tolterodine (Detrol®)	1-2 mg bid	\$83 - \$86
Tolterodine LA (Detrol LA®)	2-4 mg qd	\$75 - \$85

*costs are based on OMAP MAC, Fed MAC or AWP – 13% on July 1, 2002

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