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Clinical Differences Between Solifenacin and Tolterodine

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Abstract Overactive bladder (OAB) is characterized by involuntary detrusor contractions that result in bothersome urinary symptoms. The estimated US prevalence of OAB is 16% among men and 16.9% among women, comprising some 37.4 million Americans. The mainstay of treatment is medication. Although all drugs have variable degrees of efficacy and tolerability, several have emerged that yield good clinical results with tolerable side effects. This review focuses on two frequently prescribed drugs, solifenacin and tolterodine, and compares their clinical efficacy. A PubMed review was conducted with "solifenacin" and "tolterodine" as search words. Articles that compared the two medications were reviewed for content and number of study participants. Those with the most relevant findings and the highest number of participants were included. Both solifenacin and tolterodine show clinical efficacy for the treatment of OAB. Solifenacin seems to have better results in some series, with similar side effects. Antimuscarinic therapy is effective as OAB treatment. Both solifenacin and tolterodine have good clinical efficacy. However, in head—to-head trials, solifenacin seems to have somewhat better outcomes. Solifenacin, 5 mg, has less reported dry mouth than tolterodine, but at 10 mg, the incidence of dry mouth is similar.

Keywords Overactive bladder · Detrusor instability · Solifenacin · Tolterodine · Antimuscarinic antagonist · Antimuscarinic receptor · Urinary urgency · Urinary frequency

Clinical Trial Acronyms

NOBLE	National Overactive Bladder Evaluation
SOLAR	Solifenacin Alone and with Simplified Bladder Re-training
STAR	Solifenacin Versus Tolterodine Multinational Trial
SUNRISE	Solifenacin in the Treatment of Urgency Symptoms of OAB in a Rising Dose, Randomized, Placebo-Controlled, Double-Blind, Efficacy Trial
VECTOR	A Randomized Double-Blind Study to Assess the Safety and Efficacy of Solifenacin (Vesicare) in Comparison to Oxybutynin for Overactive Bladder Patients
VENUS	Vesicare Efficacy and Safety in Patients with Urgency Study
VERSUS	Vesicare Efficacy and Research Study US
VICTOR	Vesicare in Combination with Tamsulosin in OAB Residual Symptoms

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Introduction

Normal micturition is a complex physiologic process that usually results in acetylcholine (ACh) being released from postganglionic parasympathetic nerve terminals and subsequently activating postjunctional muscarinic receptors, leading to bladder contraction. However, the release of non-neuronal Ach directly from the urothelium as a result

of stretch is thought to activate the afferent C-fibers, leading to overactivity symptoms [1].

Overactive bladder (OAB) is a condition of the lower urinary tract characterized by involuntary detrusor contractions that can result in bothersome urinary symptoms for patients. OAB, as defined by the International Continence Society is "urgency, with or without urge incontinence, usually with frequency and nocturia" [2]. The NOBLE program found a prevalence of OAB of 16% among US men and 16.9% among US women, comprising some 37.4 million people [3]. With such a high prevalence of OAB, multiple medications have been formulated to target the release of non-neuronal Ach.

Mainstays of treatment of OAB include anticholinergic medications. Although five subtypes of muscarinic receptors exist (M1–M5), the M2 and M3 receptors are localized to bladder smooth muscle. M2 receptors are numerically more common; however, the M3 subtype is thought to provide the dominant driving force in smooth muscle contraction [4]. The M3 subtype is also localized to the salivary glands, leading to the common side effect of dry mouth noted by patients.

Although all medications have variable degrees of efficacy and tolerability in patients, several have emerged that yield good clinical results with tolerable side effects. This review focuses on two frequently prescribed drugs, solifenacin and tolterodine, and compares their clinical efficacy.

Solifenacin and Tolterodine

Approved by the US Food and Drug Administration in 2004, solifenacin is a muscarinic receptor antagonist shown in early chemical studies to have significantly greater receptor selectivity for the M3 subtype in the bladder than older drugs such as oxybutynin, tolterodine, and darifenacin [5].

Approved by the US Food and Drug Administration in 1998, tolterodine was the first of a new generation of anticholinergic medications that showed significant selectivity for muscarinic-type receptors in the urinary bladder over the salivary glands, resulting in a better side effect profile than those of traditional nonselective anticholinergics [6].

Published Efficacy Studies: Solifenacin

VENUS, a multicenter, randomized, double-blind, placebo-controlled trial of 739 patients with OAB, demonstrated the effectiveness of solifenacin in significantly reducing urgency episodes per 24-hour period when compared with placebo [6]. Additional subset analyses also showed significant improvement in patient-reported "warning time" improvement, from the first sensation of urgency to voiding, as measured by patients using stopwatches [7].

Cardozo et al. [8•] reported similar results from the SUNRISE trial, a randomized, double-blind, 16-week, placebo-controlled study of 863 patients with OAB lasting longer than 3 months. Additionally, SUNRISE showed significant decreases in incontinence and urgency-induced incontinence episodes.

Herschorn et al. [9] reported on the VECTOR trial, an 8-week, randomized, double-blind, double-dummy, multicenter Canadian study that compared the tolerability of solifenacin, 5 mg/d, with that of oxybutynin immediate release, 5 mg three times daily, in 132 patients. Both groups had improved health-related quality-of-life and efficacy scores; however, solifenacin had a significantly reduced side effect profile (dry mouth) and dropout rate secondary to side effects when compared with oxybutynin [9].

Yamaguchi et al. [10] reported on a 1584-patient, Japanese, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial that compared solifenacin with propiverine and placebo. At 12 weeks, solifenacin showed a significant reduction in mean voids per 24 h, urgency, urgency incontinence, and incontinence episodes when compared with placebo, but this was not significant compared with propiverine. However, solifenacin was found to induce significantly less dry mouth than propiverine.

Solifenacin in Male Overactive Bladder

Most published studies have evaluated OAB in women, or in men and women combined. Fewer data are available on the effectiveness of OAB medications in men only. Kaplan et al. [11•] performed a subset analysis of men from current open-label studies of solifenacin and showed significant improvements in patient perception of bladder condition and Overactive Bladder Questionnaire (OAB-q) results after 12 weeks of treatment.

In the VICTOR study, a 12-week, double-blind, placebo-controlled trial assessing the safety and tolerability of solifenacin plus tamsulosin, men with OAB and bladder outlet obstruction who did not improve after 4 weeks of treatment with tamsulosin were given solifenacin to treat residual OAB symptoms [12]. Kaplan et al. [12] found that the addition of solifenacin significantly reduced urgency episodes, but not frequency. Importantly, the combination therapy was associated with a very low rate of urinary retention requiring catheterization (three patients).

Published Efficacy Studies: Tolterodine

As with solifenacin, many studies have described the efficacy of tolterodine in treatment of OAB. A double-blind, placebo-controlled study of 854 women by Khullar et al. [13] revealed significant reductions in urge, urge incontinence, and frequency in women treated with tolterodine extended release at 8 weeks as compared with placebo. Overall, tolterodine extended release yielded significant improvement in 9 of 10 quality-of-life domains [13].

When tolterodine was first approved, comparison studies were done with the most commonly used anticholinergic on the market at that time, oxybutynin. Many studies supported the use of tolterodine over oxybutynin, citing fewer side effects and better tolerability [14]. In a meta-analysis conducted by Novara et al. [15•] that explored randomized controlled trials of antimuscarinic agents in the treatment of OAB, tolterodine immediate release was found to have a superior side effect profile compared with oxybutynin immediate release. Interestingly, however, the extended-release formulations of both drugs were found to be similar [15•].

Peeker et al. [16] reported on a prospective, observational study of 235 Swedish patients treated with tolterodine extended release and assessed by the OAB-q at baseline and at 3 and 6 months. They found a significant increase in the OAB-q quality-of-life scale and subscales at 3 and 6 months. Additionally, they noted a significant reduction in pad use at both 3 and 6 months. However, by 6 months, 50% of patients discontinued the medication due to adverse reactions (53%), insufficient improvement (23%), another treatment (10%), or for another reason (35%).

In addition to improvement in OAB symptoms, newer studies using current perception threshold testing indicate that tolterodine may improve symptoms not only by receptor activity, but also by improving urethral sensation [17].

Tolterodine in Male Overactive Bladder

As with solifenacin, few studies on the use of tolterodine in men have been completed. That noted, tolterodine has been evaluated in combination studies in men with large prostates and bladder outlet obstruction combined with OAB. Chung et al. [18] conducted an open-label study of tolterodine in 51 men with International Prostate Symptom Scores greater than 12, frequency greater than 8 voids/24 h, and prostates heavier than 30 g who had been taking dutasteride for at least 6 months and failed a trial of α-blockers. They found a significant decrease in International Prostate Symptom Scores and daytime and nighttime urgency without decreases in flow rates or increases in postvoid residuals [18].

Similar findings have been reported for tolterodine in combination with tamsulosin [19]. A multicenter, double-blind, randomized study of 879 men by Kaplan et al. [19] showed that men on combination therapy had significant improvements in urinary urgency, urge incontinence, frequency, and nocturia. Combination therapy was well-tolerated.

Solifenacin and Tolterodine With Behavioral Treatment

Mattiasson et al. [20] reported the results of the SOLAR trial, a 643-patient, randomized, open-label trial of solifenacin with or without simplified bladder training. Bladder retraining was achieved via a single instruction sheet given to patients without any medical supervision or follow-up as to whether it had been implemented. Despite this, a significant reduction in micturition frequency and an increase in patient satisfaction were seen in the bladder retraining groups at 8 and 16 weeks, with no impact on urgency or incontinence.

Similar to the Mattiasson et al. [20] study, Klutke et al. [21] reported on significant improvement in patient quality of life and satisfaction in their 16-week, open-label trial of a population of 416 patients treated with tolterodine extended release plus behavioral intervention. In their study, all recruited patients reported dissatisfaction with prior antimuscarinic treatment alone (tolterodine or other antimuscarinic medication). Patients received a two-page handout on voiding, as well as reinforcement by study staff at 8 and 12 weeks without any formal biofeedback. By week 16, 91% of patients reported some satisfaction with the combined treatment, and 64% reported being very satisfied.

These studies support that antimuscarinic therapy alone, regardless of the type of antimuscarinic, may not be enough to treat all patients. Other treatment approaches, alone or in combination with medication, should be considered in certain patient groups.

Solifenacin in Children

Outside the traditional age groups, children with OAB may also benefit from anticholinergic treatment regimens. Bolduc et al. [22] conducted a prospective, open-label, randomized trial of solifenacin using a modified dosing regimen in 72 children with a mean age of 9 years at enrollment and observed for an average of 15 months. This trial included children without correctable neurological abnormalities who had failed behavioral and medical

Table 1 Comparison studies of solifenacin and tolterodine

Study	Patients, *n*	Change in number of voids			Change in urgency episodes			Change in incontinence episodes (urge incontinence or incontinence not otherwise specified)			Nocturia episodes		
		Sol vs base	Tol vs base	Sol vs tol	Sol vs base	Tol vs base	Sol vs tol	Sol vs base	Tol vs base	Sol vs tol	Sol vs base	Tol vs base	Sol vs tol
Chancellor et al. [26] (2008)[a]	441	−2.3	−0.7[b]	−1.3 (P<0.0001)	−4.2	−1[b]	−3.3 (P<0.0001)	−2.6	−0.7[b]	−1.3 (P<0.0001)	−0.8	−0.1[b]	−0.7 (P<0.0001)
Choo et al. [29] (2008)[c]	329	−2.47	−2.14	NS	−2.35	−2.2	NS	−1.84	−1.02	NS	−0.6	−0.54	NS
Swift et al. [25] (2009) (VERSUS)[d]	440	−2.26	−0.67[b]	−1.57 (P<0.05)	−4.21	−0.83[b]	−3.41 (P<0.05)	−2.6	−0.75[b]	−1.86 (P<0.05)	−0.75	−0.07[b]	−0.72 (P<0.05)
Chapple et al. [27] (2007) (STAR)[e]	1177	−2.47	−2.49	NS	−3.08	−2.62	NS	−1.46	−1.03	NS	−0.72	−0.69	NS

[a] Trial of solifenacin, 5 or 10 mg, vs tolterodine extended release, 4 mg (12-week result)

[b] Pre- to post-washout change

[c] Trial of solifenacin, 10 mg, vs tolterodine, 2 mg twice daily

[d] Trial of solifenacin, 5 or 10 mg, vs tolterodine extended release, 4 mg (12-week result)

[e] Trial of solifenacin, 2.5 to 20 mg, vs tolterodine, 2 mg twice daily (12-week result)

Base baseline; *NS* not significant; *Sol* solifenacin; *STAR* Solifenacin Versus Tolterodine Multinational Trial; *Tol* tolterodine; *VERSUS* Vesicare Efficacy and Research Study US

therapies (oxybutynin and/or tolterodine). They found that patients treated with solifenacin had significantly greater urodynamic capacity with reduced uninhibited contractions and improved dryness, with only four dropping out secondary to drug side effects [22].

A study evaluating tolterodine in children with stable neurological disease showed similar good results. Thirty children with urodynamics-confirmed bladder overactivity were enrolled, with drug formulation and dosing determined by age. Treatment with tolterodine led to decreases in number of incontinence episodes and number of intermittent catheterizations in a 24-hour period. Mean catheterized volumes increased in all participants. The treatment formulations were well-tolerated with good long-term efficacy and safety (≥12 months) [23].

Solifenacin and Tolterodine in Older Adults

Unfortunately, very few studies of solifenacin or tolterodine in the frail older adult population exist [24]. There are data to suggest that antimuscarinic therapy in older adults should be used with caution. Further studies need to be conducted to determine the safety in this patient group—a group that can suffer greatly from OAB.

Solifenacin as Compared With Tolterodine

Table 1 compares several large studies of solifenacin and tolterodine and notes the efficacy differences, if any.

A post hoc analysis of severely overactive patients enrolled in the VERSUS trial revealed better improvement in symptoms among patients who had been taking tolterodine extended release. These patients self-reported severe symptoms and wished to change from tolterodine extended release to solifenacin after at least 4 weeks of therapy. After a minimal 2-week washout period, patients began therapy. Diary-documented improvements were seen in urge, urge incontinence, frequency, nocturia, and nocturnal voids compared with prewashout diary results. The solifenacin treatment was well-tolerated, and only 4.3% (5 of 116 patients) discontinued therapy [25].

A similar study evaluating patients who chose to try solifenacin after a trial of tolterodine extended release due to persistent urgency was conducted by Chancellor et al. [26•]. Statistically significant differences were noted with regard to urge episodes, total number of daily voids (including at night), and total incontinence and nocturia episodes from prewashout to study end. The patient perception of bladder condition scores had a mean improvement of 1.2 points. Tolerability was similar to that of other studies, with dry mouth being the most common complaint (17.5%).

The STAR study was a prospective, double-blind, double-dummy, two-arm, parallel-group, 12-week study comparing the safety and efficacy of solifenacin with those of tolterodine extended release. Patients on solifenacin showed significantly better improvements in incontinence episodes and pad usage [27]. The mean volume per void was higher in both tolterodine- and solifenacin-treated patients, and the mean number of voids per 24 h decreased for both medications [28]. The reported incidence of dry mouth was similar.

A Korean study similar to the others comparing solifenacin with tolterodine in a randomized, prospective, double-blind, multicenter fashion revealed improvements in patients treated with both medications. All recorded voiding parameters improved on treatment, regardless of medication. However, the onset to symptom improvement occurred the most quickly among patients receiving solifenacin, 10 mg. Tolerability was acceptable, with solifenacin, 5 mg, having the lowest incidence of dry mouth [29].

Conclusions

Based on published studies and those presented in this article, antimuscarinic therapy has been shown to be effective in the treatment of OAB in men, women, and children. Both solifenacin and tolterodine have good clinical efficacy. However, in head-to-head trials, solifenacin appears to yield somewhat better outcomes. Solifenacin, 5 mg, has less reported dry mouth than tolterodine, but at 10 mg, the difference in the incidence of dry mouth is similar.

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