Research Review

Solifenacin (Vesicare®) review

About the commenter -

Dr Sharon English

Sharon English is a consultant urologist at Christchurch Public Hospital, and works privately with Urology Associates. Her areas of specialty include female urology, urodynamics and neurourology. Sharon completed a fellowship in female urology and reconstructive urology with Dr Ed McGuire in Houston, Texas. Her research interests now include a number of Phase III trials on new medications for overactive bladder syndrome, in addition to researching the use of botulinum toxin in neuropathic bladders.

Dr Con Kelleher

Con Kelleher attended King's College Hospital School of Medicine, London, UK. He completed a research fellowship in Urogynaecology at King's College Hospital under the supervision of Professor Linda Cardozo. During this time he completed his MD thesis to assess the impact of urinary incontinence on the quality of life of women. During the course of his research he enrolled more than 1,000 women into the study, culminating in the design and validation of a condition-specific quality-of-life questionnaire, the King's Health Questionnaire. This instrument is now used worldwide to assess the quality of life of women with urinary symptoms in both clinical trials and clinical practice.

Dr Kelleher is currently a consultant in Obstetrics and Gynaecology at Guy's and St. Thomas' Hospitals Trust. He has published a number of peer-reviewed articles and book chapters on the topic of urinary incontinence and quality of life, and has presented the results of his studies both nationally and internationally. Dr Kelleher is a member of the Royal Society of Medicine, the International Continence Society, and the International Urogynecological Association.

Overactive Bladder Syndrome

Overactive bladder (OAB) syndrome is defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.[1] Symptoms of OAB are highly prevalent in the general population: epidemiological surveys conducted in Europe[2] and the US[3] found the incidence of OAB symptoms in adults to be approximately 16%, and increased with age. Extrapolation of these data to the New Zealand population suggest as many as 600,000 people may be affected by OAB. Symptoms of OAB can be extremely distressing to the individual and can have a significant negative impact on quality of life.[2,4] In addition, OAB is associated with increased risk of injury in a fall.[5] The syndrome is therefore associated with high social and economic costs.[6]

Current Treatment Approaches

Treatment approaches to OAB include:

- Behavioural interventions (e.g. pelvic floor exercises, bladder training, control of fluid consumption, elimination of dietary irritants)
- Pharmacological interventions (e.g. anticholinergic agents)
- Surgical interventions (e.g. insertion of a sacral nerve stimulator).

Anticholinergic agents are the treatment of choice for OAB.[7] They effectively relax bladder muscle but their use may be limited by adverse effects associated with generalised cholinergic blockade, such as dry mouth, constipation, drowsiness and blurred vision.[8]

About solifenacin

Solifenacin is an anticholinergic agent that has shown selectivity for bladder tissue over salivary glands in in vitro and in vivo studies.[9,10] General results from clinical trials indicate that solifenacin reduces key symptoms of OAB and increases the urinary volume voided. In addition, the drug is well tolerated (dry mouth is the most frequently reported event) and is associated with high rates of compliance.[11]

Solifenacin was launched in NZ in December 2006 for the treatment of patients with OAB syndrome but is not currently subsidised. The recommended adult dose of solifenacin is 5mg orally once daily, which can be increased to 10mg once daily if needed.[11]

This publication provides an independent summary of some key solifenacin studies together with comments from a New Zealand specialist indicating their conclusions from the studies and the implications for treatment in New Zealand. It is intended to provide health professionals with a concise review of advancing clinical practice in the area.

Foreword - Dr Con Kelleher

Overactive bladder (OAB) is a common and costly condition affecting up to 16% of the adult population, and increasing in prevalence with advancing age. OAB is defined by the symptom of urgency, a distressing and disabling symptom of loss of bladder control resulting in frequent toileting, embarrassing urgency incontinence and for some patients nocturnal wakening to pass urine or nocturnal enuresis. Patients become socially isolated for fear of urinary leakage, their work and domestic lives suffer and they have reduced self esteem. Quality of life studies have shown a significant impairment in the lives of sufferers and studies of emotional wellbeing have shown significant levels of both anxiety and depression amongst affected patients.

The most effective treatment of OAB involves the avoidance of known bladder irritants such as fizzy drinks and caffeine, exercises to teach improved bladder control and the prescription of antimuscarinic drug therapy. These drugs have the drawback of varying degrees of side effects such as dryness of the mouth or constipation which can affect their tolerability and is to some extent dependent on their selectivity for M3 type muscarinic receptors in the bladder. Whilst of a similar drug class not all antimuscarinics are equally efficacious in treating OAB symptoms.

Solifenacin (Vesicare) is a new once daily, relatively M3 selective, long acting antimuscarinic, available in two titratable (5 and 10mg) dosage strengths. Patients usually commence on the lower dosage although studies have shown that 50% (usually those with worse baseline symptoms) require dose escalation to 10mg once daily. Tolerability is excellent with 81 % of patients continuing treatment in a long term 40 week clinical trial with minimal side effects. Solifenacin is effective for patients with both OAB and mixed incontinence, and has both class leading tolerability and efficacy. Placebo controlled studies have shown significant improvement in all of the symptoms of OAB and improvement in the quality of life of treated patients. Of particular note were the very high levels of bladder control amongst patients and improvement in the symptoms of urgency and urgency incontinence which are undoubtedly the most troublesome symptom for patients. The manufacturers of solifenacin were so convinced regarding the efficacy of solifenacin that they conducted a head to head trial versus the market leading drug tolterodine (ER) (STAR study) shortly after its launch in Europe and the United States of America. The STAR study demonstrated superior efficacy for solifenacin in treating the cardinal symptoms of OAB.

At the present time of its introduction solifenacin may not be reimbursable in New Zealand. An important point to consider however when treating OAB is whether the patient would want, the most efficacious and tolerable or the cheapest drug therapy. Ultimately if cheaper alternatives are less well tolerated and less efficacious cost effectiveness may prove in favour of the most effective treatment and reimbursement options may need to be reconsidered.

Solifenacin[12]

Authors: Kreder KJ.

Summary: Solifenacin is a tertiary amine with antimuscarinic properties. The pharmacokinetics of solifenacin are such that it is suitable for once daily dosing, and steady state plasma concentrations are reached after 10 days. Studies in animals indicate that the effects of solifenacin on M3 muscarinic receptors may be selective for the bladder rather than salivary glands. The drug is primarily metabolised in the liver by cytochrome P450 (CYP) 3A4 enzymes so it may potentially interact with CYP3A4 inducers or inhibitors.

Clinical trials have shown that solifenacin 5 and 10mg once daily significantly reduces urinary urgency and incontintence episodes from baseline in patients with OAB symptoms ($p < 0.001$ vs placebo), and reduces micturition frequency as effectively as tolterodine. In a long-term trial, 60% of patients who had urge incontinence at baseline were dry after 1 year's treatment with solifenacin, and 74% considered efficacy to be satisfactory. The drug has also been reported to improve Quality of Life (QoL) in patients with OAB.

Dry mouth is the most frequently reported adverse events in solifenacin recipients: after 1 year's treatment with solifenacin 5 or 10mg once daily, mild, moderate or severe dry mouth was reported by 14.4%, 5.0% and 1.3% of patients, respectively. Mild constipation (5.9%) and mild blurred vision (5.2%) were also reported.[12]

Comment: This article is a review of the mechanism of action of solifenacin and the results of a number of clinical trials. Solifenacin is a selective antimuscarinic medication with affinity for the M3 receptor found in the bladder. These are also found to a lesser amount in the intestinal tract and salivary glands. Dry mouth constipation and blurry vision are the commonest reported side-effects. Solifenacin's half-life is increased in those with severe renal impairment and moderate hepatic impairment. Solifenacin does not affect the metabolism of warfarin or digoxin. Solifenacin at doses of 5mg and 10mg once daily is an effective and well tolerated treatment for overactive bladder.

Improved quality of life in patients with overactive bladder symptoms treated with solifenacin[13]

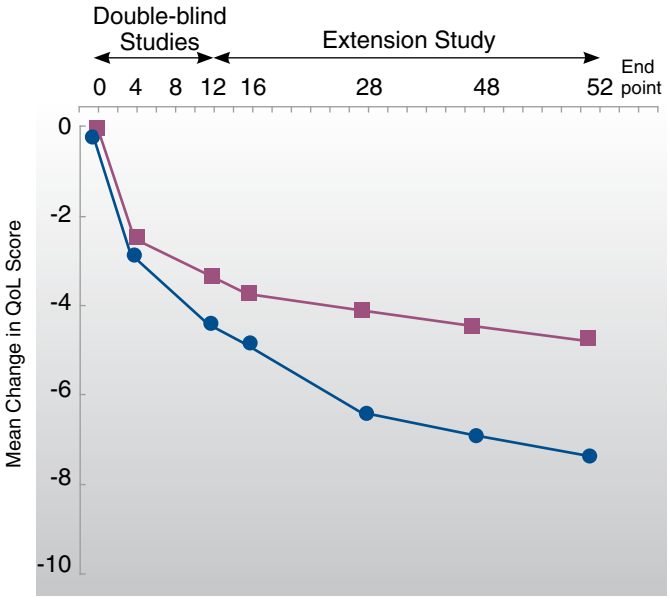
Authors: Kelleher CJ, Cardozo L, Chapple CR et al.

Summary: Solifenacin 5 or 10mg once daily improved measures of QoL in adult men and women with overactive bladder (OAB) treated for up to 1 year.

Method: 1984 men and women participated in two 12-week randomised, double-blind, placebo-controlled studies which examined the efficacy of solifenacin 5 or 10mg once daily for OAB symptoms. 1637 of these patients then took part in a 40-week open-label extension. Ten domains of the King's Health Questionnaire were used to determine the effects of solifenacin on QoL in these studies.

Results: Pooled QoL data from the 12-week studies (1033 evaluable patients) showed that both dosages of solifenacin once daily significantly improved general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, sleep/energy, severity measures and symptom severity compared with placebo. Differences from placebo were similar for each solifenacin dosage. The open-label extension (1347 evaluable patients) showed that solifenacin improved all QoL domains (except personal relationships) from baseline. General health perception improved by 17%, while the other domains improved by 35-48%.[13]

Comment: Overactive bladder syndrome has a profound negative impact on quality of life including social, physical, psychological, occupational and sexual domains. In this study QoL was assessed using a disease-specific questionnaire – King's Health Questionnaire (KHQ). Pooled data from 1890 patients in two large 12 week placebo controlled studies showed improvements in nine of the ten domains assessed including improvement in role limitations, emotions, incontinence impact and sleep/energy. The only domain that did not improve was personal relationships. This improvement was maintained during the open label extension study.



Change in KHQ domain scores for general health (blue) and symptom severity (purple) with time for the original double-blind studies (solifenacin only) and the 40-week extension study.

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Randomized, double-blind placebo and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder[14]

Authors: Chapple CR, Rechberger T, Al-Shukri S, et al., on behalf of the YM-905 study group.

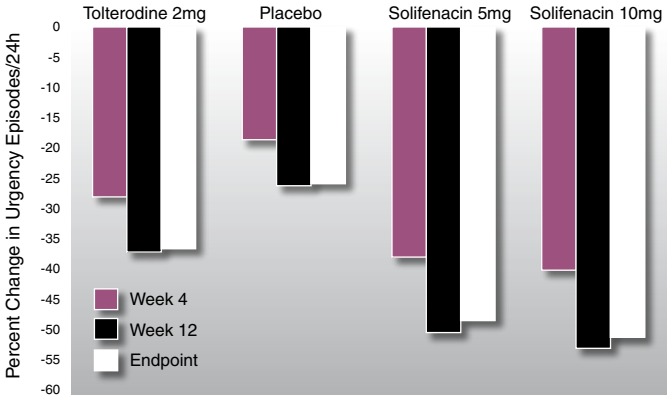
Summary: Solifenacin 5 or 10mg once daily effectively reduced urgency and other symptoms in patients with OAB in a multicentre, randomised, double-blind study.

Method: Men and women who had symptoms of OAB during a 3-day diary period (≥8 voids/24h and ≥3 episodes of urgency and/or 3 episodes of incontinence) at the end of a 2-week placebo run-in period were randomised to receive solifenacin 5mg once daily, solifenacin 10mg once daily, tolterodine 2mg twice daily or placebo for 12 weeks in a double blind, double-dummy manner. Of 1081 randomised patients, 1033 patients were evaluated for efficacy.

Results: 12 weeks' treatment with solifenacin 5mg and 10mg once daily significantly reduced the mean number of urgency episodes in 24h by 2.85 (52%) and 3.07 (55%), respectively, from baseline (both $p < 0.001$ vs placebo). Two-thirds of the final effect was evident at week 4. Tolterodine reduced mean urgency episodes in 24h by 2.05 (38%) during the 12-week period but this was not statistically significant; placebo caused a 33% reduction. Both solifenacin dosages caused significant reductions in incontinence and urge incontinence episodes/24h, mean voids/24h and mean volume voided compared with placebo.

Dry mouth was reported by 4.9% of placebo, 14.0% of solifenacin 5mg once daily, 21.3% of solifenacin 10mg once daily and 18.6% of tolterodine 2mg twice daily recipients, respectively. Withdrawal rates attributed to adverse events were low for both solifenacin dosages (<4%) and similar to that for placebo.[14]

Comment: This was one of the first studies to assess the efficacy of solifenacin in doses of 5mg and 10mg. This study also compared solifenacin to tolterodine. This was a multicentre international study with 5 centres in New Zealand involved in the research. Treatment with solifenacin resulted in a statistically significant decrease in all incontinence episodes. This was also seen with tolterodine. Number of voids per day also decreased. The reduction was greatest in those treated with 10mg of solifenacin. Treatment with solifenacin was well tolerated with only 2.9% withdrawing because of adverse events. The commonest side-effect was dry mouth which occurred in 14% and 21% at doses of 5mg and 10mg respectively. 18% of those treated with tolterodine complained of a dry mouth as did 5% in the placebo group. A smaller number in the treatment groups also reported constipation and blurred vision. The study concludes that solifenacin at 5mg or 10mg is an effective treatment for overactive bladder syndrome with a low incidence of side-effects.



Percentage change from baseline to endpoint demonstrates two-thirds of the effect obtained after 12 weeks of treatment is evident by 4 weeks.

A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial[15]

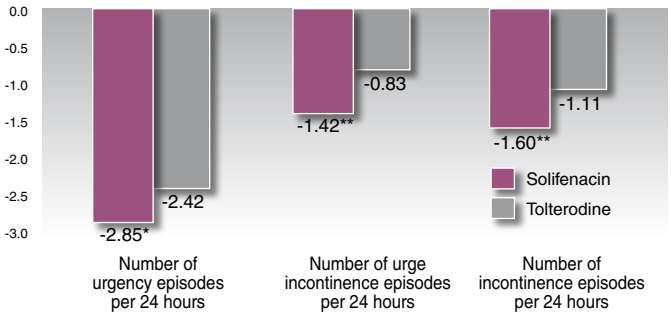
Authors: Chapple CR et al.

Summary: Solifenacin was more effective than extended release tolterodine at decreasing urgency episodes and other symptoms of overactive bladder in this well-controlled multicentre trial.

Method: 1177 patients who fulfilled study criteria for overactive bladder syndrome were randomised to solifenacin 5mg once daily or extended release tolterodine 4mg once daily for 12 weeks in a double-blind, double-dummy manner. Solifenacin dosage was doubled at week 4 if necessary.

Results: Improvements in urgency, urge incontinence and overall incontinence from baseline were significantly greater with solifenacin than with tolterodine but reductions in micturitions per 24h were similar between groups. 74% of solifenacin versus 67% of tolterodine recipients who were incontinent at baseline had a ≥50% reduction in incontinence episodes by week 12 ($p = 0.021$).[15]

Comment: This large study compares two different anticholinergic medications that are currently available. Both medications were effective in decreasing the number of incontinent episodes, nocturia and pad usage. Solifenacin decreased the urgency and urge incontinence slightly more than tolterodine. Half the patients in each group requested to go onto a higher dose. The tolterodine remained on the same dose (4mg is maximum daily recommended dose) and the solifenacin group increased to 10mg daily. There were slightly more side-effects of dry mouth and constipation in the solifenacin group though very few patients (2% and 1.2%) withdrew because of side-effects. This study demonstrated both medications are useful for the treatment of overactive bladder.



*p<0.05, **p<0.01

Mean baseline to endpoint change in overactive bladder symptoms.

Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence[16]

Authors: Kelleher C, Cardozo L, Kobashi K, Lucente V.

Summary: Once daily solifenacin was as effective and well tolerated in patients with mixed urinary incontinence (MUI) as it was in urge urinary incontinence (UUI) in this analysis of pooled data from 4 randomised, double-blind phase III studies of patients with OAB.

Method: Men and women with OAB were classified as having either MUI or UUI based on history and a cough test and all underwent a 2-week placebo run-in period. In 2 of the studies patients were randomised to solifenacin 10mg once daily or placebo for 12 weeks. In the other 2 studies patients were randomised to solifenacin 5 or 10mg once daily, placebo or tolterodine 2mg twice daily for 12 weeks. The tolterodine treatment arm was not included in the present analysis. In total, 2689 patients with UUI (61%) or urge predominant MUI (39%) were eligible for analysis.

Results: Solifenacin 5 and 10mg once daily significantly reduced incontinence episodes, micturition frequency and urgency from baseline in both the UUI and MUI cohorts. Both solifenacin dosages also increased the urinary volume voided in each cohort ($p < 0.01$ vs placebo) after 12 weeks. A greater proportion of solifenacin recipients (UUI and MUI) achieved resolution of incontinence compared with placebo after 12 weeks.[16]

Comment: 50% of women with urge incontinence also have stress incontinence (mixed urinary incontinence). This study reviewed the results of four large randomized placebo controlled studies to see if patients with MUI had the same improvement in incontinence episodes and frequency as those with pure UUI. Often the urge incontinence component of MUI is more troublesome as it is more unpredictable and may be of larger volume. 43% of patients with MUI had resolution of their incontinence compared with 55% with UUI. Urgency improved in 29% and 31% respectively on 5mg solifenacin daily. Urinary frequency returned to normal in 31% of patients with MUI and 33% with UUI. Antimuscarinic therapy is commonly used in patients with mixed forms of urinary incontinence. This study confirms that they will benefit from having the urge component treated.

	Patients acheiving continence	
	MUI	UUI
Placebo	33%	35%
Solifenacin (5mg)	43%	55%*
Solifenacin (10mg)	49%*	54%*

* p<0.001 vs placebo

Percentage of patients achieving continence in both mixed urinary incontinence (MUI) and urge urinary incontinence (UUI) with Solifenacin 5mg and 10mg vs placebo at study endpoint.

When to use antimuscarinics in men who have lower urinary tract symptoms[17]

Authors: Lee JY, Kim DK, Chancellor MB.

Summary: Men who have bladder outlet obstruction due to benign prostatic hyperplasia (BPH) often have coexisting detrusor overactivity. Symptoms for bladder outlet obstruction are similar to those for detrusor overactivity so diagnosis based on clinical presentation can be difficult and urodynamic diagnosis may be necessary.

Not all men with lower urinary tract symptoms achieve relief after treatment with α-blockers alone. Some clinicians avoid the use of antimuscarinics in men with bladder outlet obstruction because these drugs can potentially reduce detrusor contractility thereby increasing the risk of acute urinary retention. However, it has been shown in a number of clinical trials that the addition of an antimuscarinic agent to an α-blocker in men with OAB and bladder outlet obstruction improves outcomes and QOL without having a detrimental effect on urinary flow.

Preliminary evidence from an open-label study indicates that antimuscarinic monotherapy may also be an option in the treatment of lower urinary tract symptoms secondary to BPH.[17]

Comment: Lower urinary tract symptoms in men are believed to mainly originate from benign prostate hyperplasia causing bladder outlet obstruction. However many men will have symptoms of overactive bladder as well as bladder outlet obstruction (BOO) complaining of urgency, frequency and nocturia as well as decreased flow and nocturia. Antimuscarinics are often avoided in older men because of concern of causing urinary retention however a number of clinical trials have shown immediate release anticholinergics did not significantly affect urinary flow or detrusor function. These showed there was improvement in storage symptoms including voiding frequency and urgency when used in combination with doxazosin. It is not necessary to perform bladder function tests such as urodynamics prior to starting treatment. In those men that did go into urinary retention it resolved with stopping the antimuscarinic medication.

References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Urology 2003; 61 (1): 37-49
2. Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU International 2001; 87: 760-766
3. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003; 20: 327-336
4. Abrams P, Kelleher CJ, Kerr LA, et al. Overactive bladder significantly affects quality of life. Am J Manag Care 2000; 6 (Suppl. 11): S580-90
5. Wagner TH, Hu TW, Bentkover J, et al. Health-related consequences of overactive bladder. Am J Manag Care 2002; 8: S598
6. Hu TW, Wagner TH, Bentkover JD, et al. Estimated economic costs of overactive bladder in the United States. Urology 2003; 61: 1123
7. Chapple CR. Muscarinic receptor antagonists in the treatment of overactive bladder. Urology 2000; 55 (Suppl. 5A): 33-46
8. Garely AD and Burrows LJ. Current pharmacotherapeutic strategies for overactive bladder. Expert Opin Pharmacother 2002; 3: 827
9. Kobayashi S, Ikeda K, Miyata K. Comparison of in vitro selectivity profiles of solifenacin succinate (YM905) and current antimuscarinic drugs in bladder and salivary glands: a Ca2+ mobilization study in monkey cells. Life Sci 2004; 74 (7): 843-53
10. Ohtake A, Ukai M, Hatanaka T, et al. In vitro and in vivo tissue selectivity profile of solifenacin succinate (YM905) for urinary bladder over salivary gland in rats. Eur J Pharmacol 2004; 492 (2-3): 243-50
11. Vesicare Data sheet Feb 2006. CSL (New Zealand) Limited.
12. Kreder KJ, Solifenacin. Urol Clin N Am 2006; 33: 483-490
13. Kelleher CJ, Cardozo L, Chapple CR, et al. Improved quality of life in patients with overactive bladder symptoms treated with solifenacin. BJU International 2005; 95: 81-85
14. Chapple CR, Rechberger T, Al-Shukri S, et al., on behalf of the YM-905 study group. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU International 2004; 93: 303-310
15. Chapple CR, Martinez-Garcia R, Selvaggi L, et al. for the STAR study group. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. European Urology 2005; 48: 464-470.
16. Kelleher C, Cardozo L, Kobashi K, Lucente V. Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence. Int Urogynecol J 2006; 17: 382-388
17. Lee JY, Kim DK, Chancellor MB. When to use antimuscarinics in men who have lower urinary tract symptoms. Urol Clin N Am 2006; 33: 531-537

This publication has been created with an educational grant from CSL Biotherapies (NZ) Ltd.
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