Journal of
Gynecology and Women's Health
ISSN 2474-7602

Juniper Publishers
key to the Researchers

Case Report
Volume 7 Issue 1 - September 2017
DOI: 10.19080/JGWH.2017.07.555703

J Gynecol Women's Health

Key Findings of the SUNRISE Study

Ganesh Thiagamoorthy*, Linda Cardozo and Sushma Srikrishna

Department of Urogynaecology, King's College Hospital, England

Submission: September 07, 2017 ; **Published:** September 18, 2017

***Corresponding author:** Gans Thiagamoorthy, Department of Urogynaecology, Urogynaecology Subspecialty Trainee, King's College Hospital, London, England, Email:gans.t@nhs.net

Abstract

This article summarises the findings of the SUNRISE (solifenacin in the treatment of urgency symptoms of OAB in a rising dose, randomised, placebo-controlled, double blind, efficacy) study. SUNRISE was a multicentre study carried out between April 2004 to October 2005. Powered at 80% for urgency severity as the primary outcome measure, 616 participants were required. Eight hundred and sixty three patients were recruited from 14 European countries.

At 8 weeks, mean compliance was >98% and 46.5% of patients randomised to solifenacin requested a dose increase, compared to 65.8% in the placebo group. There was greater improvement in reduction of severe urgency episodes and other outcome measures from week 8 to 16 in those who requested a dose increase and were randomised to 10mg than those who randomised to continue on 5mg.

The study found that not only was Solifenacin better than placebo, those who felt they needed dose escalation benefitted more from a dose increase than those who were given a placebo increase.

Keywords: Overactive bladder; Detrusor overactivity; Urgency; Incontinence;Treatment

Disclosures: Mr G Thiagamoorthy: Sponsored to attend scientific meetings by Astellas UK. In receipt of an IUGA FRN Grant to conduct a multicentre RCT. Prof Cardozo has recently acted in the following roles Consultant / Speaker / Researcher for Allergan, AMS, Astellas, Pfizer, Teva.

Introduction

Overactive bladder (OAB) syndrome is defined as urinary urgency, usually accompanied by increased urinary frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [1]. Detrusor overactivity (DO) is the occurrence of involuntary detrusor contractions during filling cystometry [1]. These involuntary contractions are mediated by acetylcholine induced stimulation of bladder muscarinic receptors and may be the cause of OAB. OAB and DO are not synomous however. Less than 60% of women with OAB have DO and 36% of adults with DO do not suffer OAB [2,3].

OAB is a common problem with an estimated prevalence of 17% in Europe and the US [4,5]. It has a significant effect on patients' quality of life and has been shown to increase their risk of falls, fractures, urinary tract and skin infections [6]. The National Institute for Health and Care Excellence (NICE) has recommended that the first line treatment of OAB should be conservative management with bladder retraining [7]. Despite bladder retraining, many patients still require drug therapy and antimuscarinics are currently the mainstay of treatment. Due to the side effect profile of antimuscarinics the persistence of patients on these drugs for OAB is poor. Studies have found adherence to treatment at 6 months was 18-28% for OAB drugs, whereas persistence with oral hypoglycaemic for diabetes was 66% over the same period [8,9].

Solifenacin is an antimuscarinic drug which has a propensity to block the M3 receptor. This article aims to summarise the findings of the SUNRISE (solifenacin in the treatment of urgency symptoms of OAB in a rising dose, randomised, placebo-controlled, double blind, efficacy trial) study [10,11]. SUNRISE was a multicentre study carried out between April 2004 to October 2005. Eight hundred and sixty three patients were recruited from 105 centres in 14 European countries. The study was the first study to consider urgency severity as the primary endpoint. The authors of the SUNRISE study attempted to mirror real life treatment of OAB using a randomised dose escalation model (Figure 1). Each patient was given 2 tablets each day to maintain blinding: two placebo tablets; one placebo and one 5mg

tablet; or two 5mg tablets depending on the arm randomised to and the point in the study. Those who were initially randomised to placebo and at week 8 requested a dose increase, were given two placebo tablets again to ensure continuity of the double blinding. These doses were continued until the end of the study, week 16.

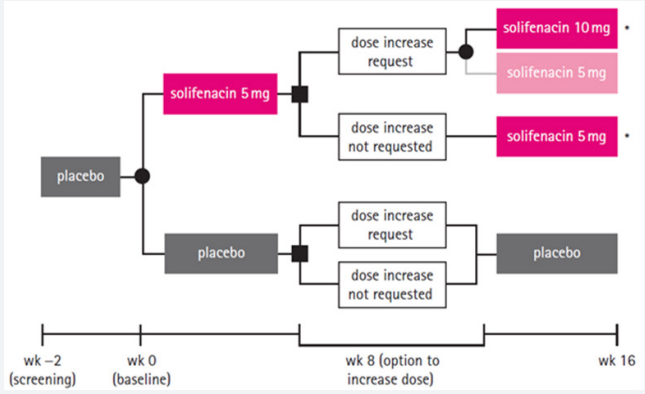

Figure 1: SUNRISE study plan. Efficacy data are presented for patients in the placebo.

Urgency is the driving force of the OAB and the only symptom required to make the diagnosis. With this in mind, the primary outcome measure was a validated urgency assessment tool, the Patient Perception of Intensity of Urgency Scale (PPIUS) (Table 1). PPIUS grades 3 and 4 represent severe urgency and urgency incontinence respectively. Powered at 80% for the primary outcome measure, the study required 616 participants. Patients completed a number of secondary outcome measures including:-

Table 1: Patient Perception of Intensity of Urgency Scale (PPIUS).

okScore	Description
0	No need to empty my bladder but did for other reasons
1	Could postpone voiding as long as necessary without fear of wetting myself
2	Could not postpone voiding for a short time without fear of wetting myself
3	Could not postpone voiding so had to rush to the toilet to not wet myself
4	Leaked before arriving at the toilet

A. Patient Perception of Bladder Condition (PPBC),

B. Total urgency score

C. Maximum urgency intensity

D. Micturition frequency

E. Speed of onset of action was measured using a 7 day diary in the first week of treatment.

F. Urgency bother visual analogue scale (UB-VAS)

G. Treatment satisfaction visual analogue scale (TS-VAS)

Men and women were invited to participate who had OAB symptoms for ≥3 months and three or more episodes of urgency in the last 3 days, as long as they could correctly complete the questionnaires. Outcome measures were assessed at various points between 0 and 16 weeks from treatment.

At 8 weeks, mean compliance was >98% and 46.5% of patients randomised to solifenacin requested a dose increase, compared to 65.8% in the placebo group. It should be noted that 34.2% of patients taking the placebo tablets did not request a dose increase at this stage, highlighting the significant impact of the placebo effect in this population. At 16 weeks, the end of the trial, there were statistically significant differences in favour of solifenacin 5 or 10mg over placebo for all primary and secondary outcome measures (Figure 2). Solifenacin was also significantly more effective than placebo as early as Day 3.

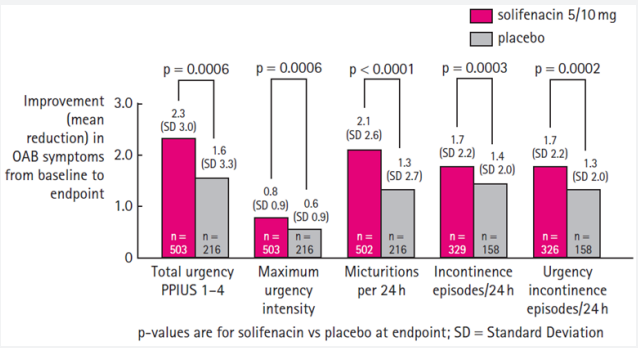

Figure 2: The mean change in secondary efficacy variables per 24h from baseline to endpoint after 16 weeks of treatment with solifenacin 5/10mg (5mg increased at 8 weeks to 10mg if requested) or placebo

*p <0.05 vs. solifenacin 5mg RD

The authors thus concluded that urgency was significantly improved with solifenacin 5 or 10mg rather than placebo.

In 2013, a sub analysis was carried out to assess the potential benefit of dose escalation versus non-escalation in the matched groups of patients. Outcome measures were re-analysed from the 8 week point in the group randomised to 5mg solifenacin at week 0 who then had requested a dose increase, in order to find out if requests for dose escalation were related to the severity of OAB symptoms at baseline. The effect of solifenacin in patients who requested dose escalation from 5mg and received 10mg compared to those who requested the dose escalation and were randomised to remain on 5mg was also assessed.

Results suggested that patients who requested a dose escalation at 8 weeks were more likely to have more severe baseline OAB symptoms and also to have had a previously failed treatment. These patients had more episodes of severe urgency (PPIUS 3 and 4), higher numbers of episodes of urgency, incontinence and urgency incontinence per 24 hours, and lesser treatment satisfaction at 8 weeks. There was a greater improvement in reduction of severe urgency episodes and other outcome measures from week 8 to 16 in those who requested a dose increase and were randomised to 10mg than those who

How to cite this article: Ganesh T, Linda C, Sushma S. Key Findings of the SUNRISE Study. J Gynecol Women's Health 2017; 7(1): 555703. DOI: 10.19080/JGWH.2017.07.555703.

were randomised to continue on 5mg (Figure 3). Statistically significant differences in 'total urgency score', 'maximum urgency intensity' and 'micturition frequency' were found. This suggests solifenacin may be an effective therapy even in those suffering with refractory OAB. Regarding PPBC, it was noted that the improvement in both groups was similar despite the other markers showing a clearer difference. This may be secondary to PPBC being a more global bladder condition assessment tool without the sensitivity to provide detailed information on the specific problem of urgency. However, this may mean that the differences in the groups did not reach a clinically relevant minimum important difference.

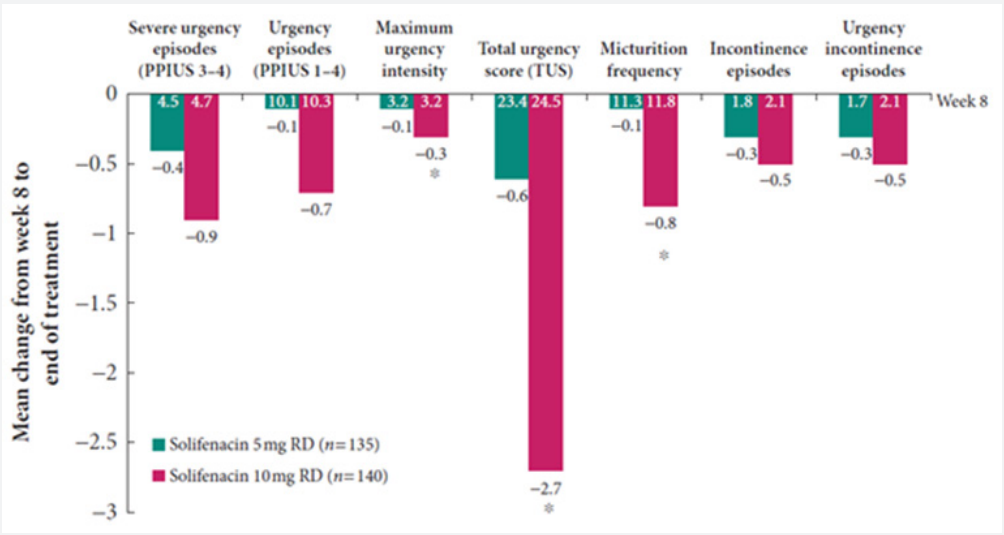

Figure 3: Mean changes in OAB variables from week 8 to end of treatment at week 16 in patients who requested a dose increase at week 8 and underwent a second randomisation.

As it became apparent that the subset of patients with severe OAB was more likely to ask for a dose increase, the authors concluded that the self selection process for dose escalation has potential to improve outcomes for those with more severe symptoms. Routine pre-treatment symptom questionnaires and bladder diaries may highlight patients who could benefit from dose increases. The initial SUNRISE analysis proved that solifenacin was more effective than placebo in the treatment of OAB. The second analysis has shown that patients who have had a previously failed treatment request higher doses. A recent analysis of 51 OAB studies stated that 95% CI for solifenacin's success rate was statistically higher than other regimens [12]. Therefore it may be argued that patients should be offered solifenacin 5mg as a first line drug treatment rather than generic oxybutnin as per the NICE guidelines [7].

Treatment emergent adverse events were found to be worse in the 10mg than the 5mg group with the incidence of any adverse event being 22.1% compared to 7.4%. This finding may have been expected. It focuses the clinician on the importance of starting OAB treatment at the lowest therapeutic dose titrating the treatment to the patient's symptoms in order to achieve the best efficacy to side effect ratio.

The study has numerous strengths. It was the first to focus on urgency which is the main symptom of OAB and utilised subjective and objective outcome measures. Double blinding reduced bias. One weakness was the large placebo effect in the treatment of OAB. A further weakness which was not highlighted may have related to the fact the study was carried out in 14 European countries and despite the inclusion criteria specifying that patients should be able to complete the questionnaire in English, it is possible there may have been language difficulties. Conversely, only recruiting fluent English speakers in these non-English speaking countries may also have biased the results.

OAB is a disease which has considerable morbidity and a deleterious effect on patients' quality of life. The primary outcome of the SUNRISE study was urgency. The SUNRISE study found that not only was Solifenacin better than placebo, the improvements were felt from as early as day 3. Patients who felt they needed dose escalation benefitted from a dose increase more than those who were given a placebo increase. This information justifies the prescription of solifenacin as first line drug management for OAB and also the subsequent dose escalation when either requested by the patient or when validated patient quality of life assessments imply the patient's OAB symptoms are relatively severe.

References

1. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, et al. (2010) An International Urogynecological Association (IUGA)/ International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 29(1): 4-20.

2. Al-Ghazo MA, Ghalayini IF, Al-Azab R, Hani OB, Matani YS, et al. (2011) Urodynamic Detrusor Overactivity in Patients with Overactive Bladder Symptoms, Int Neurourol J 15(1): 48-54.

How to cite this article: Ganesh T, Linda C, Sushma S. Key Findings of the SUNRISE Study. J Gynecol Women's Health 2017; 7(1): 555703. DOI: 10.19080/JGWH.2017.07.555703.

3. Hashim H, Abrams P (2006) Is the bladder a reliable witness for predicting detrusor overactivity? J Urol 175(1): 191-194.
4. Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, et al. (2001) How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 87(9): 760-766.
5. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, et al. (2003) Prevalence and burden of overactive bladder in the United States, World J Urol 20(6): 327-336.
6. Brown JS, McGhan WF, Chokroverty S (2000) Comorbidities associated with overactive bladder, Am J Manag Care 6(11 Suppl): S574-S579.
7. NICE Urinary incontinence guideline (CG40)
8. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB (2009) Comparing adherence and persistence across 6 chronic medication classes, J Manag Care Pharm 15(9): 728-740.
9. Choo MS, Lee JZ, Lee JB, Kim YH, Jung HC, et al. (1997) A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladdercompliance, Br J Obstet Gynaecol 104(9): 988-993.
10. Cardozo L, Hessdörfer E, Milani R, Arañó P, Dewilde L, et al. (2008) SUNRISE Study Group., Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. BJU Int 102(9): 1120-1127.
11. Cardozo L, Amarenco G, Pushkar D, Mikulas J, Drogendijk T, et al. (2013 Severity of overactive bladder symptoms and response to dose escalation in a randomized, double-blind trial of solifenacin (SUNRISE). BJU Int 111(5): 804-810.
12. Armstrong EP, Malone DC, Bui CN (2012) Cost-effectiveness analysis of anti-muscarinic agents for the treatment of overactive bladder. J Med Econ 15(Suppl 1): 35-44.

DOI: 10.19080/JGWH.2017.07.555703

How to cite this article: Ganesh T, Linda C, Sushma S. Key Findings of the SUNRISE Study. J Gynecol Women's Health 2017; 7(1): 555703. DOI: 10.19080/JGWH.2017.07.555703.