

# Management of Refractory Overactive Bladder with Incontinence -A Novel Approach

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## ABSTRACT

### BACKGROUND

Overactive bladder (OAB) syndrome is a chronic, debilitating syndrome, symptoms include urgency with or without urge incontinence (UI), frequency, and nocturia. First line management includes life style modification and anticholinergics. In patients with unsatisfactory symptomatic improvement, anticholinergic dose can be increased for therapeutic benefit but with increased side effects. Severe symptoms of overactive bladder (OAB) with urge incontinence (WET) not responding to standard dose of anticholinergics, addition of mirabegron ( $\beta_3$  -adrenoceptor agonist) may improve the symptoms. We wanted to evaluate the efficacy, safety, tolerance and side effects of combination therapy-mirabegron (50 mg) and solifenacin (5 mg) (anticholinergic) compared with monotherapy of either, solifenacin or mirabegron for a period of 6 weeks in patients with over active bladder (OAB) with urge incontinence, remaining incontinent after tolterodine (4 mg) (anticholinergic).

### METHODS

Study was conducted on 70 patients from October to December 2019, in Andhra Medical College, Visakhapatnam (Andhra Pradesh), which is a tertiary care centre. 40 patients were selected based on inclusion and exclusion criteria. 30 patients were female and 10 patients were male with a median age of 55 years. Group A (n=10) mirabegron 50 mg/day, Group B (n=10) solifenacin 5 mg/day Group C (n=20) mirabegron 50 mg plus solifenacin 5 mg/day. Efficacy was measured as a change from base line to the end of treatment (EOT), in the mean number of incontinent episodes per 24 hrs and micturition per 24 hrs. Safety assessments included Treatment Emergent Adverse Events (TEAEs), blood pressure, pulse rate, post-void residual volume (PVR), laboratory and electrocardiography (ECG) parameters.

### RESULTS

Combination therapy provides greater amelioration of symptoms in over active bladder (OAB) with incontinence (wet) compared to monotherapy. Combination therapy is well tolerated with acceptable safety profile.

### CONCLUSIONS

Patients suffering from over active bladder (OAB) with incontinence, combination therapy with solifenacin and mirabegron provides satisfactory therapeutic effect and improved quality of life (QOL), within short period of time (4-6 Weeks). Increased risk of side effects associated with dose escalation of solifenacin from 5 mg to 10 mg can be avoided.

### KEYWORDS

Over Active Bladder (OAB), Urinary Incontinence (UI) Mirabegron, Solifenacin, Combination Therapy Anticholinergics,  $\beta_3$ -Adrenoceptor Agonist

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## BACKGROUND

International Continence Society (ICS) describes over active bladder (OAB) as a complex of symptoms characterized by "urinary urgency with or without urge incontinence (UI), usually with frequency and nocturia, in the absence of urinary tract infection or other obvious pathology.<sup>1</sup> Urgency in OAB is typical with fear of leakage.<sup>2</sup> The prevalence of OAB dry which means urgency without incontinence, is higher in men, whereas women have a higher prevalence of OAB wet. Urinary urge incontinence is more frequent in elderly.<sup>3</sup> Overactive bladder (OAB) is higher in women (16.9%) compared to men (16%); attributed to sex-specific differences in the anatomy of the urinary bladder.<sup>4</sup> Above the age of 75 years, incidence is 40% in men and 30% in women. Diabetes, obesity and pelvic floor disorders contribute to OAB.<sup>5</sup> Dysfunction of bladder smooth muscle, urothelium and neuronal components of the bladder perpetuate OAB.<sup>6</sup> OAB with incontinence has a greater detrimental impact on quality of life (QoL),<sup>7</sup> much severe than other symptoms of Overactive bladder. Urinary urge incontinence in diabetes and elderly is due to reduced bladder capacity, increased detrusor instability, and loss of bladder compliance. It is a manifestation of declining bladder function, with raised post voided residual urine (PVR). The exact aetiology of the syndrome remains elusive. Predictors of OAB in men and women are gender, age, high body mass index (BMI), increased fluid intake, spicy foods, artificial sweeteners and alcohol.<sup>8,9</sup> Symptoms of OAB are mainly due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. Consequences of OAB include sleep disturbance, depression, fall related injuries and lower quality of life (QoL). Comorbidities such as diabetes can contribute to lower urinary track symptoms. Essential first-line therapy in all OAB patients, include Behavioural therapy, lifestyle changes and weight reduction, owing to their non-invasive nature. These modalities strongly rely on patient compliance and engagement in their treatment.<sup>10</sup> Concomitant pharmacotherapy is invariably instituted with an aim to control and alleviate the vexing symptoms of urgency, frequency and urinary incontinence, and to improve quality of life (QoL). Anticholinergic/antimuscarinic agents represent the cornerstone of treatment for OAB.<sup>11</sup> Urinary urge incontinence not responding with anticholinergics alone, mirabegron was added which may improve OAB symptoms. Combination therapy improves efficacy in the treatment of OAB while reducing the antimuscarinic side effects resulting from dose escalation of anticholinergics.

We wanted to evaluate the efficacy, safety, tolerance and side effects of combination therapy-mirabegron (50 mg) and solifenacin (5 mg) (anticholinergic) compared with monotherapy of either, solifenacin or mirabegron for a period of 6 weeks in patients with over active bladder (OAB) with urge incontinence, remaining incontinent after tolterodine (4 mg) (anticholinergic).

## METHODS

It is a non-randomised controlled study (NRCT) where comparison was made between monotherapy and combination therapy for OAB. Questionnaire based study was conducted.

Patients aged  $\geq 18$  years with symptoms of wet OAB for  $\geq 3$  months, average micturition  $\geq 8/24$  hrs., urgency episodes  $>3$ , /24 hrs. and  $\geq 1$  urinary incontinence episode over a 7- day micturition diary were eligible for screening. Study was conducted on 70 patients from October to December 2019, in Andhra Medical College, Visakhapatnam which is a tertiary care centre. Screened patients were enrolled for 6 weeks of treatment schedule. 40 patients were selected based on inclusion and exclusion criteria. 30 patients were female and 10 patients were male with a median age of 55 years (range 26-80 years). Bladder diary and frequency volume chart revealed the number of micturitions per day, frequency of incontinent episodes, and average voided volume. Patients are divided into three groups (A, B, C). Group a (n=10) mirabegron 50 mg/day, Group b (n=10) solifenacin 5 mg/day, Group c (n=20) mirabegron 50 mg plus solifenacin 5 mg/day. Efficacy was measured as change from base line to the end of treatment (EOT) in the number of micturitions per 24 hrs and mean incontinence episodes per 24 hrs. Safety assessments included treatment emergent adverse events (TEAEs), blood pressure, pulse rate, post void residual volume (PVR), laboratory and electrocardiography (ECG) parameters. Patients own assessment of symptomatic improvement was the basis of clinical improvement.

### Inclusion Criteria

Those who recorded on average  $\geq 8$  micturitions/24 hrs., frequency of ui  $\geq 1$ /day over 7-day micturition diary, were eligible for randomisation to treatment in a 1:1:2 ratio daily. In patients with mixed incontinence, urge incontinence had to be the predominant factor.

### Exclusion Criteria

Clinically significant bladder outlet obstruction, post-void residual (PVR) volume  $\geq 150$  ml, mixed incontinence with stress as the predominant factor, UTI, chronic inflammation of bladder, hepatic and renal impairment, CVA or CVS disease within 6 months prior to screening, electro cardiogram (ECG) with qt abnormalities, uncontrolled hypertension with bp  $>180/120$  mm.

### Statistical Methods

Descriptive statistics. Qualitative variables were analysed using proportions. Quantitative variables were analysed using mean and standard deviation.

## RESULTS

Considerable decrease in urinary frequency and incontinence episodes were observed with combination

therapy, at week 6, compared to either mirabegron or solifenacin with acceptable safety profile.

| Group   | Baseline | Week 2 | Week 4 | Week 6 |
|---------|----------|--------|--------|--------|
| Group A | 9.8      | 9      | 7.9    | 6.1    |
| Group B | 10.5     | 9.7    | 8.4    | 6.9    |
| Group C | 9.1      | 8.2    | 6.1    | 5.3    |

**Table 1. Change in Urination Frequency in Treatment Groups**

| Group   | Baseline | Week 2 | Week 4 | Week 6 |
|---------|----------|--------|--------|--------|
| Group A | 5.2      | 5      | 4.3    | 2.9    |
| Group B | 5.5      | 5.1    | 3.7    | 3.3    |
| Group C | 5.1      | 4      | 2.4    | 1.5    |

**Table 2. Change in Frequency of Urinary Incontinence in Different Treatment Groups**

Satisfactory therapeutic effect was achieved within short period of time without an increased risk of side-effects, which translates into improved quality of life and self-worth. Two class of drugs with different modes of action will improve efficacy due to synergistic action. In those patients unsatisfied with solifenacin 5 mg, increasing the dose to 10 mg will increase anti cholinergic burden. Thus combined therapy without compromising tolerability, promotes treatment persistence. There was a slightly increased frequency of TEAEs in the combined therapy group vs monotherapy. Most of the TEAEs were mild or moderate in severity there were slightly higher frequencies of dry mouth, nasopharyngitis constipation, and dyspepsia in the combined therapy groups vs. monotherapy. No remarkable changes in bladder capacity and PVR volume with small increase suggest that the combined action of mirabegron and solifenacin are unlikely to increase the risk of urinary retention. There were no concerns regarding electrocardiograms and laboratory data.

## DISCUSSION

Overactive bladder can be due to myogenic, neurogenic and bladder causes.

- 1) Myogenic- spontaneous detrusor contractions, hypersensitivity to incoming signals.
- 2) Neurogenic-abnormal afferent excitability, abnormal central sensory processing. aberration in the voiding reflex leads to involuntary detrusor contractions.
- 3) Uroepithelial factor- transmitters from urothelium which affect detrusor contractility, include acetylcholine (ACh), adenosine triphosphate (ATP), and nerve growth factor (NGF).

### Management Approaches

- 1) Non pharmacological-life style intervention, bladder retraining, pelvic floor exercises.
- 2) Pharmacological- In elderly patients with severe symptoms of OAB, the urothelium has emerged as a new target for drug therapy.

Anti-muscarinic control symptoms and improve quality of life. Addition of mirabegron has broadened or augmented the therapeutic options. Mirabegron by decreasing the

bladder afferent activity, relaxes the autonomous contractile activity of the detrusor muscle,<sup>12</sup> with improvement of overall storage function.<sup>13</sup> Thus Mirabegron increase the bladder capacity and voided volume. Half-life is 50 hours. Excreted in urine and faeces. There were statistically significant decrease in number of incontinent episodes and micturitions. Well tolerated with regard to adverse effect.<sup>14,15</sup> Cardiovascular safety appears to be acceptable at therapeutic doses and comparable with that of anti-muscarinics.<sup>16</sup> The most common side effects with mirabegron were headache and gastrointestinal upset.<sup>17</sup> Anticholinergic solifenacin (antagonize-action of m2/ m3 receptors) reduces the involuntary contractions of bladder<sup>18</sup> and improves the overall voiding function. Half-life is 45-68 hours. Excreted in urine, faces and bile. Solifenacin has higher bladder selectivity and highest rates of patient compliance,<sup>19</sup> Compared to oxybutynin, tolterodine and darifenacin. No deleterious impact on cognitive function. Significant reduction in all major symptoms of OAB such as frequency, urgency and urinary incontinence.<sup>20</sup> Risk of dry mouth was found to be significantly lower with solifenacin compared to darifenacin and tolterodine.<sup>21</sup> In patients refractory to solifenacin 5 mg, dose can be increased to 10 mg but with increased side effects of Anticholinergics. Mirabegron 50 mg was added to Solifenacin 5 mg without dose escalation. Two distinct drugs with different molecular mechanisms regulating detrusor activity are regarded to have a supplemental effect on the symptoms of OAB. Combination therapy compared to monotherapy improves OAB symptoms with reduced side-effects associated with 10 mg of solifenacin.<sup>22</sup> Mean voided volume (MVV), frequency and urgency are improved compared to monotherapy. Combination therapy can be used as a potential alternative to invasive third line therapies such as intravesical botulinum toxin, or neuromodulation, which can be burdensome due to associated adverse effects.<sup>23</sup> Combination therapy usually reflects an additive effect with incremental efficacy and greater improvement in symptoms. Combination therapy can be used as potential innovative therapeutic option in wet OAB.<sup>24</sup> Follow up visit is with 24-hour bladder diary, blood tests, ECG and quality of life assessment. Initial management includes dietary and behavioural modification, followed by drug therapy started with either anti muscarinic or  $\beta$ 3-adrenoceptor agonist. Combination therapy with both drugs can be initiated with unsatisfactory improvement in wet OAB symptoms. Two distinct class of drugs with different molecular mechanisms regulating detrusor activity are regarded to have a supplemental effect on the symptoms of OAB.<sup>25</sup> In patients refractory to monotherapy, combination therapy improves mean voided volume (MVV), frequency and urgency,<sup>26</sup> with reduced side-effects as compared to monotherapy. Combination therapy is efficacious in OAB (wet) patients irrespective of age. Synergistic action of complementary mono amino oxidase (MAO) improves overall bladder function.<sup>27</sup> Combination therapy improves efficacy without compromising tolerability, thus promoting treatment compliance,<sup>28</sup> and offers sustained treatment improvement for up to 12 months.<sup>29</sup>

## Limitations

Since the study duration was short, we had to limit the sample size for convenience.

### CONCLUSIONS

Combination of mirabegron and solifenacin has complimentary action, in wet OAB patients not having satisfactory clinical response to monotherapy. There was statistically significant decrease in number of incontinence episodes and micturitions.<sup>30</sup>

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