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A study evaluating and comparing the effectiveness of combination therapy – Duloxetine with darifenacin versus darifenacin as monotherapy on perception of symptoms, quality and standard of life in patients suffering with overactive bladder (OAB)

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ABSTRACT

Introduction: Overactive bladder is chronic debilitating condition, with physical, psychological, and economical consequences. Urinary vesicle tissue contains muscarinic receptors, M3 is principal mediator of detrusor contraction. Muscarinic receptor antagonists, comprises traditional pharmacological treatment. But due to non-selective inhibition, these agents, probably been related with safety and tolerability concerns. Drugs particular inhibiting sM3 receptor (Darifenacin) have potential to present effective relief while reducing side effects concerned with blockade of M1, M2 and M5 receptors. Duloxetine is Serotonin and nor-epinephrine reuptake inhibitor, leading increased concentration of 5-HT and NE in synaptic cleft, increases stimulation of pudendal motor neurons, thus increasing resting tone and contraction of urethral sphincter.

Materials and Methods: In present prospective, randomized, parallel group, comparative open label study with 60 OAB patients the combination therapy of Duloxetine with Darifenacin was equated with monotherapy using Darifenacin. The outcome thus analyzed using three different OAB-questionnaires and was statistically compared.

Result: We demonstrated that addition of Duloxetine has shown better result outcome in symptoms as well as quality of life, though the difference of OAB-V8, OABss mean score was non-significant, but for OAB-qSF the reduction (percentage change) in mean score was more in treatment group II as compare to group I (w6:13.82±3.17% vs 12.13±3.24% & W12 29.99±5.40% Vs 25.56±5.17%) , and was statistically significant.($p<0.05$).

Conclusion: Duloxetine has synergistic effect to Darifenacin, its ability to increase bladder capacity may be the reason for the improvement OAB symptoms, promising in controlling and treating symptoms either alone or in combination with anti-cholinergic drugs.

1. Introduction

Urinary incontinence (UI) is defined by International Continence Society as an "involuntary loss of urine which is objectively a demonstrable, social and hygienic problem".[1] This condition occurs in either sex, but primer focuses on feminine urinary incontinence because of its higher prevalence.[2] It is classified as stress urinary incontinence (SUI), urgency urinary incontinence (UUI), and mixed urinary incontinence (MUI).[3] Urinary incontinence or uncontrolled outflow on sneezing, coughing or on any exertion or effort is termed as SUI. UUI is uncontrolled

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leakage accompanied by or preceded by urgency and may be accompanying with overactive bladder syndrome (OAB). MUI is involuntary/uncontrolled leakage associated with urgency along with sneezing, coughing, exertion or effort.[1]

OAB disorder is a chronic medical state[4] defined by urgency in urine outflow, along with or without UUI, usually associated with increase in daytime frequency and nocturia as well, with no obvious pathology."[3] OAB is leads to impaired sleep quality, depression, falls, fractures, social isolation, and worse quality of life.[5] This condition is most common in patients over 40 years,[4] showing frequency increase with age, making it a substantial public health concern among aged 65 and above.[6] Various pathophysiologic mechanisms, such as primary detrusor dysfunction, overactivity of afferent arm of micturition reflex, urothelial dysfunction and primary dysfunction of higher central nervous system(CNS) inhibitory centers have been put forward.[3] It requires long-term, continuous treatment, comprising of an integrated approach involving behavioral therapy, physical therapies and pharmacological therapy.[7]

Muscarinic receptors M2 and M3 are present in human bladder tissue; M3 has been recognized as the key mediator for contraction of detrusor in reaction to cholinergic activation. Hence, antagonists of muscarinic receptors are the ongoing treatment of choice, as their activity leads to decreased and reduced forceful inappropriate bladder contractions, leading to improved bladder filling and lessen the urge incontinence.[8]

Anticholinergic drugs, represent the 'gold standard' of pharmacological treatment.[7] Various types of muscarinic receptors are thoroughly dispersed in human body. For example, salivary glands and brain has M1 receptor, connected with saliva production and cognition; cardiovascular system has M2 receptors, mediating cardiac output and heart rate; and eye has M5 receptor, concerned with contraction of ciliary muscles. Presently used antimuscarinic agents, binds to above mentioned receptors to different extent, relieving the symptoms of OAB efficiently but concerns may be related with tolerability and safety, such as tachycardia, blurred vision and cognitive impairment, limiting their use. M3 receptor selective drugs potentially confer effective relief by optimizing contractility of detrusor muscle while reducing safety problems associated with block of the M1, M2 and M5 receptors.[8]

Darifenacin((S)-2-[1-(2,3-dihydrobenzofuran5-yl)ethyl-pyrrolidinyl]-2,2-diphenylacetamidehydrobromide) is a potent, competitive and reversible antagonist for muscarinic receptor with selectivity for M3 receptor, therefore offers an alternative approach to therapy of OAB by targeting the M3 whilst sparing effects at other sites. It also displays functional selectivity, observed as greater effects on bladder than other tissues.[9]

Duloxetine((+)-(S)-N-methyl-γ-(1-naphtyloxy)-2-thiophenepropylaminehydrochloride,C18H19NOSHCl)[10] is dual serotonin(5-HT) and norepinephrine(NE) reuptake inhibitor(SNRI), demonstrating significantly increase muscle activity of striated urethral sphincter and urinary bladder capacity through central actions, but only during storage phase of micturition cycle.[11] Duloxetine improves urinary incontinence by inhibiting reuptake of norepinephrine and serotonin at the pre-synaptic neuron in Onuf's nucleus in sacral region of spinal cord. Both alpha-receptors and serotonin (5-HT2) receptors in Onuf's nucleus facilitate the storage reflex by contracting urethral external sphincter muscle. Duloxetine's ability to increase bladder capacity may be an important contributor to the improvement of urgency and frequency.[12] Duloxetine is the only drug that increases urethral striated sphincter activity.[13]

The goals of our present study were to evaluate the effectiveness and tolerability of Duloxetine as combination drug with Darifenacin, in comparison to Darifenacin alone on treatment outcome and perception of symptoms of OAB, so that a more efficient treatment with lesser adverse effects, aiming at good quality of life can be provided.

2. Materials and Methods

Study design: The present 12 weeks metacentric, prospective, randomized, parallel group, comparative open label study, conducted in Pharmacology department in association with department of Urology, Medicine and Pathology, enrolling 60 OAB patients, for evaluating the impact of Duloxetine with Darifenacin in comparison to Darifenacin alone on treatment outcome, quality of life and tolerability.

Patient enrollment: Inclusion criteria: Patients 18-85years of either sex, weighing at least 50kg, diagnosed OAB at least 6 months ago, advised behavior and physical therapies but not relieved, willing to record information regarding bladder function at regular basis and. Exclusion criteria: Patients with impaired hepatic or renal function, known hypersensitivity, uncontrolled narrow angle glaucoma, paralytic ileus, gastrointestinal/urinary obstruction, cognitive impairment, pregnant or lactating women. Patients, fulfilling the inclusion criterias and having none of the exclusion criteria, followed by informed consent in written, were registered by simple randomization procedure. Permission of Institutional Ethical Committee and required procedures followed in accordance with the declaration of Helsinki. Detailed history, clinical examination and basic blood investigations (hemogram, hepatic function test and kidney function tests) of all the enrolled patients were done at baseline visit. If patient felt any undesirable symptoms during the treatment he/she was advised to stop the drug and report immediately. These 60 patients were distributed randomly in two groups i.e. Group

I and Group II of 30 each. Group I- patients were given Darifenacin 7.5mg once daily. Group II- patients were given Darifenacin 7.5mg once daily along with Duloxetine 30mg twice daily.

Assessment parameters: The OAB-q is recommended for use in screening and monitoring OAB. [14]

1) OAB-V8 Questionnaire: is a simplified version adapted from the symptom Bother Scale of the OAB consisting of eight questions with domains of 0 to 5. The total score ranges from 0 to 40 points. [15]

2) OAB-q short form (13 ITEM HRQL Scale short form): Impact on health-related quality of life (HRQL) i.e. during the past 4 weeks, how often patient have bladder symptoms. [16]It measures three HRQL domains: coping, sleep, and emotional/social interactions. [17] It comprises of 13 items with domains of 1 to 6, where 1 stands for no interference and 6 stands for complete interference. 13 to 78 is it's score range.

3) OABss: Overactive Bladder Symptom Score (OABSS) is a symptom assessment questionnaire designed to quantify OAB symptoms into a single score. It consists of 4 questions on OAB symptoms with maximum scores ranging from 2 to 5. The total score ranges from 0 to 15 points, with higher scores describing higher symptom severity. [18]

4) Safety assessment done by recording any AE occurred or derangement of any basic blood parameters in any of the included patient.

2.1. Follow up and evaluation

A standardized initial evaluation, along with assessment parameters i.e. OAB-V8, OAB-qSF, OABSS questionnaire were done at 1^{st} visit(Day 0) then after 6 weeks (2^{nd} visit) and 12 weeks (3^{rd} visit) of starting treatment, Records of all three visits were analyzed statistically.

2.2. Statistical methods

Baseline characteristics i.e. gender was statistical analyzed using chi-square test ($\chi 2$) and for age and questionnaires analysis student't' was used. OAB-V8, OAB-q-SF, OABSS questionnaire baseline score values were compared with the values at six and twelve weeks, within the Group and also between the groups. Paired't' test used for intra-group comparison, evaluating the effectiveness of treatment. Unpaired't' test used for inter-group comparison, for comparing the effectiveness of both the drugs. p value of <0.05 was considered as statistically significant.

3. Results

3.1. Baseline comparison

20 (66.67%) females and 10 (33.33%) males in Group I and, 20 (66.67%) females and 10 (33.33%) males in Group II were included. For Group I mean for age was 60.40±6.79years and for Group II was 57.47±6.19years. Statistical analysis of both age and gender showed that the variation was not significant statistically (p>0.05) between the groups. The baseline scores of the questionnaires (OAB-V8, OAB q-SF & OABSS) of both the groups, on comparing was also statistically non-significant (Table 1).

3.2. OAB-V8 questionnaire score

As evident from Table-2 and fig. 2 & 3 both groups manifested improvement in OAB symptoms by reduction in mean scores of total OAB-V8 questionnaire. Intergroup statistical analysis in both the groups at 6 and 12 weeks, showed significant (p<0.05) reduction. The reduction (percentage change) in mean score was more in treatment group II as compare to group I (w6: 13.43±3.16% vs 12.24±3.04% & W12 27.93±6.69% Vs 25.74±5.26%) but on intragroup statistical analysis the difference between both the groups was non-significant (p>0.05).

3.3. OAB-qSF questionnaire score

As evident from Table 3 and Figures 2 and 3 both groups showed betterment in quality of life by reduction in mean scores of OAB-qSF questionnaire. Intergroup statistical analysis in both the groups at 6 and 12 weeks, showed significant (p<0.05) reduction. The reduction (percentage change) in mean score was noticed in treatment group II as compare to group I (w6: 13.82±3.17% vs 12.13±3.24% & W12 29.99±5.40% Vs 25.56±5.17%) , further this difference was statistically significant.(p<0.05) on intragroup comparison.

3.4. OABSS questionnaire score

As evident from Table 4 and Figures 2 and 3, both groups showed relief in OAB symptoms by reduction in mean scores of OABss questionnaire. Intergroup statistical analysis in both the groups at 6 and 12 weeks, showed significant (p<0.05) reduction. The reduction (percentage change) in mean score initially at 6 weeks was more in treatment group I as compare to group II (w6: 21.74±7.46% vs 18.12±5.61%) and was statistically significant (p<0.05) but later on at 12 weeks the reduction was greater in group II as compare to group I (W12 39.70±7.35% Vs 39.53±9.85%) though on intragroup statistical analysis the difference was non-significant (p>0.05).

3.5. Safety profile assessment

During the course of treatment, the AEs in patients were recorded, on summarizing no major AEs were noticed in any of the patient, however minor AEs such as gastrointestinal disturbance, nervous system disturbance and eye disorders were evident, but none led to interruption of treatment course. Moreover, on statistically comparing the difference

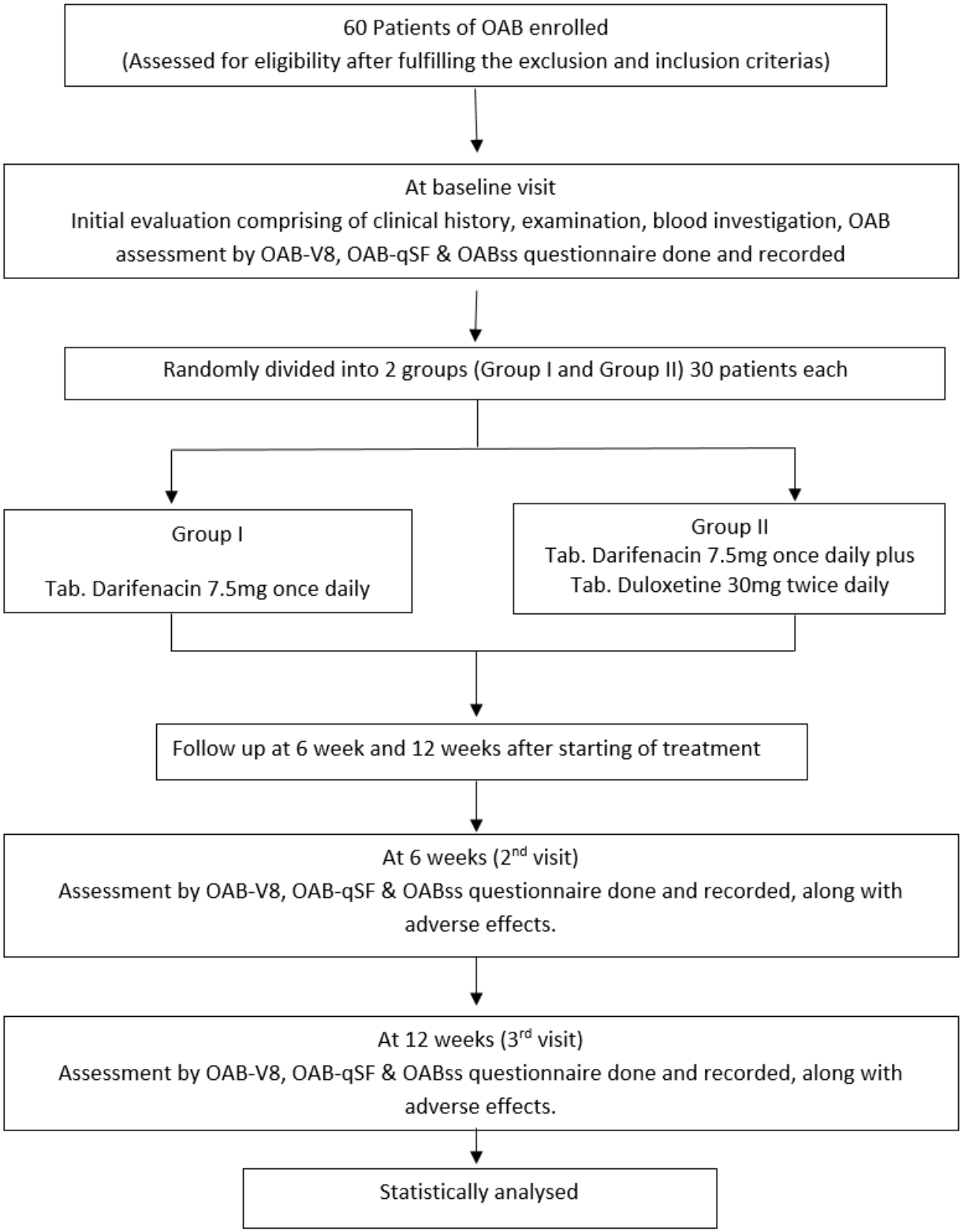

Figure 1: Flow chart for detail study design(original)

Table 1: Baseline characteristic comparison at first visit. (Original)

Baseline characteristics		Group I Darifenacin N=30	Group II Darifenacin plus Duloxetine N=30	Group I vs Group II p-value	
Mean age (in years)		60.40±6.79	57.47±6.19	0.086	NS
Gender	Male	10	10	1.000	NS
	Female	20	20		
OAB questionnaire	OAB-V8	33.87±3.74	33.60±3.68	0.782	NS
	OAB q-SF	65.70±7.51	65.17±7.35	0.782	NS
	OABSS	11.63±1.65	11.07±1.39	0.567	NS

Table 2: OAB-V8 questionnaire score comparison: (original)

Time interval	Group I		Group II		Group I vs Group II	
	Mean	±SD	Mean	±SD	Difference	P value
W0 (baseline)	33.87	3.74	33.60	3.68	0.267	0.782; NS
W6 (at 6 weeks)	29.73	3.59	29.10	3.44	0.633	0.488; NS
W12 (at 12 weeks)	25.20	3.69	24.20	3.20	1.000	0.267; NS
Change at W6 (6 weeks)	4.13**	1.11	4.50**	1.08	0.367	0.198; NS
% Change at W6 (6 weeks)	12.24	3.04	13.43	3.16	1.195	0.141; NS
Change at W12 (12 weeks)	8.67**	1.79	9.40**	2.31	0.733	0.175; NS
% Change at W12 (12 weeks)	25.74	5.26	27.93	6.69	2.190	0.164; NS

#Inter-group Comparison using Unpaired 't' test;
$Intra-Group comparison using Paired 't' test
p>0.05, Not significant(NS); *p<0.05,Significant; **p<0.001; Highly significant

Table 3: OAB-qSF questionnaire score comparison (original)

Time interval	Group I		Group II		Group I vs Group II	
	Mean	±SD	Mean	±SD	Difference	P value
W0 (baseline)	65.70	7.51	65.17	7.35	0.533	0.782; NS
W6 (at 6 weeks)	57.77	7.33	56.20	6.88	1.567	0.397; NS
W12 (at 12 weeks)	48.93	7.20	45.73	6.82	3.200	0.082; NS
Change at W6 (6 weeks)	7.93**	2.27	8.97**	2.04	1.033	0.069; NS
% Change at W6 (6 weeks)	12.13	3.24	13.82	3.17	1.687	0.046*; S
Change at W12 (12 weeks)	16.77**	3.50	19.43**	3.36	2.667	0.004*; S
% Change at W12 (12 weeks)	25.56	5.17	29.99	5.40	4.353	0.002*;S

#Inter-group Comparison using Unpaired 't' test;
$Intra-Group comparison using Paired 't' test
p>0.05, Not significant (NS); *p<0.05, Significant (S); **p<0.001; Highly significant

Table 4: OABss questionnaire score comparison: (original)

Time interval	Group I		Group II		Group I vs Group II	
	Mean	±SD	Mean	±SD	Difference	P value
W0 (baseline)	11.63	1.65	11.07	1.39	0.567	0.155; NS
W6 (at 6 weeks)	9.10	1.56	9.07	1.34	0.033	0.930; NS
W12 (at 12 weeks)	7.07	1.68	6.70	1.32	0.367	0.351; NS
Change at W6 (6 weeks)	2.53**	0.94	2.00**	0.64	0.533	0.013*; S
% Change at W6 (6 weeks)	21.74	7.46	18.12	5.61	3.614	0.038*; S
Change at W12 (12 weeks)	4.57**	1.19	4.37**	0.85	0.200	0.458; NS
% Change at W12 (12 weeks)	39.53	9.85	39.70	7.35	0.175	0.938; NS

#Inter-group Comparison using Unpaired 't' test;
$Intra-Group comparison using Paired 't' test
p>0.05, Non significant (NS); *p<0.05, Significant; **p<0.001; Highly significant

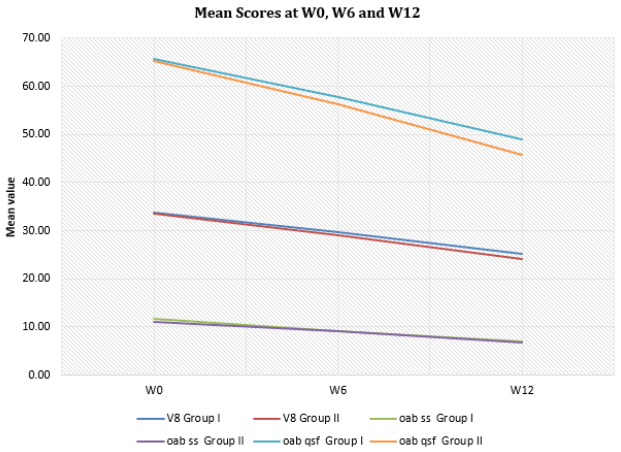

Figure 2: Comparison of mean scores of OAB-V8, OAB-qSF, OABss questionnaire over the periods in patients treated with Darifenacin alone versus Darifenacin + Duloxetine. (Original)

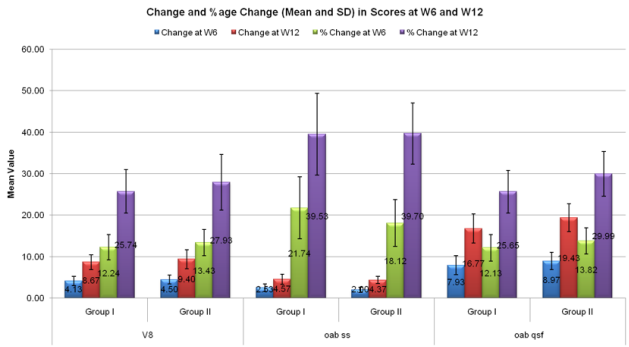

Figure 3: Change and percentage change in mean scores of OAB-V8, OAB-qSF & OABss questionnaire in treatment Group I Vs Group II patients.(original)

in both the groups was non-significant (p>0.05).

4. Discussion

Present study evaluating the efficacy of Duloxetine in combination with Darifenacin in comparison to Darifenacin alone on treatment outcome and perception of symptoms of OAB, so that a more efficient treatment with lesser AEs, aiming at good quality of life can be provided.

The multidrug therapy is proposed to be effective in the refractory OAB/UI. Combination therapy's advantage lies in acting simultaneously on different pharmacological pathways, with additive and/or synergistic effects.[3]

The presynaptic re-uptake of serotonin (5-HT) and norepinephrine (NE) is inhibited by Duloxetine, leading to increased concentration of NE and 5-HT in the synaptic cleft of sacral spinal cord, stimulating NE and 5-HT receptors on pudendal motor neurons, causing increase in resting tone and contraction strength of urethral striated sphincter.[19]

In present study both therapy groups show improvement in OAB symptoms by reduction in mean scores of total OAB-V8, OAB-qSF, OABss questionnaire. Intergroup statistical analysis of mean score of all questionnaire in both the groups at 6 and 12 weeks, show significant (p<0.05) reduction. The percentage change in mean score of OAV-V8 and OAB-qSF was more in treatment group II as compare to group I [(OAB-V8; w6: 13.43±3.16% vs 12.24±3.04% & W12 27.93±6.69% Vs 25.74±5.26%) (OAB-qSF; w6: 13.82±3.17% vs 12.13±3.24% & W12 29.99±5.40% Vs 25.56±5.17%) though on intragroup analysis the difference was non-significant(p>0.05) for OAB-V8, but was significant(p<0.05) for OAB-qSF, pointing to the additive effect of Duloxetine to Darifenacin in improving quality of life of OAB patients. The percentage change in mean score of OABss initially, was more in treatment group I as compare to group II (w6: 21.74±7.46% vs 18.12±5.61%) and was statistically significant (p<0.05) but later at 12 weeks the reduction was greater in group II as compare to group I (W12 39.70±7.35% Vs 39.53±9.85%) though on intragroup analysis the difference was non-significant(p>0.05). The AEs (dry mouth, blurred vision, anorexia, sleep disturbance, and anxiety) were minor in both the groups and were satistically non-significant (p-value>0.05).

Recently, Wrobel et al, in a rat model study, demonstrated that Duloxetine when given for 14 days (1mg/kg/day), reverses the symptoms of OAB induced by corticosterone i.e. reduction in amplitude of non-voiding contraction (p<0.0001), detrusor overactivity index (p<0.0001), and frequency of non-voiding contraction (p<0.0001) and a significant raise of bladder compliance .The central pathways were responsible for effects of Duloxetine on both depression and detrusor overactivity.[20]

In another rat model study, Wrobel et al found that Duloxetine treatment led to reduction in detrusor overactivity induced by the retinoid. Decreases were observed in detrusor overactivity index, and the amplitude and frequency of non-voiding contractions, while increases were seen in bladder compliance and the volume threshold to elicit nonvoiding contractions.[21]

A study done on cats by Schwen Z et al also demonstrated Duloxetine alone dose dependently inhibited bladder overactivity and completely restored bladder capacity to the saline control at 3 mg/kg. WAY-100635 (0.5 mg/kg) given after 3 mg/kg Duloxetine further increased (P=0.008) bladder capacity i.e. Duloxetine combined with WAY-100635, however, synergistically enhanced bladder inhibition.[22] The above mentioned pre-clinical studies revealed encouraging results with Duloxetine similar to our present study.

In a clinical trial, Mirzae et al evaluated effectiveness and tolerability of Duloxetine 20 mg/daily compared with solifenacin 10 mg/daily. One month after treatment,

frequency, nocturia, urgency and UUI were relieved in both groups. The mean of questionnaire score in the solifenacin group was 14.86 before and 9.66 after the treatment, respectively. These scores were 13.90 and 8.76 in the Duloxetine group. Duloxetine and solifenacin both showed comparable efficacy, with no statistically significant difference(p-value=0.148). These findings with Duloxetine are consistent with our study. The group of patient on solifenacin has higher frequency of AEs like anorexia, sleep disturbance, anxiety, dry mouth and blurred vision, but statistical significance was observed only in blurred vision(p-value=0.042).[23]

Wang et al. evaluated the effectiveness of Duloxetine (initially 30mg/day then escalated to 60mg/day) in a 17-year-old female suffering from OAB for 2 years. The results showed improved bladder capacity and decreased urinary frequency. Six weeks after Duloxetine initiation, her urgency and frequency as 50% better. About a month later, she no longer had nocturia, and her micturition frequency has decreased to every 2 hours during the day, her depressive symptoms including insomnia and agitation also improved.[12]

Steers et al in a clinical study, of 306 women with OAB, found that patients on Duloxetine had significant betterment as compare to those on placebo for decreases in voiding and urinary incontinence episodes, for improvement in the voiding interval during daytime, and for betterment in scores of Incontinence-Quality of life questionnaire.[24]

Ariman A et al in a study comprising of 88 patients of MUI, demonstrated that after 8weeks of Mirabegron 50 mg (once a day) and Duloxetine 40 mg (twice a day) combination treatment, International Consultation of Incontinence Questionnaire-Short Form ICIQ-SF score decreased from 14.71±3.54–7.83±6.41 (p<0.001) and OABSS from 11.00±2.26–7.02±2.17 (p<0.001).[13]

Haab F et al in a study, enrolling 561 OAB patients concluded that Darifenacin 7.5 mg and 15 mg had a rapid onset of effect. There was reduction in incontinence episodes per week from baseline by 67.7% and 72.8% with Darifenacin 7.5mg and 15mg compared with 55.9% with placebo. Darifenacin 7.5mg and 15mg respectively, were significantly superior to placebo for improvements in micturition frequency(p<0:001, p<0:001), bladder capacity(p<0:040, p<0:001), frequency of urgency(p<0:001, p=0:005), severity of urgency(p<0:001, p=0:002) and number of incontinence episodes leading to a change in clothing or pads(p<0:001, p=0:002). There was non-significant reduction in nocturnal awakenings due to OAB. The adverse events most commonly noted were mild-to-moderate dry mouth and constipation.[8]

A 12 week, study conducted by Zinner N et al in 497 OAB patients receiving 7.5 mg Darifenacin once daily with up-titrating to 15 mg after 2 weeks, for up to 12 weeks, demonstrated that Darifenacin resulted in statistically significant improvements in PPBC scores (Patient's Perception of Bladder Condition), micturition frequency, urgency and UUI episodes. The AEs most commonly noted were dry mouth and constipation, but these infrequently resulted in treatment discontinuation.[25]

5. Conclusion

As far as I am aware, present study is the first clinical study evaluating the clinical efficacy of Duloxetine as a combination drug with Darifenacin in OAB patients. Duloxetine a selective norepinephrine and serotonin reuptake inhibitor is specific for reflexes that control bladder and urethera. In our study patients on Duloxetine in combination with Darifenacin shows greater improvement as compare to patients only on Darifenacin, although on statistically comparing the mean scores of questionnaire the difference of OAB-V8, OABss was non-significant, but OAB-qSF was significant at the completion of present study. Ability of Duloxetine to increase urinary bladder capacity may be the reason for the improvement OAB symptoms. UI and frequency may be due to anxiety, in that case, relief of urinary symptoms can be result of the drug's anxiolytic effect, secondly constant urinary symptoms led to anxiety in patients, and people are inclined to consider anxiety symptoms more serious than OAB. Our study suggests Duloxetine may be encouraging in treatment of symptoms due to overactive bladder individually or in union with traditional anti-cholinergic drugs and could be a treatment option for OAB. Although further multicentric studies on larger population, of longer duration is recommended.

6. Abbreviation

OAB-Overactive bladder, UI-Urinary incontinence, SUI-Stress urinary incontinence, UUI-Urgency urinary incontinence, MUI-Mixed urinary incontinence, CNS-Central nervous system, 5-HT- 5-Hydroxy tryptamine, SNRI-Serotonin and nor-epinephrine reuptake inhibitor, OAB-q-Overactive bladder questionnaire, OAB-V8-Overactive Bladder-Validated 8-question Screener, OAB-qSF-Overactive bladder questionnaire- short form, OABss-Overactive Bladder Symptom Score, SD-Standard deviation, NE-Nor-epinephrine, AEs-Adverse effects, HRQL-Health related quality of life.

7. Conflict of Interest

None.

8. Source of Funding

None.

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