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REVIEW ARTICLE

# OVERACTIVE BLADDER: CHANGING PARADIGMS IN CURRENT GUIDELINES AND PHARMACOTHERAPY

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## INTRODUCTION

Overactive bladder (OAB) is a common clinical condition affecting about 10% of the general population.[1] While in itself the condition is not mortal, it can have a profound impact on those affected with a marked deterioration in the quality of life, psychosocial consequences and an economic burden. There is also a link between OAB and propensity to fall.[2] Given that OAB is more common in the elderly who might already be suffering from restricted mobility, such a fall can be a sentinel event in a sequence that leads inexorably from fracture of the femur to loss of ambulation and death.

Overactive bladder is defined as "urinary urgency with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia in the absence of infection or other proven pathology".[3] OAB can be associated with urinary incontinence, the "wet OAB". OAB is a symptom complex, not a singular diagnosis. The same symptoms can be noted in a variety of diseases such as urinary tract infection, bladder or lower ureteric stone and carcinoma *in situ* of the urinary bladder. Hence, the condition is a diagnosis of exclusion. This cannot be emphasized enough. Each patient presenting with the symptom complex must traverse a clinical pathway to exclude other problems before a diagnosis of OAB is offered. In the appropriate patient, periodic re-examination of the diagnosis may be appropriate.

## Treatment Recommendations

Current clinical guidelines recommend behavior modification, life-style changes, counseling regarding fluid management and pelvic floor exercises as the first step in management.[4] The bladder diary (including its most simple format, the frequency-volume chart) is an important component of this management step and can serve both as a clinician's guide as well as a simple biofeedback for the patient.

Patients who have significantly bothersome symptoms to start with or those who fail to respond to the first-line management discussed above are candidates for drug therapy.[4] The standard medication has hitherto been antimuscarinic drugs (AM). AM drugs act by blocking the muscarinic receptors of cholinergic nerve endings at various sites in the bladder including the urothelium and the detrusor. The drugs are efficacious in most patients but a significant subset of patients either fails to respond adequately or has intolerable side effects. Frail, elderly patients with a large co-prescription are more likely to have these adverse events. The usual limiting side effects are dry mouth, constipation, hyperthermia and cognitive changes.[4] There is an increasing concern about the latter especially in elderly patients on long-term therapy. Additionally, AM drugs are contraindicated in some classes of problems such as narrow angle glaucoma, patients with delayed gastric emptying and those with a history of urinary retention and marginal voiding efficiency. In the event that an AM is ineffective, one of the possible steps is dose escalation, after confirming that other factors such as compliance or fluid balance are not responsible. In those with adequate efficacy but side-effects every attempt should be made to mitigate the side-effects by aggressive measures, often pre-emptively.

In those failing AM for the reasons discussed, hitherto the only option in India was to proceed with treatment for refractory overactive bladder. This implied more invasive and markedly more expensive

therapies such as intravesical botulinum toxin injection or neuromodulation both of which have transient effects, are invasive, very expensive and yet, not universally effective.

The fall of 2017 has marked the availability of Mirabegron in the Indian market with DCGI approving the drug for sale in India. This is a singular event. The last time a new class of drug became available for OAB was over thirty years ago.

## Clinical Pharmacology

Mirabegron is a unique beta-3 adrenoceptor (AR) agonist.[5] It is highly selective and potent with an affinity that is x 150 for beta-3 as compared with beta-1 and x 33 as compared with beta-2.[5] Experimentally, beta-adrenergic stimulation had been shown to induce bladder relaxation several decades ago. However, it was only in the 1990s that the beta-3 mechanism was understood well enough to identify a drug that could work selectively against it. Another decade of clinical trials in the early 2000s was followed by approval for clinical use across the world over the last eight years.[6]

Beta-ARs are ubiquitous in the human body. The human bladder has all three forms of beta-ARs but 97% of the mRNA found in experimental tests in the bladder is from beta-3 AR.[5] All three beta-ARs are found in the brain and heart. Some other tissues with beta-3 AR are gall bladder, gastrointestinal tract, uterus and adipose tissue.

Stimulation of beta-3 AR causes relaxation of the detrusor muscle of the bladder probably via Adenyl Cyclase stimulation and consequent cAMP production.[7] Other potential mechanisms include activation of $K^+$ channels causing hyperpolarization of the cell and inhibition of $Ca^{2+}$ entry as well as a down regulation of Acetylcholine release via pre-junctional beta-3 ARs.[7]A recent study that looked at beta-AR in acetylcholinergic endings in the bladder found abundant expression suggesting a potential mechanism for beta-3AR agonists in the bladder.[8] Stimulation of beta-AR had no major impact on detrusor contractility during voiding or on post-void residuals.

Following oral intake there is rapid absorption of the drug. Mirabegron is highly lipophilic and is metabolized by the P450 system specifically the CYP2D6 pathway.[5] 55% of the drug is excreted in urine and 34% in feces. It has a terminal half-life of about 50 hours. The drug can be taken without regard to food and is approved for usage in overactive bladder in adults. It is not currently approved in children, pregnancy and lactating mothers. The recommended clinical dose is 25mg and 50mg. For patients with severe renal or moderate hepatic impairment, the lower dose should be used. It is not recommended in end stage kidney disease and severe liver failure.

While most of the published literature is on Mirabegron, several other drugs in the class have been studied. The most promising among these is Solabegron for which Phase II trials have been published. Vibegron was found to be toxic while Ritobegron has undergone Phase II and III trials that remain unpublished.[7]

## Landmark trials and efficacy

In a seminal phase IIA study published in 2008, Chapple et al compared Mirabegron 100mg, 150mg and Tolterodine against placebo in 314 patients over 4 weeks (BLOSSOM Study).[9] The study showed that both doses of the Mirabegron were effective and reduced frequency of micturitions by -2.2 (placebo -1.2) with an increase in mean voided volume. The drug was well tolerated but the higher dose of Mirabegron was associated with an increase in heart rate of 5 beats per minute. There was no tachycardia or palpitation.

A subsequent phase IIB dose ranging study compared four different doses of Mirabegron, 25mg, 100mg, 150mg, 200mg against placebo over 12 weeks and found that both frequency (reduced) and mean voided volume (increased) were impacted favorably by all doses of Mirabegron (DRAGON Study).[10] The discontinuation rate was about 3% in the treatment groups and similar to placebo. There was no episode of retention and no ECG changes. There was a mean increase of 1.6 beats per minute with 100mg and 4.1 beats per minute with the 200mg strength of the drug.

These studies were followed by large phase III trials in Europe and North America. Nitti et al compared placebo, Mirabegron 50mg and 100mg in a randomized control trial involving 1328 patients over 12 weeks (ARIES Study).[11] Entry criteria included overactive bladder symptoms for at least 3 months and the patients needed to have frequency of at least 8/day and urgency episodes at least 3 per 72 hours. Primary end point was change in the number of incontinence episodes per 24 hours and urinary frequency per 24 hours from baseline. The mean age of patients was about 60 years and 74% of patients were female. The study population was varied reflecting usual clinical

practice and included patients with urgency urinary incontinence (30%), mixed urinary incontinence (38%) (urgency-predominant) and urgency-frequency (32%). About 15% of patients were of 75years or above in age. Over half the patients had used AM drugs before and the mean frequency was 11.7/day, mean urgency or urgency incontinence episodes was 5.8/day and mean voided volume was 157ml. Both the treatment groups showed a statistically significant improvement in the primary end-points and these improvements were seen at the 4 week assessment also. The adverse events included hypertension, urinary tract infection, nasopharyngitis, headache, diarrhea and dry mouth but all these were equivalent to placebo. The discontinuation rates were around 4% and similar in all the arms. A similar phase III study by Khullar et al included a fourth arm with Tolterodine 4mg and showed essentially similar results in a group of 1978 patients (SCORPIO Study).[12] Mirabegron was not more effective than Tolterodine in this study.

A subsequent study by Herschorn et al included 25mg dose and showed efficacy with this dose equivalent to the 50mg dose (CAPRICORN Study).[13] A pooled analysis by Nitti et al in 2013 showed that there was ceiling effect at 50mg with no further beneficial effect in enhancing the dose. There was a reduction of urgency incontinence episodes of -1.49 and -1.50 and reduction of frequency by -1.75 and -1.74 per day in the 50mg and 100mg groups respectively.

These studies provided the foundation for the recommendation of 25mg and 50mg dosages in clinical practice.

Most of the studies examined predominantly female patients. Male patients with their propensity for benign prostatic hyperplasia related obstruction is potentially a different clinical setting for OAB. Otsuki et al examined 124 men as a part of a non-randomized relatively small OAB study that included a predominantly male ($3/4^{th}$ patients) population.[14] The study excluded those with a residual urine of >100ml. The drug was effective in men with significant improvement in OABSS and IPSS. There was no increase in the post-void residual and the drug was well tolerated.

A recent analysis of both pooled data (three trials) and direct comparison studies (one versus placebo, another versus Tolterodine), Mirabegron was effective in reducing frequency but not urgency and urgency incontinence in male patients in the pooled analysis.[15] The direct comparison study with placebo showed efficacy across all three parameters.

A Japanese study looked at urodynamic findings in males taking Tamsulosin offered add-on Mirabegron.[16] There was an increase in cystometric capacity from 170ml to 212ml (p=0.01) with either resolution (25%) or reduction in amplitude of phasic contractions (remaining). There was no significant difference in the $P_{det.max}$ (79cm $H_20$ versus 68cm $H_20$) and bladder contractility index (126 versus 120).

Mirabegron has also been studied in children with OAB and was found to be well tolerated and efficacious as add-on therapy in 35 children with a mean age of 10.3 years refractory to AMs.[17]

Recently, attempts have been made to compare Mirabegron with Onabotulinum toxin. A recent systematic review and network meta-analysis 56 RCTs and concluded that Onabotulinum was more effective on all parameters of efficacy at 12 weeks as compared with all oral therapies for OAB.[18]

## Side effects, safety and persistence data

To date over 27,000 patients have been studied in clinical trials involving Mirabegron and the drug has been well tolerated with no major adverse events.(19) The limiting side-effects of AM do not seem to be a problem with Mirabegron. Rates of dry mouth, constipation and urinary retention are equivalent to placebo.

Cardiovascular safety has been examined in detail given that adrenoceptors are important in the heart.[5] In a pooled report of 20 beta-3 agonist studies (Mirabegron 16, Solabegron 2 and one each for AK 677 and BRL 35135) major cardiovascular events (APTC-MACE) were equivalent to Tolterodine and placebo at both 12 weeks and one year. Hypertension was noted in 8.7% equivalent to placebo (8.5%) with a mean ≤1mm Hg reversible rise in blood pressure. There was no orthostatic hypotension. QTc prolongation was noted in 0.4% again similar to Tolterodine and placebo. Heart rate was increased by a mean of 1 beat per minute with 50mg dose. There was no increase in the incidence of palpitation or atrial fibrillation. Arrhythmias were noted in 4% similar to both Tolterodine and placebo. In contrast Tolterodine and Trospium are associated with an increase in heart rate of one and three beats

per minute.[5] Overall, the cardiovascular safety profile was considered to be satisfactory and comparable to existing drugs.

A 12month study examined the safety profile and found that Mirabegron and Tolterodine were equivalent in both safety and efficacy (TAURUS Study).[20]

The drug shows a favorable safety profile in the elderly. A large study from Japan found no increase in cardiovascular or other major side effects in a "real-world" study over one year.[21]

Persistence with therapy has been a problem with AMs. Although OAB is a chronic problem that is often incurable, most patients tend to stop drug therapy in the long term. A large study of 167,907 patients that examined persistence with therapy for six major chronic illnesses, glaucoma (prostaglandin analogues), hyperlipidemia (statins), osteoporosis (bisphosphonates), diabetes mellitus (oral hypoglycemic agents), hypertension (angiotensin receptor blockers) and OAB (AM) found that persistent with AMs was the worst of the six at one year.[22] Recently, Chapple et al studied time to discontinuation of therapy for different OAB medication in 21996 patients in the UK. Mirabegron had the longest time to discontinuation of 169 days as compared with Tolterodine (56 days) and 30-78 days for the other AMs.[23] The 12month persistence rate for Mirabegron was 38% versus 20% for Tolterodine, again a significant difference. This is possibly testimony to the better efficacy-tolerability ratio for Mirabegron although the study was not designed to evaluate the reasons for the finding. Similar persistence data has been reported recently from Japan in a large nationwide survey.[24]

## Clinical utility and guidelines recommendations

Mirabegron has been updated to second line management alongside AM in the 2015 American Urological Association Guidelines.[4] The guideline also states that Mirabegron has lower rates of dry mouth and constipation as compared to AM and is equivalent in efficacy. Mirabegron has been also been recommended in situations where AM are either ineffective or contraindicated.

The European Association of Urology Guidelines of 2017 give Mirabegron a grade A recommendation for management of OAB unless they have uncontrolled hypertension.[25] The drug has been recommended in the elderly, a group in which there are significant concerns regarding the long-term and potentially cumulative risk of cognitive dysfunction with AMs. Mirabegron has been noted to be as efficacious as AM with adverse events similar to placebo (Level 1a).

The National Institute for Health and Care Excellence (NICE) guidelines of 2013 state that Mirabegron should be prescribed only if AMs are ineffective, not tolerated or contraindicated.[26] However, this guidance seem dated with several key studies that have been published since its release.

The Sixth International Consultation on Incontinence of 2016 gives a grade A recommendation to Mirabegron for the treatment of OAB.[7]

## Combination therapies in OAB

Given the different mechanisms of action of AMs and Mirabegron as well as the unique side-effect profiles of each drug, combination of the two drugs would seem intuitive. Indeed, several key studies have attempted to address this question.

A large phase II study by Abrams et al examined 1306 adult patients (2/3$^{rd}$ women) across 141 sites in 20 countries over a 12-week period (SYMPHONY Study).[27] This detailed study compared 12 groups of patients: 6 combinations of Solifenacin (2.5, 5 and 10mg) and Mirabegron (25 and 50mg) as well as 5 monotherapy groups representing the same doses of these drugs and placebo. Combinations of Solifenacin 5mg and 10mg with Mirabegron were noted to be more effective than Solifenacin 5mg alone. All the groups were well tolerated with increase in the mean voided volume from baseline (primary end-point). Treatment associated adverse events were equivalent in between Mirabegron and placebo except for hypertension.

An even larger study of 2174 patients by Macdiarmid et al compared a combination of Mirabegron 50mg with Solifenacin 5mg with Solifenacin 5mg as well as 10mg (BESIDE Study).[28]Combination of Mirabegron 50mg along with Solifenacin 5mg seemed to perform better. A recent report of the pre-specified sub-analysis from this study of elderly patients showed that the combination was well tolerated and more efficacious compared to individual agents in patients ≥75 years age.[29]

A study from Korea recently examined the benefits of adding low-dose AM in patients with inadequate

response to 50mg of Mirabegron and found that 10mg of Propiverine resulted in significant improvement in symptoms with minor and tolerable increase in side-effects.[30]

Based on these studies, the EAU Guidelines of 2017 recommend that patients with inadequate symptom control with Solifenacin 5mg may benefit more from the addition of Mirabegron than dose escalation of Solifenacin (Grade 1b).[25] Certainly, the combination offers an option for escalating drug therapy without adding to the antimuscarinic load, an important consideration in some elderly patients.

## Combination with other drugs

Mirabegron has been combined with Tamsulosin, an alpha adrenergic blocker in men with benign prostatic hyperplasia and lower urinary tract symptoms. The drug was noted to be effective. Given that Tamsulosin has its own cardiovascular adverse event profile it was noteworthy that there was no potentiation of cardiovascular side effects in a small study of 48 men between 44-72 years.[5]

Beta blockers are often used for hypertension and there have been concerns that there might be an adverse interaction with Mirabegron. However, this does not seem to be the case. In various studies, 17% of patients in the shorter trials of 12 weeks and 19% in one-year studies have been on concomitant beta blockers.[5] Of these, between 11-18% have been on non-selective (beta-1 and beta-2) blockers. There was no reduction in the efficacy of Mirabegron and no effect of Mirabegron on the efficacy of the beta blocker Metoprolol. The tolerability of the combination was similar to Mirabegron alone.[5]

Mirabegron interferes with the metabolism of Digoxin increasing the AUC and $C_{max}$ by 27 and 29 % respectively.[31] Hence, when the two drugs are combined, the lowest dose of Digoxin should be used to start with.

## Conclusion

Mirabegron is a valuable addition to armamentarium of clinical therapies for overactive bladder. It is as effective as antimuscarinic drugs and is better tolerated. The adverse events profile appears safe in the elderly and in male patients with benign prostatic hyperplasia. Combinations of the drug with antimuscarinics appear to be more efficacious than either drug alone and this offers the opportunity for combination therapy.

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