



Mirabegron: a decade of study

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The role beta-3 receptors play in bladder function has been researched for 25 years, however it was not until 2007 that the compound YM178 (which was to become mirabegron) was described (1). This set in motion an important new therapeutic option for patients with overactive bladder (OAB). Once available for use, mirabegron rapidly became one of the most commonly used oral therapies for OAB (2,3).

The article by Chapple *et al.* described the pooled analysis of 10 regulatory clinical trials of mirabegron (4). This was a complex analysis of 11,261 patients representing several different geographic areas in the world. One should pause and consider the enormity of the work that was required to make mirabegron a reality. What is summarized in a few pages of a journal article represents an enormous investment from Astellas, researchers, and patients from around the world. In these studies, patients were treated with mirabegron, placebo or a comparator antimuscarinic (tolterodine or solifenacin) within the different clinical trial designs. Many of the patterns in the baseline data are not surprising: older patients had more urgency incontinence than younger patients, women had more urgency and incontinence than men, and a higher body-mass index was associated with more incontinence and urgency. About 1 in 4 participants had a history of hypertension, and about half had used prior OAB medications at some point.

There were two main outcomes of interest in this study. The first was safety. Reassuringly, serious treatment related adverse events were rare in all groups (<2%) and not different from placebo, and situations where the serious adverse event was likely related to the medication was extremely rare (<0.5%). However, it is important to keep in mind that these patients represent those who made it past the inclusion/exclusion hurdles of a clinical trial, and may not represent the average OAB patient that is seen

in practice. When looking at all adverse events across the three groups (placebo, mirabegron, antimuscarinic), the only thing that stands out is a much higher rate of dry mouth with antimuscarinics. It is interesting that overall, constipation did not increase significantly among antimuscarinic users. However, there was an interaction with age: those >75 years of age (of which there were only about 500 people) had almost twice as much constipation when using antimuscarinics compared to mirabegron or placebo, whereas those <75 years of age did not have a substantial difference. Aside from this, nasopharyngitis and hypertension were the most common side effects, and they did not differ substantially across the three groups. In subgroup analysis, those ≥75 years of age had a slightly higher frequency of hypertension and tachycardia with mirabegron compared to antimuscarinics or placebo. In general, women and older patients had a higher risk of adverse events.

The second outcome of interest was efficacy, and not surprisingly, active treatment was significantly better than placebo across the usual OAB endpoints, and generally women and older patients had a greater magnitude of improvement. When comparing among the active treatment groups (mirabegron, solifenacin, and tolterodine) the outcomes had overlapping confidence intervals suggesting similar efficacy.

Mirabegron has now been available for clinical use for 5–10 years. It has become the OAB therapy with the highest real-world persistence (2). This is notable as OAB is a condition fraught with patients who become disillusioned with medical therapy. The most common reason for discontinuation of OAB medication is that the patient felt it didn't work as expected, however side effects are also reported by 1 in 5 of people as the reason for stopping their

medication (5). The reasons mirabegron persistence is so high appears primarily to be related to better tolerability rather than significantly better efficacy (6), and this paper by Professor Chapple appears to support this conclusion (4).

The initial fear by physicians who were not early adopters of mirabegron centered around the risk of cardiovascular complications from stimulation of the beta receptors in the heart. Concerns about the risk of hypertension or arrhythmia/tachycardia were cited as limitations of mirabegron. While uncontrolled hypertension remains a contraindication to the use of mirabegron, there has not been evidence that there is a significant risk of new hypertension or serious arrhythmias. Certainly the analysis by Chapple *et al.* of industry sponsored randomized control trials (4) found only a small increased risk of hypertension and tachycardia among patients older than 75 years of age. Similarly, a large administrative data study of the use of mirabegron in the real-world setting did not find an additional risk of clinically relevant cardiac complications (7).

The cardiovascular safety of mirabegron has been well studied and appears acceptable. As with any medication, care should be taken when prescribing it in the elderly population. The other potential benefits of mirabegron over antimuscarinics include a lack of ocular side effects (8) and a medication class that does not have the stigma of cognitive dysfunction. The negative effect of antimuscarinic medications on cognition has been well studied (9,10), and seems to persist when studied in the OAB population (11).

Currently used therapeutic options for OAB include conservative measures, two classes of oral medications, neuromodulation and intravesical onabotulinum toxin. Mirabegron appears to be a well-tolerated and efficacious medical option for patients. The potential addition of vibegron in the near future will offer an alternative beta-3 agonist which may offer a different efficacy profile (12,13).

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References

1. Takasu T, Ukai M, Sato S, et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. *J Pharmacol Exp Ther* 2007;321:642-7.
2. Chapple CR, Nazir J, Hakimi Z, et al. Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. *Eur Urol* 2017;72:389-99.
3. Tadrous M, Elterman D, Khuu W, et al. Publicly funded overactive bladder drug treatment patterns in Ontario over 15 years: An ecological study. *Can Urol Assoc J* 2018;12:E142-5.
4. Chapple CR, Cruz F, Cardozo L, et al. Safety and Efficacy of Mirabegron: Analysis of a Large Integrated Clinical Trial Database of Patients with Overactive Bladder Receiving Mirabegron, Antimuscarinics, or Placebo. *Eur Urol* 2020;77:119-28.
5. Benner JS, Nichol MB, Rovner ES, et al. Patient-reported reasons for discontinuing overactive bladder medication. *BJU Int* 2010;105:1276-82.
6. Staskin D, Herschorn S, Fialkov J, et al. A prospective, double-blind, randomized, two-period crossover, multicenter study to evaluate tolerability and patient preference between mirabegron and tolterodine in patients with overactive bladder (PREFER study). *Int Urogynecol J* 2018;29:273-83.

7. Tadrour M, Matta R, Greaves S, et al. Association of Mirabegron With the Risk of Arrhythmia in Adult Patients 66 Years or Older-A Population-Based Cohort Study. *JAMA Intern Med* 2019. doi: 10.1001/jamainternmed.2019.2011.
8. Novack GD, Lewis RA, Vogel R, et al. Randomized, double-masked, placebo-controlled study to assess the ocular safety of mirabegron in healthy volunteers. *J Ocul Pharmacol Ther* 2013;29:674-80.
9. Risacher SL, McDonald BC, Tallman EF, et al. Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults. *JAMA Neurol* 2016;73:721-32.
10. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018;361:k1315.
11. Welk B, McArthur E. Increased risk of dementia among patients with overactive bladder treated with an anticholinergic medication compared to a beta-3 agonist: a population-based cohort study. *BJU Int* 2020. doi: 10.1111/bju.15040.
12. Edmondson SD, Zhu C, Kar NF, et al. Discovery of Vibegron: A Potent and Selective β_3 Adrenergic Receptor Agonist for the Treatment of Overactive Bladder. *J Med Chem* 2016;59:609-23.
13. Yoshida M, Takeda M, Gotoh M, et al. Efficacy of vibegron, a novel β_3 -adrenoreceptor agonist, on severe urgency urinary incontinence related to overactive bladder: post hoc analysis of a randomized, placebo-controlled, double-blind, comparative phase 3 study. *BJU Int* 2020. doi: 10.1111/bju.15020.

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