



Comment on: Safety and efficacy of mirabegron: analysis of a large integrated clinical trial database of patients with overactive bladder receiving mirabegron, antimuscarinics, or placebo

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Overactive bladder (OAB) is a complex syndrome with a high prevalence. It affects all ages, but is increasingly prevalent as age increases (1-4). Many treatments have been proposed for the management of the condition, including physical therapies (magnetic stimulation, electrical stimulation, posterior percutaneous tibial nerve stimulation) (5) and intravesical injections with botulinum toxin A. Drug treatment with antimuscarinic and beta 3 agonist, however, is the therapy of choice for most patients. Antimuscarinic drugs are an early treatment option for adults with OAB, while mirabegron has only been available since 20135 and three different systematic reviews demonstrated significant efficacy and safety in treating symptoms of OAB (6-8), thus expanding therapeutic possibilities for the treatment of syndrome.

In this issue of *European Urology*, Chapple *et al.* (9) summarize efficacy and safety reporting of mirabegron treatment for OAB syndrome. They pooled data from global double-blind, 12-week studies in patients with OAB receiving as monotherapy mirabegron, antimuscarinic (solifenacin or tolterodine) or placebo. Analyses evaluated safety, tolerability, and efficacy of each treatment and assessed differences in baseline characteristics and among subgroups: age <65 versus >65 year, age <75 versus >75 year, and men versus women. Authors found that drug-related adverse events are more frequent with antimuscarinics (AM) followed by mirabegron (MIRA) and then placebo. The incidence of dry mouth for AM group is higher (8.7%) than

that for MIRA (2.7%) or placebo (2.4%) group. Overall frequency of treatment-emergent adverse events (TEAEs) is 5–10% higher for older versus younger patients and 6–7% higher for women versus men. TEAEs increased with age more in the AM than in the MIRA population and in particular constipation was seen with high frequency in AM group. Hypertension frequency is similar in treatment groups and urinary retention is <1% in all treatment groups, age groups and in both sexes. At the end of treatment mirabegron (25 and 50 mg) and antimuscarinics (solifenacin 5 mg and tolterodine 4 mg) were associated with a higher improvement versus placebo in the mean number of incontinence episodes/24 h, urgency episodes/24 h, volume voided/micturition and nocturia episodes. The significance of changes from baseline was, in general, greater in older patients, women and those who had received prior OAB medication.

How to interpret this data? The greatest incidence of dry mouth and the highest rate of constipation in older patients in antimuscarinic group does not surprise us, due to anticholinergic effects of antimuscarinics. Vazquez Roque *et al.* (10) showed that aging process of the enteric nervous system, pelvic floor dysfunction like a decreased rectal compliance, increased urge thresholds for defecation, decreased rest and squeeze pressures in the anal canal, anatomic abnormalities and a delayed colonic transit may be the cause of the higher incidence of constipation in

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the elderly. The anticholinergic effects of antimuscarinic overlap with this precarious pathophysiology.

White *et al.* (11) demonstrated no evidence of increased cardiovascular risk for mirabegron or antimuscarinics over placebo in the treatment of OAB. Chapple *et al.* (9) shows that the incidence of hypertension is similar in all groups but it is slightly higher in older patients and in mirabegron group. As suggested by authors themselves, this may be due to the fact that in mirabegron studies there were strict requirements to report hypertension and these requirements were not in historic antimuscarinics studies.

The incidence of urinary retention is low in all treatment and age groups. Kelleher *et al.* (12) in a systematic literature review and network meta-analysis established that mirabegron 50 mg had a significantly lower frequency of urinary retention compared with seven active treatments (fesoterodine 4 and 8 mg, oxybutynin IR 9 mg, solifenacin 10 mg, solifenacin 5 mg combined with mirabegron 25 or 50 mg, and trospium 60 mg) and no significant differences for the remaining four comparators (placebo, propiverine 20 mg, solifenacin 5 mg, and tolterodine ER 4 mg).

Considering the drug efficacy at the end of treatment is not unexpected that older patients in treatment groups have a greater improvement of symptoms. As suggested by authors, elderly population has a more severe symptomatology at baseline and therefore a higher opportunity for improvement.

So how to choose the best therapy for management of OAB? Following the considerations of Chapple *et al.* (9), we may affirm that there is no the best therapy for management of OAB, but there is the therapy that best fits patient's characteristics. The choice of the drug should consider age, sex, also, comorbidities, medications, symptoms at baseline and costs. In general mirabegron may be the best choice for elderly and in patients susceptible to constipation.

In conclusion Chapple *et al.* (9) reaffirm the safety, tolerability and efficacy of mirabegron, solifenacin and tolterodine in different age groups and in both sexes. Adverse events are more frequent with AM compared to MIRA and the incidence of dry mouth, due to anticholinergic effects, is higher in AM group than in the MIRA group. Future studies should consider on a large scale the safety, efficacy and adverse events in some particular categories of patients, such as patients with neurological diseases.

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