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SAFETY PROFILE AND DISCONTINUATION OF MIRABEGRON 50 MG, MIRABEGRON 100 MG AND TOLTERODINE 4 MG FOR PATIENTS WITH OVERACTIVE BLADDER/STORAGE LUTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hypothesis / aims of study

The standard of care for pharmacological therapy for overactive bladder (OAB)/storage LUTS are the antimuscarinics. However, due to inadequate symptom control and/or intolerable treatment-emergent adverse events (TEAEs) more than 60% of patients discontinue antimuscarinics over a 12-month period. The aim of our study is to analyze the safety/tolerability profile of mirabegron 50 mg, mirabegron 100 mg and tolterodine 4 mg as a comparator for the treatment of OAB/storage LUTS.

Study design, materials and methods

A MEDLINE, EMBASE, Cochrane Library, and Science Citation Index Expanded Medline search was performed to identify all published randomized placebo-controlled clinical trials evaluating mirabegron for the treatment of OAB/storage LUTS. The most common reported Treatment-Emergent Adverse Events (TEAEs) were recorded and analyzed.

Results

After an extensive research, 491 studies were identified from the databases. After a full evaluation of each study, a total of 8 randomized studies were identified eligible for this meta-analysis.

Tolterodine 4 mg (Tol) was associated with a greater risk of overall TEAEs rate than placebo (OR: 1.38; p<0.0001). Conversely, mirabegron 50 mg (Mir50) and mirabegron 100 mg (Mir100) were not associated with an increased risk of TEAEs when compared to placebo (OR: 0.94; p=0.32 and OR:0.97; p=0.31, respectively)

In particular, Mir50 was not associated with an increased risk of hypertension (OR: 1.02; p=0.90), while with mirabegron 100 mg this risk was slightly increased (OR: 1.41; p=0.08) in comparison to placebo. Also the risk of cardiac arrhythmia was not significantly increased over placebo with Mir50 (OR: 1.0; p=1.00), but slightly with Mir100 (OR: 2.18; p=0.06).

The risk of dry mouth was statistically greater for Tol (OR: 2.97; p<0.001) vs. placebo, but also vs. Mir50 and Mir100 (OR: 2.49; p<0.00001, and OR: 2.43; p<0.001, respectively).

The discontinuation rate due to adverse events was not greater for Mir50 (OR: 0.97; p=0.80), Mir100 (OR: 0.89; p=0.63) or Tol (OR:1.42;p=0.12) vs placebo. (Figure 1).

Interpretation of results

Results showed a better TEAEs profile of β_3 -adrenoceptor agonist compared to Tol, that can be explained by the different selectiveness of the drugs. β_3 -adrenoceptor receptors are present in bladder and adipose tissue, while muscarinic receptors are well represented in many organs, leading to a higher rate of TEAEs in the Tol arm compared to mirabegron.

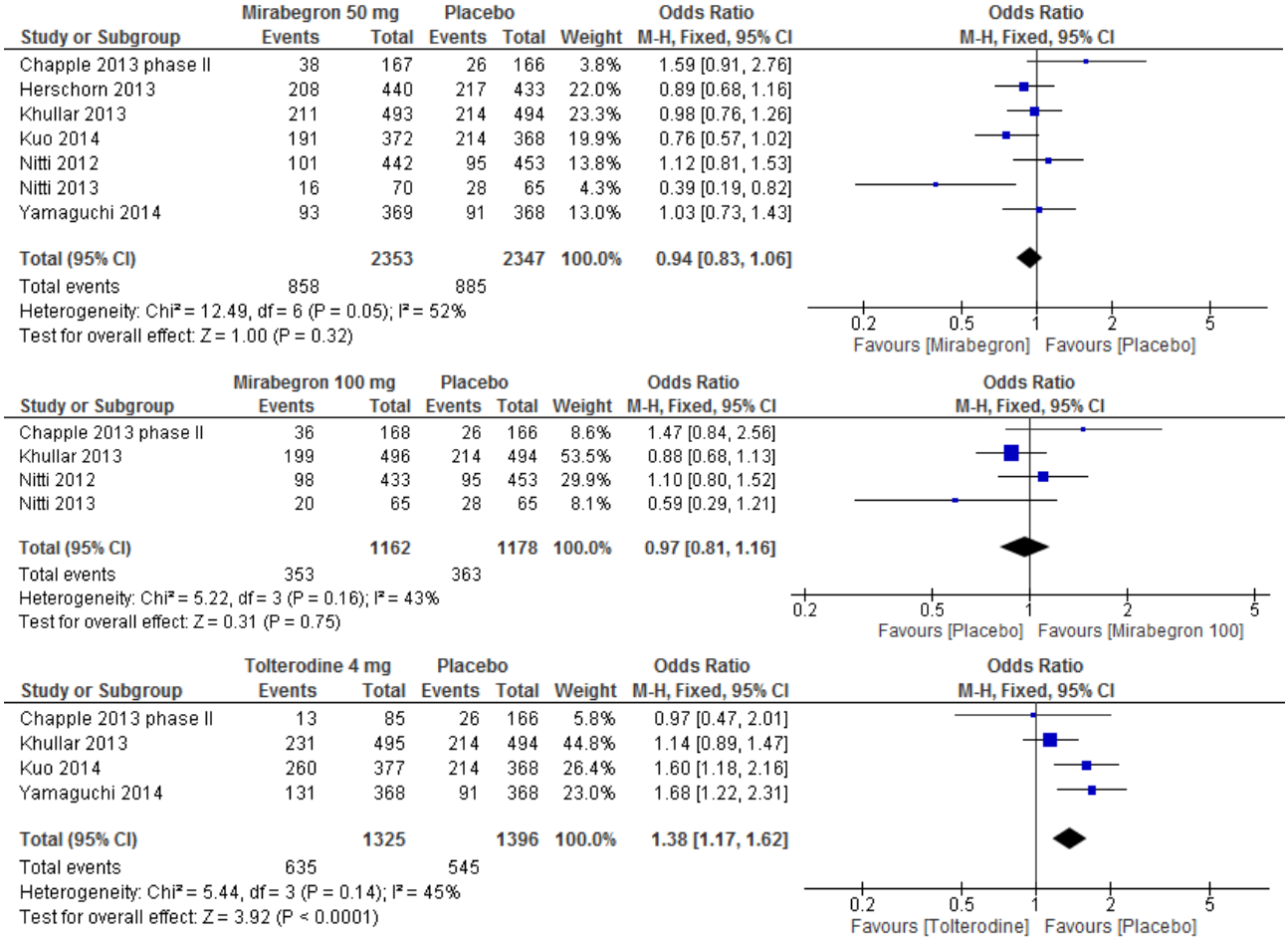
Mirabegron's adverse effects, like hypertension can be explained to the intrinsic alfa-agonist activity of the drug that is concentration related, so higher dosages can bring higher rates of hypertension. Dry-mouth sensation can be also related to pharmacodynamics, but the adrenergic component is not as predominant as the muscarinic one on salivary glands, so that's why Tol results more bothersome.

The discontinuation rate due to adverse effects shows that almost every drug is well-tolerated, independently to the TEAEs. The reason can be that the OAB/Storage LUTS are usually more bothersome than TEAEs, allowing a better compliance for the patients.

Concluding message

Mir50 and Mir100 are associated with an acceptable safety profile. For Mir50 and Mir100, the risk of TEAEs and the discontinuation rate due to TEAEs is not superior to placebo. However, Mir100 is associated with a slight increase in hypertension and cardiac arrhythmia. Conversely, Tol was found associated with an increased risk of overall TEAEs vs placebo, but not with treatment discontinuation due to TEAEs. These findings should be considered when evaluating the risk-benefits of prescribing drugs for OAB/storage LUTS.

Figure 1. Risk of TEAEs.



Disclosures

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