

Drugs for the overactive bladder: are there differences in persistence and compliance?

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The overactive bladder (OAB) syndrome, characterized by urinary urgency with or without urgency urinary incontinence (UUI) and usually associated with increased daytime frequency and nocturia (1), is a common condition worldwide. Independent of the methodology used (telephone survey, postal survey) several epidemiologic studies in Europe, Canada, the United States, and Japan have shown the OAB syndrome to be present in 8.0% to 16.5% of adults, with similar rates between men and women (2,3). OAB and UUI are highly prevalent disorders, progress dynamically over time (2,4,5), and are characterized by both considerable incidence and remission rates. Irwin *et al.* (2) performed a systematic review to assess whether the severity of OAB and UUI symptoms progresses dynamically over time. They also assessed, as a secondary aim, the factors that may be associated with symptom progression and regression. Their results supported the hypothesis that OAB dry progresses to OAB wet and that the severity of UUI symptoms increases over time. Irwin *et al.* (2) suggested that the recognition of OAB and UUI as progressive conditions called for a shift from the current treatment paradigm of symptom control alone to one of symptom management, including measures to prevent the condition worsening. Such measures might include increasing adherence to treatment regimens (compliance) and behavioural modifications, such as bladder training, pelvic floor muscle exercises, and lifestyle modifications. This should also include pharmacologic treatment, which

currently is regarded to be symptomatic only. It should be kept in mind that OAB is a heterogeneous condition with a multifactorial underlying pathophysiology, and even if there may be a common theme in their pharmacological profile (6), the detailed mechanisms of action of currently established therapies (antimuscarinics and β_3 -adrenoceptor agonists), and why they are effective, have not been established. It has been demonstrated that after discontinuation of drug treatment there is a relapse of OAB symptoms (7,8), which indicates that treatment is effective. However, it has never been demonstrated that long-term pharmacologic therapy really can modify (delay) or stop the progression of the condition. This does not exclude that this may occur in some cases, and that long-term pharmacological treatment beside symptom relief and consequent benefits of e.g., quality of life, may improve the underlying disorder. However, for long-term medication to be effective, good persistence and compliance with the OAB medication(s) is essential.

Terminology

To be able to adequately assess differences in persistence and compliance, use of clear definitions are required. This has not always been the case, and the terms persistence, compliance, and adherence have been used across different therapeutic areas and have been defined in various ways. The International Society for Pharmacoeconomics and

Outcomes Research (ISPOR) Work Group for Compliance and Persistence, after 3 years of discussion, arrived at the following definitions (9):

- (I) Medication persistence refers to the act of continuing the treatment for the prescribed duration. It may be defined as “the duration of time from initiation to discontinuation of therapy”;
- (II) Medication compliance (synonym: adherence) refers to the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency. It may be defined as “the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen”.

Differences of persistence and compliance between OAB drugs

In the pharmacologic treatment of OAB, a limitation is that available approved drugs are restricted to several antimuscarinics and the β_3 -adrenoceptor agonist, mirabegron. In general, persistence to OAB drugs is lower than for other types of chronic medications, such as antihypertensives and drugs for treatment of diabetes (10). Even if there seem to be no consistent differences in efficacy between antimuscarinics and the β_3 -adrenoceptor agonists, for long-term use it is desirable to establish if there are relevant differences in persistence and compliance not only between antimuscarinics and β_3 -adrenoceptor agonists (mirabegron), but also between different antimuscarinics. These issues have been discussed by several investigators (3,11-16), and recently in a study by Chapple *et al.* (17).

The investigation by Chapple *et al.* (17) was a retrospective, longitudinal, observational study, using anonymised data from the UK Clinical Practice Research Datalink GOLD database, and they compared the persistence and adherence with mirabegron versus tolterodine extended release (ER) and other antimuscarinics in routine clinical practice over a 12-month period. The study population included 21,996 patients, and the antimuscarinics studied, beside tolterodine ER, were darifenacin, fesoterodine, flavoxate, oxybutynin ER or immediate release (IR), propiverine, solifenacin, tolterodine IR, and trospium chloride. The primary endpoint was persistence (time to discontinuation), and secondary endpoints included 12-months persistence rates and adherence, assessed using medication possession ratio (MPR). The median time-to-discontinuation was

significantly longer for mirabegron (169 days) compared to tolterodine ER (56 days) and other antimuscarinics (range, 30–78 days). The 12-month persistence rates, 38% and 20%, respectively, and MPR were also significantly greater with mirabegron than with all the antimuscarinics investigated. Improvements with mirabegron were maintained in predefined sub-cohorts of treatment-naïve, treatment-experienced, and older patients.

Why the differences?

For the population in the Chapple *et al.* (17) study, it thus seems that mirabegron has better persistence and compliance during long-term treatment than antimuscarinics, which is in agreement with previous studies (15,18). This raises questions: “why this difference between antimuscarinics and mirabegron?” “Why is the persistence with prescribed antimuscarinic therapy so conspicuously low?” and “are there relevant differences between antimuscarinics?” (12,14,19,20). In a retrospective cohort study comprising 31,996 OAB patients newly treated with oxybutynin, and 24,855 newly treated with tolterodine, the persistence (after 2 years of follow-up) with oxybutynin (9.4%) was significantly lower than with tolterodine (13.6%, $P < 0.0001$). The median time to discontinuation of oxybutynin and tolterodine was 68 and 128 days, respectively (12). An analysis of prescription data for patients receiving these drugs for treatment of the OAB syndrome over a 12-month period, showed that at 12 months, the proportions of patients still on their original treatment were: solifenacin 35%, tolterodine ER 28%, propiverine 27%, oxybutynin ER 26%, trospium 26%, tolterodine IR 24%, oxybutynin IR 22%, darifenacin 17%, and flavoxate 14%. The longest mean persistence was reported for solifenacin: 87 *vs.* 77–157 days for the other treatments (14). These figures should be compared with those for mirabegron in the study by Chapple *et al.* (17) median time for discontinuation 169 days, and persistence rate at 12 months 38%.

Reasons for discontinuation

Chapple *et al.* (17) found that discontinuation of antimuscarinics was less common among men than among women and generally occurred within 1–3 months, compared to a median of 5.6 months with mirabegron. A limitation of this study was that it did not capture reasons for discontinuation. Reasons for discontinuation have

been discussed by several investigators (3,21). Benner *et al.* (21) examined in a 2-phase survey reasons for discontinuing OAB pharmacotherapy. Expectations about treatment efficacy (46.2%) and side-effects (21.1%) were the most important considerations. Other factors such as cost and unwillingness to take long-term treatment may contribute. Can these causes explain the differences between mirabegron and antimuscarinics? It does not seem that there are differences in efficacy between them (22,23), which means that differences in the adverse effect profile could be a main cause.

Adverse effect profiles

The common adverse events of antimuscarinic drugs are expected and well known, and result from the blockade of muscarinic receptors in, e.g., the salivary gland, colon, and ciliary smooth muscle, inducing dry mouth, constipation, and blurred vision, respectively (24). Madhuvrata *et al.* (25) analyzed 86 trials including 31,249 adults with OAB symptoms in order to compare preferences for various antimuscarinics. In their analysis, a main effect determining drug preference was the occurrence of dry mouth. Kessler *et al.* (26) analyzed 69 trials enrolling 26,229 patients with OAB with the aim to compare adverse events of antimuscarinics using a network meta-analytic approach that overcomes shortcomings of conventional analyses. They found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride, but not for oral oxybutynin when currently used starting dosages were compared.

Antimuscarinics are generally considered to be “safe” drugs. Questions have been raised related to cardiac adverse effects, particularly QT prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes), and increases in heart rate (HR) (27,28). However, based on experiences both from clinical trials and extensive clinical use, the cardiovascular safety of antimuscarinics is generally considered acceptable. However, concerns have been raised concerning the effects of antimuscarinics on cognitive functions (24) and more recently with respect to the risk of producing dementia (29).

Generally, the adverse effect profile of mirabegron has been benign, with a frequency of events similar to that of placebo (30). Gastrointestinal disorders, including constipation, dry mouth, dyspepsia, and nausea, have been the most commonly reported. One concern with the

use of β_3 -AR agonists has been the possibility of negative cardiovascular effects. Even if the cardiovascular effects of mirabegron observed in clinical studies have been minimal and not clinically relevant, long-term data is needed to assess efficacy and safety (30).

How to improve compliance and persistence?

More effective strategies for improving compliance and persistence with OAB pharmacotherapy are needed. Assessing the individualized needs of each patient and goal achievement for the most bothersome symptoms as well as patient support programs can be good strategies. Since the most common causes for discontinuation are lack of efficacy and adverse effects it is important to inform the patients on these issues to promote realistic expectations. It should be emphasized that drugs are second line treatment, and a combination of behavioral therapy and drug intervention seems to be the most efficacious in terms of patient satisfaction, perceived improvement, and reduction of bladder symptoms (31).

Summary/conclusions

Current evidence indicates that OAB is a dynamic progressive disorder increasing with age. The fact that there is a high relapse rate after discontinuation of pharmacological treatment suggests that such therapy is effective, even long-term, for counteracting symptoms. It is therefore desirable to optimize treatment by improving persistence and compliance to the current therapeutic options. Antimuscarinics, still first line therapy, have a conspicuously low persistence rate depending on modest efficacy and an unfavorable adverse effect profile, dry mouth and constipation being the most common. However, there has been an increasing concern with respect to possible negative effect on cognition and risk of dementia development, particularly during long-term treatment. Mirabegron, the only β_3 -adrenoceptor agonist approved for clinical use, has an efficacy comparable to that of antimuscarinics, but has a better adverse effect profile, often similar to that of placebo. However, the effect of long-term treatment on e.g., cardiovascular function is not known. Effective long-term treatment of OAB requires good compliance and persistence to the chosen therapy. Based on available evidence, the persistence and compliance to mirabegron during long-term treatment are better than to antimuscarinics. This seems attributable to a better

relation between efficacy and adverse effects. To improve compliance and persistence with OAB pharmacotherapy, more effective strategies needed.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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