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Combination Therapy for Overactive Bladder: Should We Define Refractoriness?

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Overactive bladder (OAB) is not a life-threatening disease but it seriously impairs patients' quality of life. However, it is considered an under-reported and under-diagnosed disorder because of different individual, cultural, and even welfare factors. First-line treatment should be tailored using individualised behavioural and physical therapies (including pelvic floor muscle training). According to clinical guidelines, drug treatment should be considered as a second-line treatment [1,2].

In this issue of *European Urology*, Gratzke et al [3] present the results from a systematic literature search to identify evidence of the efficacy and safety of combination therapy with either mirabegron and an antimuscarinic agent or two antimuscarinics. We have already suggested that combination therapy with solifenacin and mirabegron may optimise efficacy with an acceptable tolerability profile in comparison to a higher antimuscarinic dose, providing greater patient satisfaction, contributing to higher adherence and persistence rates, and yielding a better efficacy-tolerability balance [4].

The European Association of Urology guidelines on urinary incontinence [1] recommend (with a strong rating) considering dose escalation or offering an alternative antimuscarinic formulation, or mirabegron, or a combination if monotherapy with an antimuscarinic treatment proves ineffective. The 2019 American Urological Association guidelines [5] also advise the use of combination therapy if monotherapy with either antimuscarinics or β3 agonists has failed in patients with idiopathic OAB. However, no definitions of the criteria and/or thresholds for assessing unsatisfactory outcomes of therapy to declare OAB refractory have been described.

Another problem is that no minimum time for assessing efficacy has been defined. Only the National Institute for Health and Care Excellence guidelines [2] suggest offering a review 4 wk after starting anticholinergic treatment (they do not recommend mirabegron as first-line drug treatment [6]), and if there is no or suboptimal improvement (or intolerable adverse effects) they recommend changing the dose or trying an alternative medicine for OAB at a lesser possible cost and waiting a further 4 wk. There is no specific proposal on the indication for combination therapy or for two anticholinergics or the addition of mirabegron.

Furthermore, there is no symptom-based definition or even a universal patient-reported outcome in the literature for deciding on whether or not patients have responded to conservative and/or antimuscarinic treatment [7,8]. Moreover, patients' individual evaluation of treatment success is characterised by different expectations and perceptions. Patients usually favour treatment discontinuation because it "did not work as expected", but management of patient expectations is not mandatory before changing treatment. Even in studies evaluating refractory OAB in which patients experienced a "lack of efficacy/benefit", no objective measurement is provided [9]. Phé et al [8] suggested that endpoints in clinical studies evaluating patient responses to OAB treatment should focus on changes in urgency, with or without other symptoms, and quality of life. Schwantes et al [10] hypothesised that increasing patient motivation to adhere to prescribed treatments, managing patient expectations before beginning a therapy, excluding other underlying causes, and tailoring pharmacological therapy to each patient might improve treatment outcomes among OAB patients.

Symptom improvement in clinical trials is usually not reproducible in clinical practice because a defined, regular follow-up schedule may increase patient motivation [9]. Another question that might be asked is whether it is

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the bladder that is refractory or the patient. According to clinical guidelines, urodynamic studies should only be performed if the findings might change the choice of further treatment [1]. A third-line treatment (ie, with botulinum toxin) can be offered even if detrusor overactivity has not been demonstrated [2]. Should both the physician and the patient address the symptoms, disregarding their pathophysiological basis? OAB is a symptom complex rather than a disease, and re-evaluation of a clinical diagnosis is not considered in management algorithms.

How should we define refractoriness? Should we include the management of patient expectations in the guideline algorithms? Should we consider combination therapy as part of second-line or as third-line treatment? Should we design multicentre clinical trials comparing combinations of two antimuscarinics and the addition of either an antimuscarinic or a β3 agonist in patients not responding to monotherapy? All these questions are still open.

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