Combination pharmacotherapy for the treatment of the overactive bladder syndrome: a new solution for an old problem?

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Overactive bladder syndrome (OAB) is a chronic urological condition that affects almost 20% of the population with a significant adverse impact on the quality of life. OAB may also have serious health consequences including mortality secondary to the increased risk of depression, falls and fractures. Thus far, the use of antimuscarinic therapy in OAB patients has been disappointing with reported compliance rates between 17%–35% after 2 years. Critical appraisal of novel pharmacological modalities for treatment of OAB, therefore, remains a research priority.

Successful treatment of OAB requires proper clinical evaluation. In addition, patient counseling is important as compliance with treatment is instrumental in improving therapeutic efficacy. The treatment algorithm for OAB is a stepwise approach beginning with conservative measures [1] and ending with more invasive procedures.

Pharmacotherapy is frequently resorted to after the failure of conservative therapy or initially in appropriately selected patients. Antimuscarinics are commonly used; however, discontinuation rates are very high because of bothersome side effects or inadequate clinical response. To improve efficacy, providers may increase the dose of the drug [2], switch to a different antimuscarinic or try a combination of antimuscarinics to improve the therapeutic efficacy at the expense of producing higher rates of side effects [3].

The β 3-adrenergic receptor agonist mirabegron is another class of medication that has been in use since 2012 for treatment of OAB with similar clinical efficacy to antimuscarinics. Mirabegron acts through activation of the pre-junctional β 3-adrenoceptors of the urinary bladder.

Treatment of OAB with β 3-adrenergic receptor agonists has gradually gained acceptance in recent years as most clinical trials showed a better pharmacological profile and improved patient compliance compared with antimuscarinics [4–6].

When pharmacotherapy of OAB with either antimuscarinics or β 3-adrenergic receptor agonists does not achieve satisfactory results, then the next line of treatment becomes more invasive or inconvenient with increased risks of complications [7, 8]. Invasive options include onabotulinumtoxin-A intradetrusor injection, sacral neuromodulation or posterior tibial nerve stimulation [8]. In May 2018, the FDA approved combination therapy of a β 3-adrenergic agonist and an antimuscarinic, solifenacin, as another pharmacological treatment option for OAB [9]. This may offer an additional promising non-invasive therapeutic management step between single-agent pharmacotherapy and more invasive approaches for the treatment for patients with OAB.

The FDA decision was based on three seminal, multicenter and prospective randomized, double-blind, placebo-controlled trials, the SYMPHONY trial [10], BESIDE trial [11] and SYNERGY trial [12]. These demonstrated a significant improvement in urgency, urgency incontinence and other storage symptoms in the combination therapy arm compared with placebo or monotherapy. In all three studies, combination therapy was better tolerated with minimal side effects that were comparable to single drug treatment, and this was associated with improved quality of life. The adverse events reported with combination therapy were not significantly more bothersome than with monotherapy [10, 12]. This effect continues to be demonstrated in the elderly population.

In conclusion, the FDA approval of combined drug therapy has expanded our pharmacological armamentarium in monotherapy-refractory OAB before considering invasive procedures. The combination drug has a different pharmacological profile and seems to be safer and better tolerated by patients than a combination of two drugs from the same class. Until more clinical data are available, we believe that combining anticholinergics with a β 3-adrenergic receptor agonist is a good pharmacotherapy option for OAB patients who failed

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monotherapy and may be an appropriate step before moving on to more invasive or inconvenient therapeutic options. The future will tell if there will be a new therapy that will contain the combination therapy in one pill form and if insurance coverage will be expanded to cover this combination therapy.

Compliance with ethical standards

Conflict of interest None.

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