Overactive bladder - pharmacological treatment

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

Overactive bladder syndrome is defined by the International Continence Society (ICS) as a clinical syndrome characterized by lower urinary tract dysfunction, including symptoms of urgency, with or without urge incontinence, usually accompanied by increased frequency of urination and nocturia in the absence of associated metabolic factors, infectious or local[1]. With the objective of mitigating the symptoms and improving the quality of life, the main therapeutic modalities employed include non-pharmacological clinical treatment (which includes general measures, behavioral treatment, and physical therapy) and pharmacological treatment. Muscarinic antagonists represent the first line of treatment for patients with overactive bladder that is idiopathic or secondary to underlying neurological diseases[2,3]. They are used to stabilize the detrusor muscle, through their connection and antagonism to muscarinic receptors. This results in a reduction of detrusor hyperactivity and improvement of symptoms[4]. Patients with neurogenic detrusor hyperactivity may require higher doses than patients with idiopathic detrusor hyperactivity[5,6].

METHODOLOGY

We used the P.I.C.O. Acronym to formulate the synthetic question. P corresponds to patients with overactive bladder; I to intervention using muscarinic antagonists, antidepressants, alpha-adrenergic receptor antagonists, and beta-adrenergic receptor agonists; C for comparison; and O to the outcome of effectiveness and damage. From the structured question, we identified the keywords used as a basis for the evidence search in the databases Medline-PubMed and Scielo. Since the approach is a treatment, we opted for a controlled randomized clinical trial type of study. We included studies available in Portuguese, English, Spanish, or Italian. Through the research strategy ((((((Urinary Bladder, Overactive

OR Overactive Detrusor))) AND ((Adrenergic beta-3 Receptor Agonists OR Mirabegron))) AND RANDOM, we recovered 2782 papers; of these, 65 were selected to answer the clinical questions, and after the update process another 05 were included.

RESULTS

What is the role of muscarinic antagonist drugs in the treatment for overactive bladder?

Vesical contractions are the result of the cholinergic stimulation of muscarinic receptors. There are five well-known types of receptors (M1 to M5), and at the bladder M2 and M3 are found – the latter, the most important in the detrusor contraction. The cholinergic or muscarinic antagonists, through their parasympatholytic action, prevent the interaction of acetylcholine with the receiver by inhibiting the transmission of the postsynaptic impulse. They act by decreasing the amplitude of involuntary vesical contractions, increasing the vesical volume up to the first involuntary contraction and increasing the functional capacity of the bladder. They are the medicines most used in the treatment of overactive bladder syndrome and have recognized superiority in relation to the placebo[7,8]**(A)**. However, although some drugs currently available are more selective to the bladder muscarinic receptors M2 or M3, unpleasant systemic effects are frequent, particularly those related to the stimulation of muscarinic receptors present in other organs, causing, amongst other, a sensation of dry mouth, blurred vision and inhibition of intestinal peristalsis, causing constipation. Other central effects include dizziness, loss of memory, and drowsiness. These adverse effects often are intense enough to cause the patient to abandon the treatment.

Oxybutynin chloride

It is a tertiary amine of mixed action, commonly administered orally, which associates effects of antispasmodic, muscarinic antagonist, and local anesthetic on the smooth muscles, and it is currently the most widely used drug[9]**(A)**. Its main effect, however not specific, is inhibiting the M1 and M3 receptors. It was the first anticholinergic agent used in the treatment of overactive bladder, with success rates ranging from 61 to 86%, with its effectiveness limited by its side effects[10-12]**(D)**. It is currently under formulation with immediate release, and it is the first agent of its class to be used in the treatment of OAB or of slow release (not currently available in our area). Other possibilities of administration, aiming to minimize the side effects, but that are not available in the Brazilian market, including a transdermal format and a gel for topical use.

Tolterodine tartrate

It is a tertiary amine with a powerful muscarinic antagonist action which has shown eight times greater affinity for bladder muscarinic receptors (M2) in comparison to the salivary glands[10]**(D)**. It is also available in immediate and slow release formats, with the latter demonstrating greater patient tolerability and adherence due to its lower serum fluctuation[9]**(A)**. Its greater selectivity gives its better tolerability profile[13]**(D)**. A randomized clinical trial analyzing both forms of presentation identified best results in the slow release format, in addition to more discrete side effects[14]**(A)**.

Oxybutynin chloride versus tolterodine tartrate

Several studies have compared the two drugs in different doses, formulations, forms of release, and treatment times. Direct comparisons between oxybutynin, tolterodine suggest that both drugs have similar effects on episodes of urinary incontinence, although studies reported better results on the number of episodes of urge incontinence, incontinence, and urinary frequency with the use of oxybutynin of slow release in comparison with immediate-release tolterodine [15-21]**(A)**. However, when comparing the two agents in their prolonged action form, tolterodine proved to be better tolerated by patients[14]**(A)**. With respect to quality of life and the data on the perception of cure or improvement of symptoms identified by patients, both treatments were similar[22,23]**(A)**. Analyzing tolerability, individuals undergoing treatment with tolterodine, in both immediate and slow forms, had a lower probability of abandonment because of adverse events (between 34 and 60%)[17,21,23]**(A)**.

Darifenacin hydrobromide

It is the anticholinergic most selective to M3 of its class, reducing the effects secondary to the blockade of M1 and M2 receptors. Placebo-controlled studies have demonstrated its effectiveness in the treatment of patients with symptoms related to overactive bladder. It proved to be effective in reducing the number

of episodes of urge incontinence, urinary frequency, and intensity of urgency[24-27](A). Despite its selectivity, there are side effects, mainly dry mouth and constipation[24](A). Central effects are reduced due to the selectivity and low penetration in the central nervous system[28](B).

Solifenacin succinate

It is an antagonist of muscarinic receptors specific to M2 and M3 with a long duration, which allows for a single daily dose. Its use by overactive bladder patients showed an improvement in symptoms of urgency and urge incontinence, also increasing the volume per urination[29.30](A)[31](B). The adverse effects found did not differ from those of other drugs previously mentioned and are reported as mild and moderate. Randomized studies demonstrated a lower risk of cognitive deterioration in elderly patients who received treatment with solifenacin, in comparison with the oxybutynin[32.33](A).

Solifenacin succinate versus tolterodine tartrate

Comparisons between solifenacin and tolterodine suggest, regarding the first, best results in respect of quality of life, symptoms of urinary urgency and urge incontinence and perception of improvement of the symptoms identified by the patients, although some studies show similar effects between both drugs[30,34-36](A)[37,38](B). Although studies have demonstrated similar or even better results with the use of solifenacin and lower frequency of complaints related to dry mouth, abandonment of treatment due to adverse events were similar [35](A)[38](B).

Trospium chloride

It is a quaternary amine and as such does not exceed the blood-brain barrier, significantly reducing side effects on the central nervous system. By means of mixed action, combining the effects of anticholinergic and muscle relaxers, it is effective in the treatment of patients with symptoms related to overactive bladder[39](A). It is a powerful competitor of acetylcholine, with high affinity for M1, M2, and M3 receptors. Placebo-controlled, randomized studies comparing the trospium chloride to oxybutynin showed similar effectiveness and side effects (except on the central nervous system) [40-42](A). This is not available for commercial use in our area.

RECOMMENDATION

The primary therapy for overactive bladder syndrome is clinical-pharmacological treatment. Currently, anticholinergic agents are the drugs most often used for managing this disease. The use of these substances is associated with side effects, which may lead to the abandonment of treatment in most cases. Oxybutynin, tolterodine, darifenacin, and solifenacin are considered the drugs of first choice for the treatment of overactive bladder. They are contraindicated for individuals with narrow-angle glaucoma and should be used with caution in the elderly and in cases of infravesical obstruction due to the possibility, albeit small, of causing urinary retention. **(A)**

What is the role of antidepressants in the treatment for overactive bladder?

These drugs have severe systemic anticholinergic action, in addition to the inhibition of serotonin reuptake. Among antidepressants, the most widely used in the treatment of overactive bladder has been imipramine, a tricyclic antidepressant. Peripherally, it has an important anticholinergic effect, however with a small muscarinic antagonist effect on the musculature detrusor muscle. It also has an indirect alpha-adrenergic action, since it inhibits the reuptake of norepinephrine and serotonin, promoting relaxation of the detrusor muscle and increased intraurethral pressure [30](D). It consequently decreases the episodes of urinary leakage and can be an alternative, especially in cases of mixed urinary incontinence. Although studies have demonstrated the beneficial effect of this drug, with the reduction or improvement of incontinence, they are comprised of small series of cases or non-controlled trials assessing the combined effect of other drugs associated to imipramine [43](D). A small placebo-controlled clinical trial showed no significant difference between the treatments[44](B). Adverse events, especially cardiovascular ones, with a possibility of arrhythmias, has limited its use[45](A). Side effects include dry mouth, constipation, tachycardia, and blurred vision, in addition to fatigue, excessive sweating, headache, muscle tremors, and epigastric discomfort.

RECOMMENDATION

Imipramine is the tricyclic antidepressant most often used to treat overactive bladder syndrome, despite the lack of randomized clinical trials. It should

not be prescribed to patients with psychiatric disorders of the mania type or who use MAO inhibitors. Its clinical application may be limited in patients with an increased risk of arrhythmias (prolonged QT interval). **(D)**

What is the role of alpha-adrenergic receptor antagonists in the treatment for overactive bladder?

Alpha-blockers have a potential effect of improvement of symptoms related to overactive bladder. However, there is currently no scientific information that supports its clinical use[46] **(B)**.

RECOMMENDATION

Even though there are studies demonstrating the improvement of symptoms, the use of alpha-adrenergic antagonists in the treatment of overactive bladder is still not routinely indicated as a monotherapy. **(B)**

What is the role of beta-adrenergic receptor agonists in the treatment for idiopathic overactive bladder?

Beta-3 agonists represent a new class of drugs for the treatment of idiopathic overactive bladder. Three subtypes of adrenergic receptors (B1, B2, and B3) have been identified in the human detrusor and urothelium, with a predominant expression of beta-3 receptors in the detrusor. The activation of these beta-3 adrenergic receptors causes relaxation of the detrusor, secondary to the activation of adenyl cyclase and formation of cyclic adenosine monophosphate. Mirabegron is the first beta-3 agonist drug to be part of the clinical practice[47-50] **(D)**.

A recent systematic review of the literature with network meta-analysis [51] **(A)** of 64 randomized clinical trials (2000-2017; n = 46,666 patients) and analysis of the quality of the studies included assessed the efficacy and tolerability of mirabegron 50mg for treating overactive bladder (OAB), including "detrusor hyperactivity" or "urinary urgency", but excluding "neurogenic detrusor activity" and men with lower urinary tract symptoms associated with benign prostatic hyperplasia. The intervention treatments used were a muscarinic antagonist, mirabegron 50 mg, or combinations, and the control treatments included a muscarinic antagonist (different drugs, formulations or dose) or placebo. Mirabegron 50 mg was significantly more effective than the placebo for all outcomes of effectiveness [frequency of urination, urgency urinary incontinence (UUI), number of patients with zero episodes of incontinence or reduction of 100% of these episodes and reduction of 50% of incontinence]. In an analysis of the data of this study considering only mirabegron 50 mg compared with any muscarinic antagonist monotherapy, we found:

- Urinary frequency in 24 hours

Analysis based on 42 studies (n = 34,992). The effectiveness of mirabegron 50 mg was not significantly different from other active treatments, except for solifenacin 10 mg in monotherapy, which was more effective than mirabegron (mean variation: –0.37 [CI95%: –0.62, –0.13)

- Urgency urinary incontinence (UUI) in 24 hours

Thirty-seven studies (n = 25,494) were included. The effectiveness of mirabegron 50 mg was not significantly different from other active treatments, except for fesoterodine 8 mg, which was more effective than mirabegron 50 mg in monotherapy.

- Number of patients with zero episodes of incontinence or reduction of 100% of these episodes

Analysis based on 22 studies (n = 19,442). The effectiveness of mirabegron 50 mg was not significantly different from other active treatments, except for trospium 60 mg, solifenacin 10 mg, and fesoterodine 8 mg, which were all more effective than mirabegron 50 mg.

- 50% reduction in episodes of incontinence

Ten studies (n = 9,379) were included. No significant differences were observed between mirabegron 50 mg and other active treatments.

- Episodes of incontinence in 24 hours

No significant differences were observed comparing mirabegron with other active treatments, except for solifenacin 5 and 10 mg in monotherapy, which were more effective than mirabegron 50 mg.

This study suggests that mirabegron 50 mg provides similar effectiveness (no significant differences) to most muscarinic antagonists. However, solifenacin 10 mg was significantly more effective in comparison with mirabegron 50 mg for all parameters of effectiveness, except for UUI and 50% reduction in episodes of incontinence.

Tolerability evaluations showed that mirabegron 50 mg presents significantly less risk of dry mouth, constipation, and urinary retention. Similar overall tolerability was observed between mirabegron 50 mg and all other treatments (including the placebo)

for all other outcomes (blurred vision, hypertension, ITU, tachycardia) [51]**(A)**.

RECOMMENDATION

The data indicate that mirabegron 50 mg has a favorable balance of effectiveness and tolerability and represents an option of alternative treatment to muscarinic antagonist monotherapies for OAB patients. **(A)**

What is the role of combined therapy (mirabegron and muscarinic antagonist) in the treatment for idiopathic overactive bladder?

A phase II RCT, multicenter, double-blind, placebo-controlled monotherapy, and with a follow-up of 12 weeks, included 1306 female patients ≥ 18 years with symptoms of OAB ≥ 3 months and assessed the effectiveness of the combination solifenacin/mirabegron with monotherapy of solifenacin 5 mg. The secondary objective was to explore the dose-response relationship (solifenacin 2.5, 5, or 10 mg and mirabegron 25 or 50 mg) and the safety/tolerability in comparison with placebo and monotherapy. The combined therapy of mirabegron/solifenacin showed significant improvement in comparison with the monotherapy (solifenacin 5 mg) concerning the volume eliminated through urination, urinary frequency, and urgency; it also did not increase adverse events associated with muscarinic antagonist therapy, except for constipation [52]**(B)**. Another study, this one a phase IIIB, included patients resistant to the use of solifenacin 5 mg/day. They were randomized for a combination of solifenacin/mirabegron, or monotherapy with solifenacin 5 mg or 10 mg and were followed-up for 12 weeks. The drug combination proved to be superior to the of solifenacin 5 mg regarding the number of daily urinations and reduction of episodes of urinary incontinence. The combination was worse than the monotherapy of solifenacin 10 mg in reducing episodes of urinary incontinence (urination journal for three days) and was better in reducing the daily number of urinations [53]**(B)**.

RECOMMENDATION

The combined therapy of solifenacin/mirabegron can be an option to monotherapy with solifenacin 5 mg in patients with OAB. **(B)**

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