Overactive bladder: pharmacological treatment

Bexiga hiperativa: tratamento farmacológico

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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 procedures 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.

Description of evidence collection method

The review of scientific articles in this guideline was carried out from MEDLINE, Cochrane and SciELO databases. The search for evidence was based on actual clinical scenarios and used keywords (MeSH terms) grouped in the following syntax: (Overactive Detrusor OR Overactive Urinary Bladder OR Urinary Bladder, Overactive OR Urinary Incontinence) AND (Cholinergic Antagonists OR Anticholinergic Agents OR Agents, Cholinergic Blocking OR Muscarinic Antagonists OR Antimuscarinics OR Parasympatholytics OR Antispasmodics OR Imipramine OR Beta-3 Adrenergic Receptor Agonist OR Mirabegron OR Adrenergic Beta-3 Receptor Agonists OR Beta-3 Adrenergic Agonist). The articles were selected after a critical evaluation of the strength of scientific evidence, and the publications of greatest strength were used for recommendation. The recommendations were elaborated from discussions in the group. The entire guideline was reviewed by an independent group specializing in evidence-based clinical recommendation.

Grades of recommendation and levels of evidence

- **A:** Experimental or observational studies of higher consistency.
- **B:** Experimental or observational studies of lower consistency.
- **C:** Cases reports (non-controlled studies).
- **D:** Opinion without critical evaluation, based on consensus, physiological studies or animal models.

Objective

To describe the main recommendations in the pharmacological treatment of overactive bladder.

Introduction

Overactive bladder syndrome is defined by the International Continence Society (ICS) as a clinical syndrome characterized by lower urinary tract dysfunction that includes urgency symptoms, with or without urge incontinence, usually accompanied by pollakiuria and nocturia, in the absence of metabolic and infectious factors or associated diseases.[1] **(D)** In order to minimize symptoms and improve quality of life, the main therapeutic modalities are non-pharmacological (general measures, behavioral and physiotherapeutic treatment) and pharmacological. Antimuscarinics represent the first line of medical treatment for patients with overactive bladder, both idiopathic and secondary to the underlying neurological disease.[2,3] **(D)** They are used to stabilize the detrusor muscle, through binding and blocking muscarinic receptors. This results in improvement of bladder functional capacity, reduction of detrusor overactivity and improvement of symptoms.[4] **(A)** Patients with neurogenic detrusor overactivity may need higher doses than patients with idiopathic detrusor overactivity.[5] **(A)**[6] **(B)**

1. What is the role played by antimuscarinic drugs in the treatment of the overactive bladder?

Bladder contractions are due to the cholinergic stimulus of muscarinic receptors. Five types of receptors are well-known (M1 to M5). In the bladder, types M2 and M3 occur, the latter being the most important for contracting the detrusor muscle. Anticholinergic or muscarinic antagonists act through parasympatholytic action, which prevents the interaction of acetylcholine with the receptor by binding to the muscarinic receptors in the postganglionic synaptic cleft, reducing the amplitude of the contrac-

tions, increasing the volume at the first contraction, and thus the functional capacity of the bladder. These are the drugs most used in the treatment of overactive bladder syndrome, with recognized superiority over placebo.[7,8] **(A)** However, none of the currently available drugs selectively targets muscarinic receptors M2 or M3 in the bladder, where they predominate. They therefore cause unpleasant systemic effects, particularly related to salivary secretion and intestinal function, which are often intense enough to lead the patient to cease treatment. Potential side effects of antimuscarinic drugs include dry mouth, visual turbidity and inhibition of intestinal peristalsis, causing constipation. Other central effects are dizziness, memory loss and drowsiness.

Oxybutynin chloride

This is a tertiary amine with mixed action, commonly used orally, which associates antispasmodic, antimuscarinic and local anesthetic action on the smooth muscle, and is currently the most widely used drug.[9] **(A)** Its main effect, although not specific, is the inhibition of M1 and M3 receptors. It was the first anticholinergic used in the treatment of overactive bladder, with success rates ranging from 61 to 86%, but with limited effectiveness due to side effects.[10-12] **(D)** It is available as immediate release, the first agent of this class to be used in the treatment of overactive bladder symptoms, or extended release formulation. Other possibilities of administration aiming to minimize the side effects, but not commercialized in Brazil, include a transdermal patch, intravesical and topical gel. In these forms, it is possible to control the serum fluctuations of the drug, which are responsible for the appearance of most of the side effects.

Tolterodine tartrate

It is a tertiary amine with potent antimuscarinic action that demonstrated eight times greater affinity for the muscarinic receptors in the bladder (M2) than in the salivary glands.[10] **(D)** It is also available in forms of immediate and extended release, the latter having shown greater tolerability and adherence by patients due to less serum fluctuation.[9] **(A)** Its greater selectivity gives it a better tolerability profile.[13] **(D)** A randomized clinical trial analyzing the two forms of presentation identified better results with the extended release form, in addition to more discrete side effects.[14] **(A)**

Oxybutynin chloride versus tolterodine tartrate

Numerous studies have compared the two drugs in different dosages, formulations, release forms and treatment times. Direct comparisons between oxybutynin and tolterodine suggest that both drugs have similar effects on urinary incontinence episodes, although studies report better results on the number of episodes involving urge incontinence, urinary incontinence and urinary frequency using extended release oxybutynin compared with immediate release tolterodine.[15-21] **(A)** However, when comparing the two agents in long-acting presentation, tolterodine was shown to be better tolerated by patients.[14] **(A)** Regarding quality of life and data on the perception of cure or improvement of symptoms identified by the patients, both treatments were similar.[22,23] **(A)** As for tolerability, subjects receiving tolterodine, either immediate or extended release, were less likely to cease treatment because of adverse events (34-60%).[17,21,23] **(A)**

Darifenacin hydrobromide

This anticholinergic agent is highly selective for M3 receptors, reducing the side effects of M1 and M2 receptor blockade. Placebo-controlled studies have demonstrated its efficacy in treating patients with overactive bladder-related symptoms, proving to be effective in reducing the number of urge incontinence episodes as well as in voiding frequency and intensity of urgency.[24-27] **(A)** However, despite its selectivity, side effects are observed, affecting about half of the patients.[24] **(A)** Central effects are reduced by selectivity and low penetration in the central nervous system.[28] **(B)**

Solifenacin succinate

This is a long-acting M3 receptor-specific muscarinic receptor antagonist, which allows for a single daily dose. Its use to treat overactive bladder has resulted in improvements in urgency and urge incontinence symptoms, also increasing volume per urination.[29,30] **(A)**[31] **(B)** Adverse effects do not differ from those of the other drugs cited above and have been reported as mild and moderate. Randomized studies have shown a lower risk of cognitive impairment in elderly patients receiving solifenacin compared to oxybutynin.[32,33] **(A)**

Solifenacin succinate versus tolterodine tartrate

Comparisons between solifenacin and tolterodine suggest better results with the former regarding quality of life, urgency and urge incontinence symptoms, and perceived improvement of symptoms identified by patients, although studies have shown similar effects between both drugs.[30,34-36] **(A)**[37,38] **(B)** Some studies have reported dry mouth complaints less commonly in subjects receiving solifenacin, others have shown similar or even superior results with

the use of this drug. However, therapeutic withdrawals related to adverse events were similar.[35] **(A)**[38] **(B)**

Trospium chloride

It is a quaternary amine and, as such, it does not cross the blood-brain barrier, significantly reducing side effects on the central nervous system. Through an anticholinergic effect, it has efficacy in the treatment of patients with symptoms related to overactive bladder.[39] **(A)** It is a potent competitor of acetylcholine, with high affinity for M1, M2 and M3 receptors. Randomized placebo-controlled studies comparing trospium chloride to oxybutynin showed similar efficacy and side effects.[40-42] **(A)**

Recommendation

The main therapeutic modality of overactive bladder syndrome is clinical pharmacological treatment, and anticholinergic agents are currently the most widely used drugs in the management of this condition. These substances are associated with side effects, which lead the patient to abandon treatment in most cases. They are contraindicated in individuals with closed angle glaucoma and should be used with caution in cases of infravesical obstruction due to the risk of urinary retention. **(A)**

2. What is the role played by antidepressants in the treatment of the overactive bladder?

These drugs have intense systemic anticholinergic action, in addition to the inhibition of serotonin reuptake. In this class, the drug most commonly used to treat overactive bladder has been imipramine, which is a tricyclic antidepressant. Peripherally, it has an important anticholinergic effect, but the antimuscarinic effect on the detrusor muscles is limited. It also has an indirect alpha-adrenergic action, as it inhibits the reuptake of noradrenalin and serotonin, promoting relaxation of the detrusor muscle and increased intraurethral pressure.[30] **(D)** It reduces the episodes of urinary loss, being an alternative especially in cases of mixed urinary incontinence. Although studies have shown a beneficial effect of this drug, with reduction or improvement of incontinence, they comprise small series of cases or uncontrolled trials evaluating the combined effect of other drugs associated with imipramine.[43] **(D)** A small placebo-controlled clinical trial did not show a significant difference between treatments.[44] **(B)** Adverse effects, mainly cardiovascular events leading to the onset of arrhythmias, have limited their use.[45-48] **(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 commonly used in the treatment of overactive bladder syndrome, despite the lack of randomized clinical trials. It should not be prescribed for patients with mania-type psychiatric disorders and those who are taking MAO inhibitors. Its clinical application may be limited in patients at increased risk of cardiac arrhythmias (prolonged QT interval). **(D)**

3. What is the role played by alpha--blockers in the treatment of the overactive bladder?

α-blockers have the effect of improving symptoms related to overactive bladder. However, there is currently no scientific information to support its clinical use.[49] **(B)**

Recommendation

Despite studies showing improvement of symptoms, the use of α-blockers to treat overactive bladder is not yet routinely indicated. **(B)**

4. What is the role played by beta-agonists in the treatment of the overactive bladder?

β3-adrenergic receptor agonists represent a new class of drugs for the treatment of idiopathic overactive bladder. Three subtypes of adrenergic receptors (β1, β2 and β3) were identified in detrusor muscle and human urothelium, with a predominant expression of β3 receptors in the detrusor muscle. Activation of β3 adrenergic receptors causes relaxation of the detrusor muscle secondary to the activation of adenylyl cyclase and formation of adenosine cyclic monophosphate. Mirabegron is the first β3 agonist to be used in clinical practice.[50-53] **(D)** To assess the efficacy and tolerability of this drug therapy in the treatment of idiopathic overactive bladder (IOAB), two phase II[54,55] **(B)** and six phase III[56-61] **(A)** randomized clinical trials (RCTs) recruited more than 10,500 adult patients. Of these, seven were randomized, double-blind and placebo-controlled with follow-up of four (one study) and 12 (six studies) weeks, and one was non-placebo-controlled (vs. tolterodine) with 12-month follow-up. All studies recruited male and female patients over 18 years of age with IOAB symptoms for at least three months prior to the start of the study. Most studies compared several doses of mirabegron to placebo and/or long-acting (LA) tolterodine, 4 mg, and

the primary efficacy endpoints considered were number of micturitions and number of episodes of incontinence over 24 hours (results expressed as average).

A systematic review (SR), with all the studies above, concludes that mirabegron is as effective as most antimuscarinics, including LA tolterodine, 4 mg, compared to placebo in relation to the primary outcomes (number of micturitions and number of episodes of incontinence over 24 hours). Regarding tolerability, the data suggest that patients who took mirabegron had a similar rate of adverse events compared to those in the placebo group, whereas the rate in the antimuscarinic group was the highest.[62] **(A)**

The most common adverse events observed with mirabegron include: hypertension, nasopharyngitis, urinary tract infections, headache, constipation, upper respiratory tract infection, arthralgia, diarrhea, tachycardia, abdominal pain and fatigue.[63] **(A)**

A SR with meta-analysis included data from six RCTs[54,55,57-59] and showed that mirabegron (25, 50 and 100 mg) was more effective than placebo in treatment of IOAB regardless of dose, in the analysis of the following outcomes: number of episodes of incontinence and number of micturitions in 24 hours. Compared with placebo, mirabegron showed a similar risk of adverse events. Compared with tolterodine, mirabegron was more effective in terms of mean number of incontinence episodes over 24 hours (MD -0.25; 95CI -0.43--0.06; p=0.009), but there was no difference in mean number of micturitions over 24 hours (MD -0.17; 95CI -0.35-0.01; p=0.07). Mirabegron also showed a lower rate of adverse reaction in this comparison [OR 0.9; 95CI 0.8-1.0; p=0.04].[64] **(A)**

Recommendation

β3 adrenergic receptor agonists have the effect of improving symptoms related to overactive bladder. Patients who may benefit from mirabegron include those who are unsuitable for the use of antimuscarinics or who have already presented adverse events with them. **(A)**

5. Combination therapy (mirabegron and antimuscarinics)

A multicenter, double-blind, placebo-controlled, phase II RCT with a follow-up of 12 weeks included 1,306 female and male patients ≥ 18 years with symptoms of IOAB ≥ 3 months and assessed the efficacy of combination solifenacin/mirabegron compared to solifenacin 5 mg alone. The secondary endpoint was to explore the dose-response relationship (solifenacin 2.5, 5 or 10 mg and mirabegron 25 or 50 mg) and safety/tolerability compared to placebo and monotherapy. Combination therapy with mirabegron/solifenacin demonstrated a significant improvement over monotherapy (solifenacin 5 mg) as to volume eliminated by urination, voiding frequency and urgency, without increasing adverse events associated with antimuscarinic therapy, except for constipation.[65] **(B)**

Recommendation

Combination therapy solifenacin/mirabegron may be an option for solifenacin 5 mg as monotherapy in patients with IOAB. **(B)**

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