Conitec

Recomendation report

DRUGS

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Antimuscarinics (Oxybutynin, Tolterodine, Solifenacin and Darifenacin) for the treatment of Storage Dysfunction in patients with Neurogenic Bladder

Brasília – DF
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Technologies: Antimuscarinics (oxybutynin, tolterodine, solifenacin and darifenacin).

Indication: Storage dysfunction in adult patients with neurogenic bladder.

Background: Neurogenic bladder is a term applied to a malfunctioning urinary bladder and urinary sphincter, due to neurologic dysfunction emanating from internal or external trauma, disease or injury. Some patients with neurogenic lower urinary tract dysfunction experience symptoms that relate to impaired urine storage, such as increased frequency of micturition, urinary urgency and urinary incontinence.

Question: What is the efficacy and safety of oxybutynin, tolterodine, solifenacin and darifenacin for storage dysfunction in adult patients with neurogenic bladder?

Scientific evidence: For the question about the efficacy and safety of antimuscarinics (oxybutynin, tolterodine, solifenacin and darifenacin), 868 references were retrieved through the search strategies, of which five randomized controlled trial (RCTs) were selected. The main efficacy outcomes assessed by these RCTs were: maximal bladder capacity, number of incontinence episodes per day, number of catheterizations per day, Incontinence Quality of Life (I-QoL), and Patient Perception of Bladder Condition (PPBC) score. In addition to the efficacy outcomes, adverse events were also assessed. One of the RCTs reported that intravesical oxybutynin provided a greater increase in cystometric volume than oral oxybutynin (mean increase [standard deviation - SD] of 116.6 [27.5] mL and 18.1 [27.5] mL, respectively, p = 0.009). Another RCT reported that solifenacin 5 mg and 10 mg and oxybutynin 15 mg provided a significant increase in cystometric volume compared with placebo (mean increase [SD] of 77.8 [115.4] mL, 134.2 [124.7] mL and 134.2 [124.7] mL, respectively, p <0.01 for all comparisons versus placebo). Two RCTs compared tolterodine versus placebo for the cystometric volume outcome, one of which reported no difference between the groups, and the other reported a dose-response effect for tolterodine, with 4 mg being the most effective dose compared with placebo (p = 0.009). In regard to the outcome of number of urinary incontinence (UI) episodes per day, a RCT reported that, after four weeks, the group receiving oxybutynin 15 mg showed a mean reduction (SD) of 2.71 (2.84) UI episodes/day, while solifenacin 10 mg showed a reduction of 0.57 (2.29) UI episodes/day (p <0.01). An RCT comparing oxybutynin with tolterodine at a tailored dose (mean of 12.5 mg/day and 8.4 mg/day, respectively) reported no significant difference between the therapies for any of the efficacy outcomes assessed. As for the primary outcome of quality of life (I-QoL), and also for functionality (PPBC), there was no comparison results in the RCTs analyzed, except for an RCT comparing intravesical versus oral oxybutynin for I-QoL, with no statistically significant difference (p = 0.730). Moreover, even for the outcome of reduction in UI episodes, there is uncertainty about the clinical significance of the result, given that the mean reduction in episodes was < 2 in most RCTs, for a baseline scenario of 2-5 episodes/day. The methodological quality of the RCTs was low, and there are no direct comparisons of the four antimuscarinics (oxybutynin, tolterodine, solifenacin and darifenacin).

Economic evaluation: The RCTs analyzed in this report did not include analysis of darifenacin. Furthermore, they did not evaluate antimuscarinics against a common comparator, and, even if an indirect comparison among the antimuscarinic agents would be made, only one RCT assessed the primary outcome of quality of life. Besides, the RCT that would allow more comparisons (Amarenco et al. 2015), since it included solifenacin 5 mg and 10 mg, oxybutynin and placebo, did not report the differences between the arms in relation to quality of life gain (I-QoL), between baseline and end of

study. Therefore, we performed statistical tests and verified that all differences, without exception, were not significant. Finally, considering the high risk of bias in the study by Amarenco et al. 2015, the lack of evidence on darifenacin, and the absence of I-QoL outcome across the RCTs, it would not be reasonable to carry out an economic evaluation using surrogate or (statistically and clinically) non-significant outcomes.

Budget impact analysis: The budget impact analysis was conducted from the perspective of the Brazilian Public Health System (SUS), over a five-year time horizon (2020-2024). The treatment cost was limited to the purchase price of medicines (oxybutynin, tolterodine, solifenacin, darifenacin and mirabegron) according to the Health Price Database. Given the absence of specific data on individuals with neurogenic bladder, the four main causes of neurogenic bladder were considered: Parkinson's disease, multiple sclerosis, stroke, and spinal cord injury. The percentages of use of antimuscarinic agents were based on a publication of the National Health Service (NHS) of the United Kingdom (UK). Thus, the budget impact of incorporating both antimuscarinics and mirabegron in this scenario was estimated to be BRL 2,095,249,966.02, in the first year, and after five years, this amount would be BRL 10,679,375,762.42. Alternative scenarios were developed considering the incorporation of only one of the drugs. In these scenarios, the budget impact of incorporating each of the antimuscarinics and mirabegron, after five years, would range from BRL 3,486,573,869.54 to BRL 20,415,826,991.67, being oxybutynin and tolterodine, respectively, the lowest and highest cost scenarios.

International recommendations: The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends both darifenacin and solifenacin for the treatment of overactive bladder, but it has not made a recommendation for neurogenic bladder. The UK's National Institute for Health and Care Excellence (NICE) recommends antimuscarinic drugs for people with spinal cord disease.

Technology horizon scanning: Searches were carried out on ClinicalTrials.gov and Cortellis™, in order to identify potential drugs for the treatment of adult patients with neurogenic bladder. No drugs were found as part of clinical trials, but it was identified fesoterodine in a study of pediatric patients with urinary incontinence related to neurological conditions.

Considerations: The antimuscarinics currently available in Brazil are: oxybutynin, tolterodine, solifenacin and darifenacin. However, there is little scientific evidence about the efficacy and safety of these drugs, and which would be ideal for the treatment of storage dysfunction in adult patients with neurogenic bladder. The methodological quality of the RCTs was low and there are no direct comparisons of the four antimuscarinics (oxybutynin, tolterodine, solifenacin and darifenacin).

Initial Recommendation: Conitec, at its 82nd Ordinary Meeting, on October 9th, 2019, decided not to recommend the incorporation of antimuscarinics (oxybutynin, tolterodine, solifenacin and darifenacin) in the scope of SUS, for the treatment of neurogenic bladder. Apart from the financial aspect, it was considered, primarily, the absence of significant clinical benefit, as well as the low quality of the evidence analyzed.

Public consultation: Nine experience or opinion contributions were received, seven of which disagreed with the preliminary recommendation, one neither agreed or disagreed, and one was excluded for not having analyzable content. Conitec decided that there was no sufficient reason to change the preliminary recommendation.

Final Recommendation: The Conitec's members present at the 85th Ordinary Meeting, on February 4th, 2020, unanimously decided not to recommend the incorporation of antimuscarinics (oxybutynin,

tolterodine, solifenacin and darifenacin) in the scope of SUS, for the treatment of storage dysfunction in patients with neurogenic bladder.

Decision: Not to incorporate antimuscarinics (oxybutynin, tolterodine, solifenacin and darifenacin) for the treatment of storage dysfunction in patients with neurogenic bladder, in the scope of SUS, according to Ordinance No. 9, published in the Official Gazette of the Federal Executive No. 49, Section 1, page 187, on March 12th, 2020.