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PHARMACOTHERAPY OF OVERACTIVE BLADDER: A 10 YEARS SYSTEMATIC REVIEW

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ABSTRACT

Background: *OAB is a stigmatized condition that significantly affects quality of life. The current first-line pharmacological approach to treating OAB involves various medications, primarily antimuscarinic agents and β3-adrenoceptor agonist. This study aims to provide a 10 year systematic review of pharmacological approach in OAB treatment.*

Methods: *This systematic review adhered to the PRISMA 2020 standards and included full-text English literature published between 2014 and 2024. Exclusion criteria involved editorials, review articles from the same journal, and submissions lacking a DOI. Literature was gathered from online sources such as PubMed and SagePub.*

Result: *Our search in PubMed yielded 997 articles, while SagePub produced 357 articles. Focusing on the last 10 years (2014-2024), PubMed had 667 articles and SagePub had 160 articles. Ultimately we selected 5 papers that met our criteria, 3 from PubMed and 2 from SagePub.*

Conclusion: *Due to the the improvements in urgency, frequency, and incontinence as well as fewer treatment-related adverse events, β3-adrenoceptor agonist mirabegron is recommended as the first-line treatment for OAB.*

Keyword: *Urinary bladder, overactive, pharmacotherapy*

INTRODUCTION

The International Continence Society defined overactive bladder (OAB) as a prevalent condition in society marked by unpredictable contractions of the bladder, leading to feelings of urgency, frequent urination, and nighttime awakenings (nocturia) without any identifiable underlying disease. Overactive bladder syndrome is highly prevalent, and increasingly so with aging (>65 years). Extensive research indicates that over 10% of the overall population experiences symptoms of this syndrome.[1]

Urinary incontinence such as OAB is a stigmatized condition that significantly affects quality of life. Patients often under-report these issues due to misconceptions, such as considering incontinence a normal part of post-partum or aging, or believing that effective treatment is unavailable. OAB is more prevalent in women, particularly in younger individuals, and there is a minor racial disparity, with slightly higher prevalence among African Americans compared to Hispanics and whites in both men and women.[2]

OAB is an idiopathic condition associated with various risk factors, both modifiable and non-modifiable. Non-modifiable factors include age, female gender, metabolic syndrome, post-menopause, benign prostatic hyperplasia, and pelvic organ prolapse in women. Modifiable factors encompass alcohol consumption, smoking, obesity, caffeine intake, carbonated beverages, spicy foods, and bladder stones. Identifying and addressing these factors is crucial in the initial treatment of OAB.[3]

OAB symptoms are primarily linked to detrusor overactivity. A neuropathic bladder from diseases of the central nervous system may result in neurogenic detrusor overactivity, a disease process that is high risk and requires complex urological input. Similarly, urothelial carcinoma of the bladder can result in irritative voiding and patients presenting with voiding dysfunction; therefore, symptoms similar to OAB may be the first signs of high-grade bladder cancer. Pertinent key differential diagnoses must be considered and excluded prior to the diagnosis of OAB being confirmed. It is crucial for the healthcare provider to identify any underlying conditions contributing to these symptoms for targeted primary intervention. A thorough patient history can guide the provider in accurately diagnosing a condition that manifests OAB as a secondary effect. These medical history includes factors like benign prostatic hyperplasia in men, neurological diseases, prior abdominal and pelvic surgeries, hematuria, fluid intake, and recurrent urinary tract infections.[4]

Treatment for OAB is categorized into lines of therapy based on invasiveness. Ideally, treatment should progress from least to most invasive, with the possibility of combining different modalities for effective symptom management. The initial approach involves non-invasive methods like lifestyle changes and pelvic floor therapy, including timed voiding, urge suppression, fluid reduction, avoidance of bladder irritants, and pelvic floor muscle strengthening. The second line employs drug therapy with antimuscarinics or beta-3 agonists. This study aims to provide a 10 year systematic review of pharmacological approach in OAB treatment.

METHODS

Protocol

The author followed the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 to ensure that this study adhered to the requirements. This method was chosen to guarantee the accuracy of the conclusions drawn from the inquiry.

Criteria for Eligibility

This systematic review was done by assessing evidence on post vaccination immune response in children with IBS. Evidence was compiled and analyzed thoroughly to provide an explanation and enhance the handling of patients' treatments. The primary objective of this paper is to demonstrate the relevance of the identified main points as a whole.

The inclusion criteria for this study are as follows: 1) The paper must be written in English, and 2) The studied papers include several that were published between 2014 and 2024. The exclusion criteria for this study are: 1) Editorials; 2) Submissions without a DOI; 3) Review articles that have already been published; and 4) Identical entries in published journals.

Search Strategy

We used “urinary bladder”, “overactive” and “pharmacotherapy” as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields]) AND ("overactive"[All Fields] OR "overactivity"[All Fields]) AND ("drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "pharmacotherapies"[All Fields] OR "drug therapy"[MeSH Subheading] OR "pharmacotherapy"[All Fields])) AND ((ffrft[Filter]) AND (fft[Filter])).*

Data retrieval

The authors assessed studies by reviewing their abstracts and titles to determine their eligibility. We selected relevant studies based on their inclusion criteria, focusing on research that aligned with their article's objectives. A consistent trend across multiple studies led to a conclusive finding. The selected submissions were required to be in English and previously unpublished.

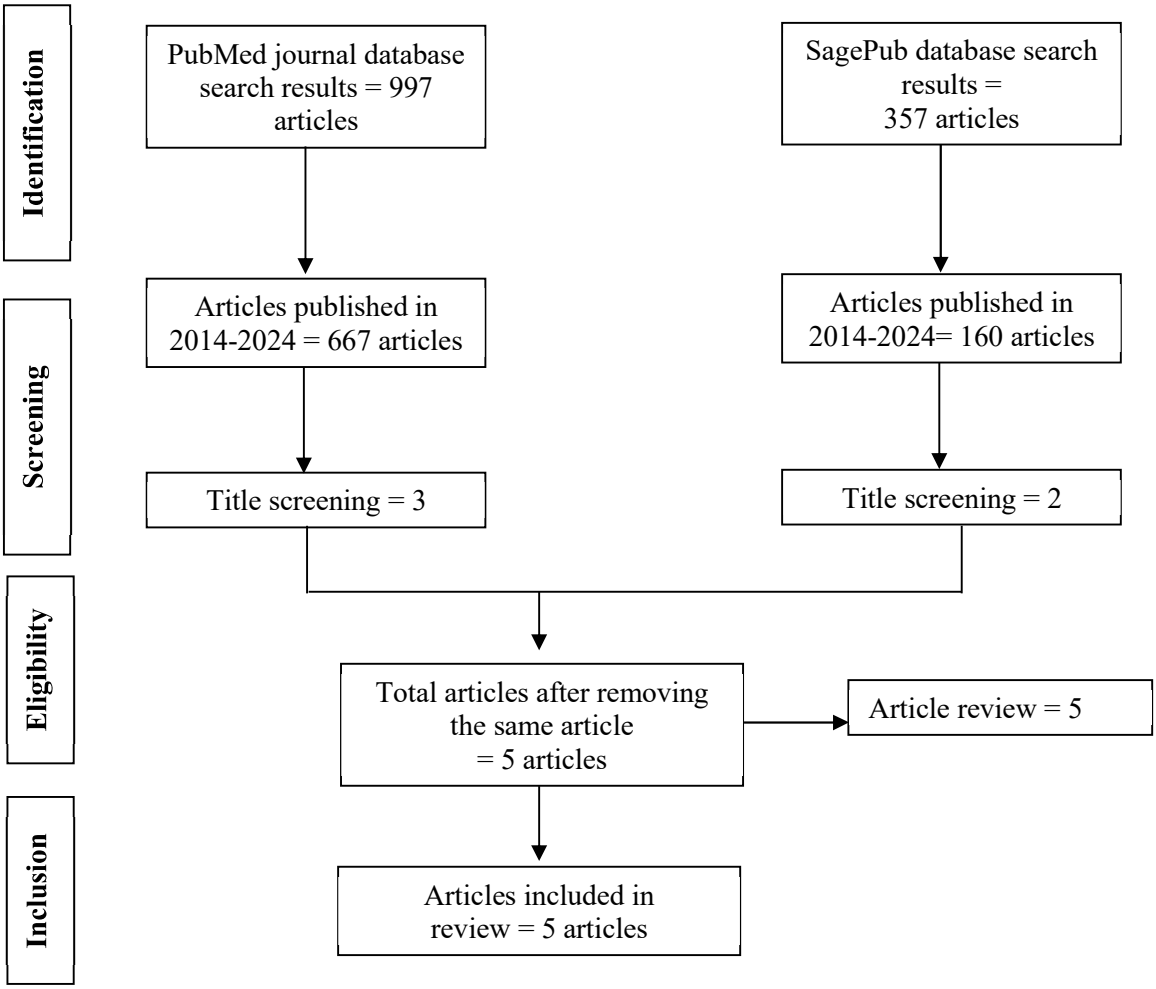

Figure 1. Article search flowchart

This systematic review only considered literatures that met all inclusion criteria and relevance to the topic. Studies not meeting these criteria were excluded, and their conclusions were not considered. The subsequent analysis delved into various details uncovered during the research inquiry, including names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author individually examined the research mentioned in the publication's title and abstract before deciding which publications to explore further. The next step involves evaluating all articles that meet the criteria set for inclusion in the review. Based on the uncovered findings, decisions will be made regarding which articles to include in the review. This criteria streamlines the process of selecting papers for further assessment, discussing the earlier investigations conducted and the elements that make them suitable for inclusion in the review.

RESULT

In our search on the PubMed database, we found 997 articles, while on SagePub, the search yielded 357 articles. Specicifally, ten years filter (2014-2024) search on PubMed produced 667 articles and SagePub produced 160 articles. Ultimately, we selected a total of 5 papers, with 3 from PubMed and 2 from SagePub. The study includes five literatures that met the criteria, and Table 1 displays the literature included in this analysis.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Tubaro, et al.[5] (2017)	Multicenter	Randomized controlled trial	2,829 patients	Mirabegron 50 mg exhibited superiority over placebo in pooled studies, specifically in reducing micturition frequency, with a treatment difference of -0.37 (95% confidence interval: -0.74, -0.01). However, there were no significant differences in improvements for urgency and incontinence compared to placebo. In the BEYOND study, mirabegron 50 mg showed comparable efficacy to solifenacin 5 mg in reducing micturition frequency, urgency, and incontinence episodes. The tolerability of mirabegron was good over 12 and 52 weeks, with overall treatment-emergent adverse events (AEs) similar to those observed with placebo.
Newgreen, et al.[6] (2017)	Multicenter	Double blind randomized controlled trial	189 patients	In children, solifenacin demonstrated superiority over placebo in terms of the change from baseline to End of Treatment (EoT) for maximum voided volume (MVV), with a solifenacin-placebo difference of 12.1ml (95% confidence interval [CI] 0.2-24.0; p=0.046). Additionally, the adjusted mean change from baseline for solifenacin-placebo was 31.9ml (95% CI 4.3-59.5; p=0.024) for Detrusor Maximum Voided Volume (DMaxVV), and there was a significant difference in volume-time-bounded (VTB) adjusted micturition frequency (p=0.028). Other endpoints did not show significant differences. Solifenacin

				was well tolerated in this group. For adolescents, drawing firm efficacy conclusions was challenging due to the low number of participants recruited.
Jamil, et al.[7] (2023)	Abbottabad, Pakistan	Comparative cross sectional study	60 patients	In this study, Group S (average age 37.47±12.48 years) and Group M (average age 39.93±7.93 years) comprised exclusively females. After a 4-week follow-up, side effects such as dizziness, dry mouth, constipation, hypertension, and blurred vision showed no significant differences between the two groups, with p-values of 0.312, 0.161, 0.076, 0.076, and 0.313, respectively. The OABSS score significantly improved in both groups, with scores of 4.20±1.32 in Group S and 3.43±1.13 in Group M after therapy. The frequency of treatment withdrawal did not exhibit a significant difference, with a p-value of 0.150.
Krhut, et al.[8] (2014)	Ostrava, Czech	Prospective study	377 patients	The median time for persistence with the first line anticholinergic treatment was 6.53 ± 3.84 months. Patients receiving extended-release anticholinergic medication exhibited significantly higher persistence compared to those treated with immediate-release anticholinergics. The primary reasons for treatment discontinuation were the resolution of symptoms (35.9%), low effectiveness (30.9%), and side effects (23.7%).
Kraus, et al.[9] (2022)	Multicenter, USA	Cross sectional study	200 patients	n a study involving 200 patients, 86.5% reported

				active participation in treatment decision-making, with the doctor's recommendation being the most influential factor (84.4%). Approximately 71% of patients were unaware of combination therapy. Among those aware, the primary reason for not using it (21%) was physicians recommending other treatments (69.8%). In terms of physician perspectives (N=50), effectiveness (92.0%) and side effects (84.0%) were the most considered factors when prescribing OAB treatment, with 70% opting for combination therapy, mainly based on symptom severity (82.9%). The main reasons for not prescribing combination therapy were cost/insurance coverage (80%) and a lack of information (53.3%).

Tubaro, et al.[5] (2017) showed that oral antimuscarinics or β3-adrenoceptor agonists (mirabegron) are recommended as first-line pharmacotherapy for the treatment of OAB. However, antimuscarinics poses certain anticholinergics side effects such as dry mouth and constipation. This study demonstrated that mirabegron 50 mg provided similar improvements in urgency, frequency, and incontinence as solifenacin 5 mg in OAB patients with or without lower urinary tract symptoms related to benign prostate enlargement.

Newgreen, et al.[6] (2017) anti muscarinics solifenacin oral suspension given once daily exhibited superiority over placebo in the change from baseline to End of Treatment (EoT) for the maximum voided volume (MVV). The treatment was well-tolerated in children aged 5–<12 years with OAB. Additionally, solifenacin demonstrated good tolerability in adolescents aged 12–<18 years.

Jamil, et al.[7] (2023) showed that both solifenacin and mirabegron are effective in alleviating symptoms of OAB. However, mirabegron is associated with fewer treatment-related adverse events. Therefore, it is recommended to consider mirabegron as the first-line treatment for OAB. Solifenacin can be employed if patients no longer experience the desired effects from mirabegron.

Krhut, et al.[8] (2014) showed that the majority of OAB patients expressed dissatisfaction with their first-line pharmacological treatment. Exploring alternative options is advisable, including adjusting the medication, dosage, or potentially combining different treatments.

Kraus, et al.[9] (2022) suggested the same idea that the use of combination therapy could potentially fulfill certain unmet needs in the therapeutic management of OAB. However, the effectiveness of combination therapy in addressing these needs may be impeded by a lack of awareness among both physicians treating OAB and the patients themselves.

DISCUSSION

Overactive bladder (OAB) is characterized by a sense of urinary urgency, often accompanied by increased frequency and nocturia. This condition may involve urgency incontinence and occurs without the presence of urinary tract infection or apparent pathologies. OAB affects around 12% of individuals aged over 40, with its prevalence rising with age. The impact of OAB on the quality of life (QoL) is considerable in both men and women, and it is generally perceived as more bothersome than voiding symptoms.[5]

Following an OAB diagnosis, patients are initially recommended behavioral therapies. If behavioral therapies are deemed to be ineffective, pharmacotherapies are administered. The current pharmacological approach to treating OAB involves various medications, primarily antimuscarinic agents such as darifenacin, gesoterodine, imadafenacin, oxybutynin, propiverine, solifenacin, tolterodine, and trospium.[4]

Oxybutynin is currently the only accessibble antimuscarinic approved for paediatric OAB patients. Trospium is approved for OAB patients aged 12 years, and propiverine for children aged 5 years. Solifenacin succinate has demonstrated efficacy and tolerability in adult clinical trials. Solifenacin oral suspension can be given once daily and proved to be superior to placebo in changing maximum voided volume (MVV) in children (5–<12 years) and adolescents (12–<18 years) with OAB while maintaining good tolerability.[6]

Antimuscarinic agents are effective and showed symptoms improvement in 70% of patients. However, it often come with notable side effects such as dry mouth and constipation. In addition, blurred vision, pruritus, tachycardia, somnolence, impaired cognition, and headache may occur. This was caused by the presence of muscarinic receptors throughout the body and there are no antimusarinic with significant selectivity for the lower urinary tract, hence the side effects happen globally.[4,7]

When adverse events pose obstacles to continued use of OAB medications, it is recommended to explore options such as dose modification or switching to a different agent.[7,8] More than half of OAB patients are not satisfied with their first line treatment. The use of combination therapy could potentially fulfill certain unmet needs in the therapeutic management of OAB. However, the effectiveness of combination therapy in addressing these needs may be impeded by a lack of awareness among both physicians treating OAB and the patients themselves.[9]

Mirabegron was introduced in 2011 and it presents an alternative approach by targeting human β3-adrenoceptors. This mechanism induces relaxation of the detrusor muscle and aids urine storage in the bladder. Mirabegron has shown comparable efficacy to antimuscarinics in pivotal 12-week phase III studies and pooled data, including studies in Japanese and Asian populations. It demonstrated long-term tolerability in a 52-week phase III study. Notably, mirabegron exhibited a better tolerability profile, leading to significantly higher 12-month adherence and persistence rates compared to antimuscarinics.[5]

Recent studies in the last decade showed favor in the use of β3-adrenoceptor agonist mirabegron in OAB patients. Jamil, et al.[7] (2023) showed that both solifenacin and mirabegron are effective in alleviating symptoms of OAB, but mirabegron is associated with fewer treatment-related adverse events. Therefore, it is recommended to consider mirabegron as the first-line treatment for OAB. Tubaro, et al.[5] (2017) supported this idea and demonstrated that mirabegron 50 mg provided similar improvements in urgency, frequency, and incontinence as solifenacin 5 mg in OAB patients with or without lower urinary tract symptoms related to benign prostate enlargement. Solifenacin can be employed if patients no longer experience the desired effects from mirabegron.[5,7]

CONCLUSION

The current first-line pharmacological approach to treating OAB includes the use of antimuscarinic agents and β3-adrenoceptor agonist. Due to the the improvements in urgency, frequency, and incontinence as well as fewer treatment-related adverse events, β3-adrenoceptor agonist mirabegron is recommended as the first-line treatment for OAB.

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