Review

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Comparison of antimuscarinic drugs to beta adrenergic agonists in overactive bladder: A literary review

Mudassir M. Wani[a,*], Mohammad I. Sheikh[b], Tahir Bhat[b], Zubair Bhat[b], Arshad Bhat[c]

[a]Department of Urology, Glangwili General Hospital, Carmarthen, Wales, UK; [b]Department of Urology, Medway Maritime Hospital, Gillingham, Kent, UK; [c]Department of Urology, Hereford County Hospital, Hereford, Herefordshire, UK

Abstract

Background: The purpose of this study was to carry an extended literature review to compare antimuscarnics with beta adrenergic agonists (mirabegron) in treatment of overactive bladder.

Materials and methods: A literature review was carried out, using key words in different databases including MEDLINE, PUBMED, and EMBASE. All relevant published articles during last 5 years with full texts available were included in this review for critical analysis and evaluation. In total, there were 20 studies including 7 systemic reviews, 6 retrospective cohort, 3 prospective cohort, 2 randomized controlled trials, and 2 cross sectional studies.

Results: After critical evaluation the results were considered under parameters of efficacy, adverse effects, adherence and persistence, tolerability, cost-effectiveness. In 9 studies efficacy was evaluated, 5 studies dealt with adverse effects, same number evaluated adherence and persistence. Cost effectiveness was compared in 3 and same number of studies also compared tolerability.

Conclusions: To conclude, we found mirabegron is as efficacious as any other antimuscarnics, has better tolerability (including elderly), has better adverse effect profile, is cost effective, has better persistence and adherence rates at 12 months.

Keywords: Antimuscarnics; Beta-adrenergic agonists; Mirabegron; Overactive bladder

1. Introduction

Overactive bladder (OAB) is a clinical entity having complex chronic symptoms which impact quality of life (QoL) in a good proportion of population.[1] It is characterized by urgency (sudden and compelling feeling to pass urine) with or without urge incontinence (urgency associated with involuntary urinary leakage), usually associated with urinary frequency (passing urine eight or more times in 24 hours) as well as nocturia (awaken more than once to urinate during night). In absence of an underlying metabolic or pathological condition.[2–4]

Studies have established that around 16.0% of men and 16.9% of women in the United States, report having OAB symptoms.[5] In a similar study in Europe, a survey carried out on 16,677 adults, 16.6% reported suffering from OAB, which is approximately around 22 million individuals.[6] OAB does have economic as well as QoL implications. In United States in year 2000, it was estimated that $12.02 billion were spent on treatment of OAB.[7] In other study carried out in Europe (including United Kingdom) and Canada, the total direct cost burden was € 3.9 billion annually. Moreover, it revealed that costs involved in nursing homes were around €4.7 billion per year and OAB related absenteeism from work was around €1.1 billion per year.[8] In addition to financial implications, OAB does impact QoL, different QoL indices—Short Form questionnaires, King's Health Questionnaire[9] have revealed that OAB is associated with poor QoL, high depression scores and poor sleep quality.[5]

The primary aim of treating physician after diagnosis of OAB is to help in reduction of occurrence of bothersome symptoms and improve QoL for the patient in a meaningful way.[10] Usually two most commonly used approaches for treatment of OAB syndrome are life style modifications (including bladder retraining) and pharmacotherapy. The former approach needs considerable patient motivation and often attrition rates are very high either due to lack of regular follow-up or due to lack of efficacy. These measures are more often used as adjuncts to pharmacotherapy.[11]

The antimuscarnics drugs have been pharmacological cornerstone for management of OAB. They reduce bothersome OAB symptoms and improve QoL.[12,13] However, antimuscarnics have their limitations due to efficacy issues as well as having side effects like dryness of eyes, dryness of mouth, vision blurring, constipation, and occasionally issues with cognition.[3,14] Studies have revealed that persistence/adherence rates of antimuscarnics for OAB can be less than 35% within first year of initiating treatment.[15] In quest for alternative to OAB treatments, β3-adrenoceptor agonists are emerging as promising class of novel drugs, with an improved efficacy as well as tolerability profile to existing treatments. Although, the positioning of beta adrenergic agonists is being evaluated for the management of OAB, it is becoming clear that they can take role as either second line or adjuvant therapy or alternate therapy.[16]

* Corresponding Author: Mudassir M. Wani, MCh Urology Fellow, Canteburry Christ Church University, 30 Pembrooke, Gillingham, Chatham, ME4 4UF, UK. E-mail address: mudassir.wani@nhs.net (M.W. Wani).

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This literature review will focus on critical analysis of comparing antimuscarnics medications with beta adrenergic agonists in management of OAB addressing efficacy, adverse effects, cost, and other relevant properties.

2. Materials and methods

Preferred Reporting Items for Systematic Review and Meta-analyses guidelines (PRISMA) were followed for the conduct of this study. We used Healthcare Databases Advanced Search Export software to facilitate search in Medline and EMBASE, and also searched other databases from 2015 to 2020. Searched terms included: "Overactive bladder," "Muscarinic receptor antagonist," "Anticholinergic drugs in overactive bladder," " Beta-3-receptor agonists in overactive bladder," "Antimuscarinics drugs in overactive bladder," " Detrusor receptors," "Anticholinergic and Beta adrenergic agonists," "Mirabegron." Boolean operators included "or" and "and."

One hundred fifty-one articles matched the initial search on Medline/EMBASE and the first 100 articles were considered from a search on Google scholar. After removing duplicates, 103 articles remained. Seventy-four were screened, after excluding 21 studies, 53 full text articles were assessed for inclusion. Using the SQR3 (Survey, Question, Read, Recite, and Review) technique, 20 articles were included in the final qualitative analysis[17] (Table 1, Fig. 1).

Each of the 20 studies were critically evaluated. The main aspects analyzed were the methodology followed for the research work, research question being dealt in the study, strengths as well as limitations and finally the main conclusion or recommendation (Tables 2 and 3).

It is evident that most studies are based on reviews so the number of patients included in this review is quite high. Studies included were from across the globe, included all relevant age groups as well as both sexes and all important aspects of these two groups of drugs in treatment of OAB have been evaluated. The main characteristic analyzed in these studies were:

2.1. Efficacy

The term efficacy has dual meaning. In the setting of pharmacological research efficacy of a drug refers to maximal response achieved, however, in the clinical setting it is the therapeutic benefit patient have by its use.

2.2. Adverse effects

It refers to an unwanted harmful consequence resulting from a medication or any other medical intervention.

2.3. Persistence and adherence

Adherence means that patient follows the instructions as recommended for taking a drug including dose, frequency, etc. Persistence refers to duration for which a patient needs to take a drug with full adherence.

2.4. Cost effectiveness

It is a method by which comparison in terms of cost of two or more medications is performed, which although may not be same in terms of dose or efficacy but are used to treat same clinical entity.

2.5. Tolerability

It refers to the extent a patient can tolerate adverse effects of a drug.

3. Results

The results from the extended literature revealed following

3.1. Efficacy

Nine studies analyzed efficacy of these two groups of medications. Results from all the studies concluded that mirabegron is as efficacious as any other anticholinergic. It has been found to decrease even postvoid residual urine.

3.2. Five studies compared adverse effects. They revealed that mirabegron has less side effects as compared to antimuscarnics. Dry mouth as an adverse effect with mirabegron is that of a placebo.

3.3. Persistence and adherence

Five studies have found that persistence as well as adherence is better with mirabegron (including median as well as yearly persistence/adherence).

3.4. Cost effectiveness

Three studies across globe have proven that mirabegron is cost effective as compared to anticholinergics.

3.5. Tolerability

Three studies established that mirabegron has better tolerability as compared to antimuscarnics. It has been found tolerable even in elderly as compared to antimuscarnics.

3.6. OAB in females

Two studies involved female only patients. These results revealed that mirabegron is a very good alternative to antimuscarinics in OAB.

3.7. Combination of antimuscarinics and mirabegron

Two recent research works have found that combination is providing better results. Most studies have found mirabegron and solifenacin as an excellent combination.

Table 1

Study characteristics.

Study methodology	Literature review
Area of interest	Comparison between anticholinergic and beta adrenergic agonist (mirabegron) in overactive bladder
Database sources	National Library of Medicine (PUBMED/Medline), Elsevier database
Key words	"Overactive bladder," "Muscarinic receptor antagonist," "Anticholinergic drugs in overactive bladder," " Beta-adrenergic agonists in overactive bladder," "Antimuscarinics drugs in overactive bladder," " Detrusor receptors," "Anticholinergic and Beta adrenergic agonists," "Mirabegron"
Literature reviewed	179 articles matched on initial research from databases and 11 from other sources. With further refinement of including articles published during last 5 years, 151 articles matched.
Final sample	Finally 20 most relevant articles with full texts were shortlisted. (SQ3R Shield's method)

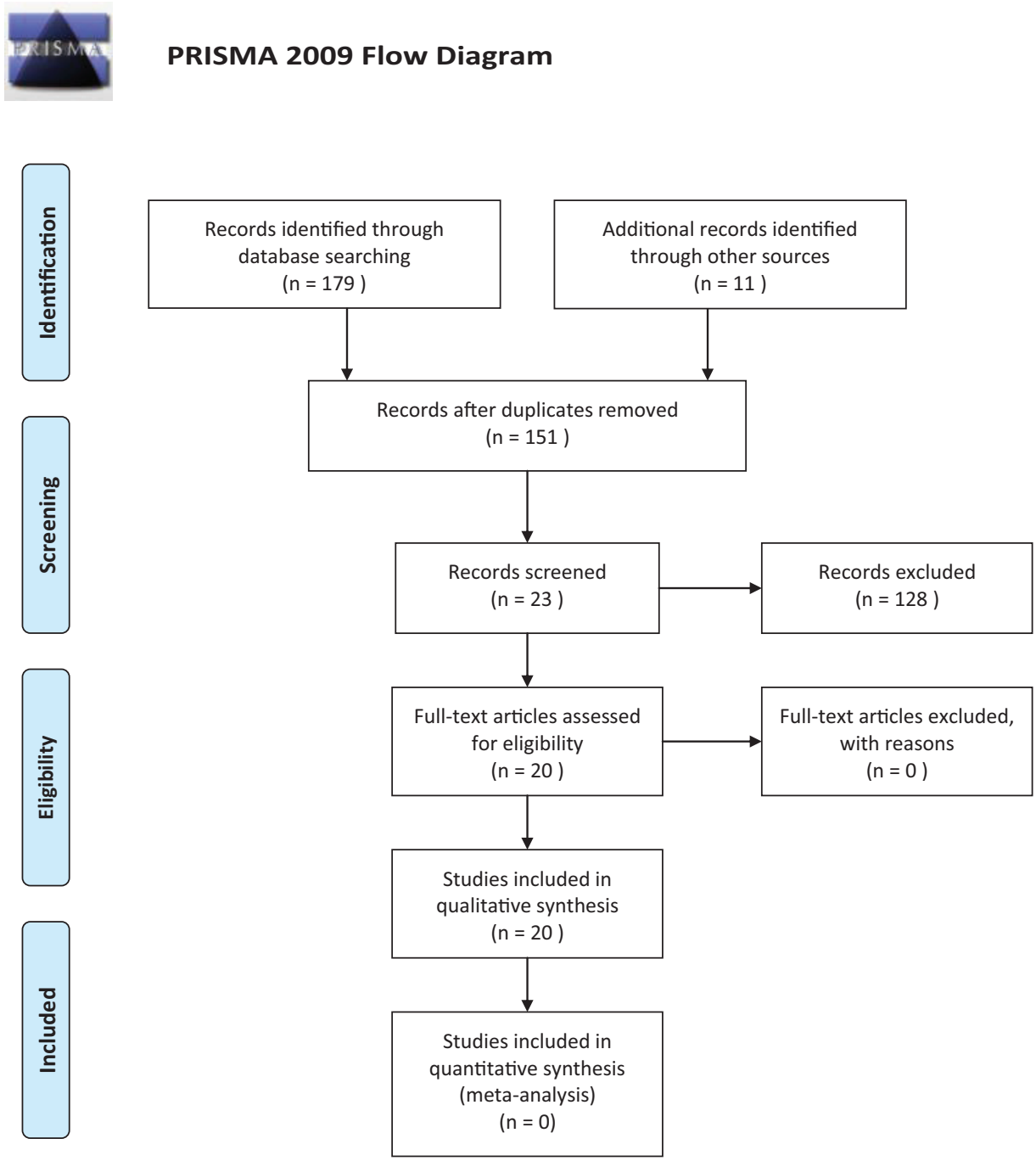

Figure 1. PRISMA flow.

3.8. Switching from antimuscarnics to mirabegron

One study has revealed that switching had excellent results in that group of patients in terms of efficacy, tolerability and adverse effect profile.

3.9. Urodynamic results

One study found that there is improvement in urodynamics after change to mirabegron in terms of postvoid volumes particularly in females.

However on the flip side, some of the issues with included studies were that were being retrospective, heterogeneous sources, based on prescriptions rather than real patients,

Table 2

Nature of studies evaluated.

Study type	Number of studies
Systemic reviews	7
Retrospective cohort	6
Prospective cohort	3
Randomized controlled trial	2
Cross sectional	2
Total	20

Table 3

Critical reviews of studies.

Year	Reference	Research question	Method of study	Strengths/limitations	Main conclusion
2014	Maman et al.[18]	Evaluation of efficacy and safety of medical treatments in overactive bladder	Systemic review	Strength: It included 44 RCT, 27309 patients. Limitations: 1. Bayesian Mixed treatment comparisons (MTC) model used; 2. Heterogeneous source of studies.	Mirabegron 50 mg has an efficacy equal to anticholinergics, with dry mouth incidence that of a placebo.
2014	Aballéa et al.[19]	Comparison of cost effectiveness of mirabegron and tolterodine in United Kingdom	Prospective	Strength: Markow model use; Estimation was made for 5 years. Limitations: 1. Sponsored by a pharma company; 2. Reasons other than adverse effects for discontinuation not mentioned	Mirabegron 50 mg is cost effective strategy as compared to extended release tolterodine (For UK NHS)
2015	Nazir et al.[20]	Comparison of cost effectiveness of mirabegron and antimuscarinics in United Kingdom	Prospective	Strength: 1. Markow model used; 2. Treatment discontinuation and treatment switch considered separately. Limitations: 1. Heterogeneous source of studies; 2. Certain parameters included without real world data; 3. Only two adverse effects taken into consideration: dry mouth and constipation	Mirabegron 50 mg is cost effective strategy as compared to standard oral antimuscarinics (For UK NHS)
2016	Liao and Kuo[21]	Evaluation of switching from antimuscarinics to Mirabegron	Observational study	Strength: Unique study comparing results in patients who were switched from Solifenacin or Tolterodine to Mirabegron. Limitations: 1. Small sample size; 2. Heterogeneous group of population; 3. Reason of switching not provided.	Study found that 50% patients exhibited better outcomes after switching with significantly lower adverse effect rates.
2016	Wagg et al.[22]	Evaluation of Mirabegron to antimuscarinics in elderly	Review	Strength: Mirabegron usage in patients aged $\geq$ 65 and $\geq$ 75 years analyzed. Limitations: Out of 4 trials 3 based on 12 week outcomes only	Compared to antimuscarinics, mirabegron has better tolerability profile in elderly population.
2016	Vecchioli Scaldazza and Morosetti[23]	Evaluation of mirabegron and Solifenacin in OAB in females	RCT	Strengths: Patient response evaluated using overactive bladder symptom score as well as with urodynamic studies. Limitations: 1. Small group of 80 patients; 2. Comparison performed after 12 week, does not allow evaluation for persistence as well as adherence.	Mirabegron is better than Solifenacin succinate both in efficacy as well as tolerability.
2017	Chapple et al.[24]	Comparison of Mirabegron and antimuscarinics in terms of persistence and adherence in OAB patients in UK	Retrospective, longitudinal, observational study	Strengths: 1. Majority of anticholinergics considered along with Mirabegron; 2. Well defined primary and secondary end points. Limitations: 1. Retrospective design; 2. Prescription records used; 3. Reasons for discontinuation not elucidated.	Statistically significant persistence as well as adherence with mirabegron as compared to all other antimuscarinics.
2017	Kato et al.[25]	Evaluation of persistence of antimuscarinics and mirabegron in Japan	Retrospective	Strengths: 1. Majority of anticholinergics considered along with mirabegron 2. Large group of patients included Limitations: 1. Retrospective design; 2. Sponsored by pharma company.	Compared with five antimuscarinics, Mirabegron had better persistence both in terms of median persistence as well as persistence at one year.

(*continued*)

Table 3
(continued).

Year	Reference	Research question	Method of study	Strengths/limitations	Main conclusion
2017	Herschorn et al.[26]	Comparison of cost effectiveness of mirabegron and tolterodine (in Canada)	Retrospective	Strengths: Markow model used. Limitations: 1. Retrospective design; 2. Study model was dependent upon micturition frequency and incontinence, but not urgency.	Mirabegron 50 mg once daily is cost effective strategy as compared to standard tolterodine 4 mg once daily.
2017	Schiavi et al.[27]	Evaluation of mirabegron compared with solifenacin in OAB in females	Retrospective	Strengths: 342 females evaluated, with subjective and objective responses. Limitations: 1. Retrospective design; 2. Study results based only on questionaries' no urodynamic evaluation performed.	Both Solifenacin and mirabegron had similar efficacy in OAB but Solifenacin had more adverse effects.
2017	Sussman et al.[28]	Comparison of Mirabegron and antimuscarinics in terms of persistence and adherence in OAB patients	Observational	Strengths: 1. More than 4,000 patients included; 2. 12 month continuous evaluation analyzed. Limitations: 1. Retrospective design; 2. Data based on medical and pharmacy claims; 3. Pharma sponsor.	Adherence at one year was 44% compared to 31% for anticholinergic. Persistence was 19% for mirabegron and 12% for acetyl choline over a period of one year.
2018	Yeowell et al.[29]	Comparison of Mirabegron and antimuscarinics in terms of persistence and adherence in OAB patients	Systemic literature review	Strengths: 1. More than 30 studies evaluated; 2. Only observational studies were included; 3. Age and sex was also evaluated. Limitations: 1. Patient expectations, counselling role not taken into consideration; 2. Non uniformity on definitions on persistence and adherence; 3. Pharma sponsor.	Study reveals that the persistence as well as adherence is far better with Mirabegron in comparison with antimuscarinics. Mirabegron can be used as first-line oral therapy.
2018	Nazir et al.[30]	Comparison of Mirabegron and antimuscarinics in terms of persistence and adherence in OAB patients (Spain)	Retrospective study	Strengths: 1975 patient records evaluated. Limitations: 1. Retrospective design; 2. Groups not matched; 3. Based on prescription records.	Study reveals that the persistence as well as adherence is far better with mirabegron in comparison with antimuscarinics at 12 months.
2018	Sebastianelli et al.[31]	Evaluation of efficacy of mirabegron with tolterodine and placebo	Systematic review and meta-analysis	Strengths: 1. Eight RCT included; 2. More than 10,000 patient included; 3. All symptoms of OAB were individually analyzed. Limitations: 1. Most studies limited to 12 month period; 2. Most studies included were sponsored by pharma companies; 3. Mirabegron 25 mg not evaluated.	Mirabegron is effective as well as safe for treatment of patients with OAB, with symptomatic relief of all bothersome symptoms.
2018	Kobayashi et al.[32]	Evaluation of efficacy as well as tolerability of antimuscarinic agents and mirabegron	Prospective	Strengths: 1. Prospective RCT; 2. All parameters were analyzed including side effects. Limitations: 1. Sample size only 117; 2. Assessments at 4 and 8 weeks.	Mirabegron is a reasonable choice for initial therapy for OAB in terms of efficacy and tolerability as compared to antimuscarinics.
2018	Kelleher et al.[33]	Comparison of mirabegron with antimuscarinic in terms of efficacy and tolerability	Systemic review and network analysis	Strengths: 1. 64 studies were included; 2. Well defined outcome measurements and end points. Efficacy assessments as well as tolerability assessments.	Mirabegron 50 mg is clinically as efficacious as commonly used antimuscarinic with fewer side effects. Further, the efficacy improves with combination with Solifenacin

(*continued*)

Table 3
(continued).

Year	Reference	Research question	Method of study	Strengths/limitations	Main conclusion
				Limitations: 1. Endpoint definitions were non homogenous in different trials 2. Data used was heterogenous.	
2018	Hsiao et al.[34]	Evaluation of mirabegron and tolterodine for treatment of female OAB	RCT	Strengths: 1. RCT; 2. Based on clinical as well findings on urodynamic evaluation. Limitations: 1. Very small sample size (33); 2. Funded by pharma company	In females with OAB, Mirabegron and Tolterodine are equally efficacious, however Mirabegron has advantage of decreasing post-void residual urine.
2019	Marcelissen et al.[35]	Pharmacologic (oral) management of OAB	Narrative review	Strengths: All types of comparisons analyzed, individual usage of antimuscarinics, mirabegron as well as combination treatment. Limitations: Narrative review.	This study concludes that addition of Mirabegron has widened therapeutic approach in treatment of OAB. However, it does recommend that each patient needs to be tailored for specific treatment strategy. It also gives insight into usage of combined treatment of antimuscarinics and Mirabegron.
2019	Gratzke et al.[36]	Evaluation of combination pharmacotherapy in OAB	Review	Strengths: 1. 21 publications and one abstract included; 2. Some studies included were doing trials on combination of two antimuscarinics. Limitations: 1. All studies included were interventional clinical trials; 2. No real world studies.	Study concludes that mirabegron and solifenacin when used in combination do improve efficacy as well as tolerability for OAB patients.
2019	Hsu et al.[37]	Evaluation of different drugs used in OAB using RCT available	Systemic review	Strengths: 1. 52 head to head RCTS (31 studies and 20 trials); 2. Dual review. Limitations: 1. Lack of network analysis; 2. Adverse effect reporting was inconsistent in studies.	This study concludes that patients discontinue OAB medication more due to adverse effects rather than efficacy issues. Combination therapy of Mirabegron and Solifenacin has synergistic effect but with increased adverse effects.

OAB = overactive bladder; RCT = randomized controlled trial.

sponsored by pharma companies. It is worthwhile to mention that majority of the studies evaluated did not discuss life style modifications, patient expectations, patient concerns regarding treatment (Table 4).

4. Discussion

The urinary system in humans is broadly classified into upper tract and lower tract. Kidneys and ureters constitute upper tract while as urinary bladder and urethra constitute lower tract.

Table 4
Limitations of the studies evaluated.

Limitation	Frequencies
Heterogeneous source	3
Sponsorship/funding	4
Small sample size	3
Short trial/follow-up	2
Source of information/data collection	4
Retrospective	4
Others	2

Lower urinary tract is mostly concerned with the process of urination which involves two phases—storing urine without leakage (storage phase) and emptying urine at will (voiding phase).

During storage phase, as bladder distension takes places, muscular afferent signals are conveyed though the pelvic and hypogastric nerves to central nervous system (pontine center).[38] Brain controls spinal cord continence center which acts via the sympathetic hypogastric nerve (LI–L2) which in turn relax detrusor smooth muscle by stimulating β3-receptors present in the body and fundus of bladder. At the same time through activation of alpha 1 receptors present in bladder neck, internal urethral sphincter is contracted. External urethral sphincter is under voluntary control and is also contracted through pudendal nerve. This process by which bladder relaxes (fills and expands, keeping intraurethral pressure lower than sphincters) and sphincters remain closed such that urine can be stored for hours without leakage is termed as receptive relaxation.[39]

The voiding phase is mainly voluntary and starts at around the age of 2 years. Voiding is mainly a para-sympathetic event. It starts when afferent nerves are stimulated by bladder wall stretching at around 400 ml. From spinal cord these afferent signals ascend to pontine micturition center and cerebrum. Once a voluntary decision to pass urine is made, the pontine center

excites sacral preganglionic neurons. Subsequently, parasympathetic stimulation of pelvic nerve (S2–4), which in turn causes release of acetylcholine, which acts on M3 receptors present in detrusor muscle leading to contraction and increase in intravesical pressure.[40] At the same time, pontine center causes reduction in sympathetic contraction of internal urethral sphincter by inhibiting Onuf's nucleus. The external urethral sphincter voluntary contraction gets reduced by conscious reduction, helping in passage of urine. Although variable, most people urinate 6–7 times in 24 hours. During night time the urine production is low so that a person can sleep for 6–8 hours without getting up.

The International Continence Society (ICS) has recommended use of the terms OAB syndrome and detrusor overactivity for a group of lower urinary tract symptoms. The term detrusor overactivity is diagnosed on basis of urodynamic evaluation which reveal involuntary detrusor contractions occurring during storage phase. It is further classified into idiopathic detrusor overactivity and neurogenic detrusor overactivity. ICS in 2002 introduced term OAB which is based on symptomatic diagnosis. OAB is characterized by urgency, with or without urge incontinence, and usually with frequency and nocturia.[2–4] The ICS endorsement of the term OAB recognizes that patients with this symptom syndrome are almost always treated by nonsurgical means on an empirical basis, that is without a urodynamic confirmation of the presumed diagnosis, detrusor overactivity.[41] The two most important classes of drugs used are antimuscarnics and beta adrenoreceptors.

Antimuscarnics drugs act by inhibiting the acetylcholine action. Acetylcholine causes acts on muscarinic receptors and stimulates detrusor contraction. Within parasympathetic system there are five different subtypes of muscarinic receptors. Only M2 and M3 receptors are present in bladder. Although, M2 is more frequent, it is M3 which is more involved in detrusor function.[42] Most of the anticholinergics have similar efficacy in terms of symptomatic relief.[43] Side effect profile however varies depending on affinity of receptor, drug levels in serum and the mode of administration of drug (Table 5).

There are 3 types of β-adrenoceptors (β1, β2, β3) in bladder detrusor muscle as well as urothelial lining,[44] β3 being most predominant of them.[45] β3 receptors excitation causes detrusor smooth muscle relaxation.[46] Mirabegron which is β3 receptor agonist, has been extensively used as well as studied for treatment of OAB. Mirabegron has been found to be safe, effective, well-tolerated. As far as incidence of dry mouth is concerned, it had similar results to placebo in almost all trials.[47]

Our review reveals that mirabegron is as efficacious as any other antimuscarnics, has better tolerability (including elderly), has better adverse effect profile, is cost effective, has better persistence and adherence rates at 12 months. However, this study had its limitations in terms of being a literary review, study being limited to last 5 years and only articles with full articles included.

Table 5

Different types of antimuscarinics.

Type	Selectivity	Efficacy	Route of delivery
Oxybutynin	M1 and M3	1A	Oral, transdermal, Elixir
Tolterodine	Nonselective	1A	Oral
Propiverine	Nonselective	1A	Oral
Trospium	Nonselective	1A	Oral
Solifenacin	Predominantly M3	1A	Oral

5. Conclusions

To conclude, we found mirabegron is efficacious and safe to be used as a first line therapy in OAB. In future more research needs to be conducted in using combination of mirabegron and solifenacin in OAB, however, all such studies and trials must consider patient understanding and expectations factors which are essential in management of these patients.

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None.

Statement of ethics

This was a review and did not require ethical approval.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

Mudassir M. Wani: Concept, design, resources, literature search, data collection, analysis, interpretation, writing;
Mohammad I. Sheikh: Analysis, interpretation, supervision, critical review;
Tahir Bhat: Analysis, interpretation, supervision, critical review;
Zubair Bhat: Data collection, analysis, interpretation;
Arshad Bhat: Data collection, analysis, interpretation.

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