

Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019

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ABBREVIATIONS

1. AHRQ Agency for Healthcare Research and Quality
2. AUA American Urological Association
3. ICS International Continence Society
4. OAB Overactive bladder
5. RCT Randomized controlled trial
6. TEAE Treatment-emergent adverse event
7. UUI Urgency urinary incontinence

ABSTRACT

Purpose: The purpose of this guideline is to provide a clinical framework for the diagnosis and treatment of non-neurogenic overactive bladder (OAB).

Materials & Methods: The primary source of evidence for the original version of this guideline was the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment Number 187 titled *Treatment of Overactive Bladder in Women* (2009). That report was supplemented with additional searches capturing literature published through December 2011. Following initial publication, this guideline underwent amendment in 2014 and 2018. The current document reflects relevant literature published through October 2018.

Results: When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate), or C (low). Such statements are provided as Standards, Recommendations, or Options. In instances of insufficient evidence, additional guidance information is provided as Clinical Principles and Expert Opinions.

Conclusions: The evidence-based statements are provided for diagnosis and overall management of OAB, as well as for the various treatments. Diagnosis and treatment methodologies can be expected to change as the evidence base grows and as new treatment strategies become obtainable.

Keywords: urinary bladder, overactive; overactive bladder therapeutics

INTRODUCTION

OAB is a clinical diagnosis characterized by the presence of bothersome urinary symptoms. Most studies of OAB, including this guideline, exclude individuals with symptoms related to neurologic conditions. The International Continence Society (ICS) defines OAB as the presence of “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection or other obvious pathology.”¹ OAB studies have used varying combinations of these symptoms to identify patients for study inclusion and to define treatment response.

Urgency is defined by the ICS as the “complaint of a sudden, compelling desire to pass urine which is difficult to defer.”¹ Urgency is considered the hallmark symptom of OAB, but it has proven difficult to precisely define or to characterize for research or clinical purposes. Therefore, many studies of OAB treatments have relied upon other measures (e.g., number of voids, number of incontinence episodes) to measure treatment response.

Urinary frequency can be reliably measured with a voiding diary. Traditionally, up to seven micturition episodes during waking hours has been considered normal,² but this number is highly variable based upon hours of sleep, fluid intake, comorbid medical conditions, and other factors.

Nocturia is defined by the ICS as the complaint of interruption of sleep one or more times because of the need to void.¹ In one study, three or more episodes of nocturia constitutes moderate or major bother.³ Like daytime frequency, nocturia is a multifactorial symptom that is often due to factors unrelated to OAB (e.g., excessive nighttime urine production, sleep apnea).

UUI is defined as the involuntary leakage of urine, associated with a sudden compelling desire to void. Incontinence episodes can be measured reliably with a diary, and the quantity of urine leakage can be measured with pad tests. However, in patients with mixed urinary incontinence (both stress and urgency incontinence), it can be difficult to distinguish between incontinence subtypes. Therefore, it is common for OAB treatment trials to utilize total incontinence episodes as an outcome measure.

Patient Presentation

Symptoms. When symptoms of both daytime and nighttime urinary frequency and urgency (with or without urgency incontinence) are self-reported as bothersome, the patient may be diagnosed with OAB.⁴ Additionally, a caregiver or partner may perceive these symptoms as bothersome and lead the patient to seek care. It is common for patients to have suffered with their symptoms for an extended time before seeking medical advice.

Differentiation. OAB symptoms may occur only at night, causing a single symptom of nocturia. The differential of nocturia includes nocturnal polyuria (the production of greater than 20 to 33% of total 24 hour urine output during the period of sleep, which is age-dependent with 20% for younger individuals and 33% for elderly individuals),⁵ low nocturnal bladder capacity, or both. In nocturnal polyuria, nocturnal voids are frequently normal or large volume as opposed to the small volume voids commonly observed in nocturia associated with OAB. Sleep disturbances, vascular and/or cardiac disease and other medical conditions are often associated with nocturnal polyuria.

OAB also must be distinguished from other conditions such as polydipsia. In OAB, urinary frequency is associated with many small volume voids. Frequency that is the result of polydipsia and resulting polyuria may mimic OAB; the two can only be distinguished with the use of frequency-volume charts. In polydipsia, urinary frequency occurs with normal or large volume voids, and the intake is volume matched. In this case, the frequency is appropriate because of the intake volume, and the patient does not have OAB. Frequency due to polydipsia is physiologically self-induced OAB and should be managed with education, with consideration of fluid management.

The clinical presentation of interstitial cystitis/ bladder pain syndrome shares the symptoms of urinary frequency and urgency, with or without urgency incontinence; however, bladder and/or pelvic pain, including dyspareunia, is a crucial component of its presentation in contradistinction to OAB. Other conditions also can contribute to OAB symptoms and should be assessed. For example, in the menopausal female patient, atrophic vaginitis can be a contributing factor to incontinence symptoms. There is some evidence for symptom improvement with the use of vaginal (but not systemic) estrogen.⁶

Methodology

The AHRQ report that served as the primary source of evidence for the initial version of this guideline searched PubMed, MEDLINE, EMBASE and CINAHL for English-language studies published from January 1966 to October 2008 relevant to OAB.⁷ The American Urological Association (AUA) conducted an additional literature search to capture articles published between October 2008 and December 2011.

The AUA update literature review process, in which an additional systematic review is conducted periodically to maintain guideline currency with newly-published relevant literature, was initiated in 2014 and 2018. These reviews identified an additional 72 (2014) and 37 (2018) articles relevant to treatment. These articles were added to the database, and AUA's qualitative and quantitative analyses were updated as appropriate. The review panels determined that each update review warranted targeted updates to the document, thereby creating the 2014 and 2019 amendments. The subject of this current review is the 2019 amendment, which provides additional guidance related to the use of combination therapy for the treatment of OAB.

The AUA Nomenclature System used for this guideline can be found in Table 1. Please refer to Figure 1 for the diagnostic and treatment algorithm associated with this guideline.

UPDATED GUIDELINE STATEMENT

The 2019 amendment was based on the inclusion of combination therapy for the treatment of OAB. All other statements in the previous guideline iteration remain unchanged. The clinician should bear in mind that the treatment framework does not require that every patient go through each line of treatment in order. There are many factors to consider when identifying the best treatment for a particular patient, including information regarding allergies, sensitivity to various adverse drug events, patient ability and motivation to comply, and availability of and access to specific treatments. To review the full document, please visit www.AUAnet.org/Guidelines.

Second-Line Treatments: Pharmacologic Management

Clinicians may consider combination therapy with an anti-muscarinic and β_3 -adrenoceptor agonist for patients refractory to monotherapy with either anti-muscarinics or β_3 -adrenoceptor agonists. *Option (Evidence Strength Grade B)*

The 2019 update literature review uncovered a number of studies looking at combination therapy

for the treatment of OAB. Typical pharmacotherapy options for the management of OAB include both anti-muscarinics and β_3 -adrenoceptor agonists. While these therapies have different mechanisms of action, co-administration appears to have no noticeable effects on pharmacokinetics.⁸ Further, studies have demonstrated improved efficacy with combination therapy without any significant effect on the safety profile when compared to monotherapy. While the strongest evidence for combination therapy comes from the SYNERGY I/II^{9,10} and BESIDE¹¹ trials, which utilized solifenacin (5 mg) and mirabegron (25 or 50 mg), additional combinations utilizing various other drug classes and dosing schedules have been tested and are discussed below. At this time, the Panel feels that such data are less robust; as such, more data will be required before such additional combinations can be recommended.

In the 18-week SYNERGY trial, Herschorn et al. (2017)⁹ randomized 3,398 wet OAB patients (77% women) to solifenacin (5 mg) plus mirabegron (25 mg), solifenacin (5 mg) plus mirabegron (50 mg), placebo, mirabegron (25 mg) monotherapy, mirabegron (50 mg) monotherapy, or solifenacin (5 mg) monotherapy in a 2:2:1:1:1:1 ratio. While the solifenacin/mirabegron 50 mg group was superior to solifenacin monotherapy for mean adjusted difference in urinary incontinence episodes per 24 hours (-0.20, 95% CI -0.44 to 0.04, $P= 0.033$), statistical superiority was not seen versus mirabegron 50 mg monotherapy (-0.23, 95% CI -0.47 to 0.01, $P= 0.052$). In secondary analyses, all active treatment groups showed greater improvements in urinary incontinence episodes per 24 hours versus placebo (nominal P values all <0.05). Effect sizes for the combined therapy groups (solifenacin/mirabegron 25 mg: -0.70; solifenacin/mirabegron 50 mg: -0.65) were higher than those obtained with monotherapy (range -0.37 for mirabegron 25 mg to -0.45 for solifenacin 5 mg). All active treatment groups had greater improvements in the mean numbers of micturitions per 24 hours versus placebo, with effect sizes for the combined therapy groups (solifenacin/mirabegron 25 mg: -0.85; solifenacin/mirabegron 50 mg: -0.95) higher than with mirabegron monotherapy (25 mg: -0.36; 50 mg: -0.39) and solifenacin 5 mg (-0.56). Researchers noted that the combined solifenacin/mirabegron 50 mg group was statistically significantly superior to both monotherapies at end of treatment for UUI episodes, urgency episodes and nocturia, with effect sizes that appeared to be additive. Adverse events including dry mouth, constipation, and dyspepsia, were slightly increased in the combination therapy groups compared to monotherapies. Additionally, events indicative of urinary retention were reported more frequently in the combination groups compared to

monotherapy and placebo.

In the follow up SYNERGY II trial, Gratzke et al. (2018)¹⁰ evaluated the safety and efficacy of combination therapy over 12 months. The trial randomized 1,829 wet OAB patients (80% women) to combination 5 mg solifenacin plus 50 mg mirabegron, solifenacin monotherapy, mirabegron monotherapy, or placebo. The primary objective was safety as measured by treatment-emergent adverse events (TEAEs); additionally, efficacy was measured as the change from baseline to the end of treatment in the mean number of incontinence episodes and micturitions per 24 hours. TEAEs were reported more frequently in the combination group (49%) than in the mirabegron group (41%) or solifenacin group (44%), with dry mouth being the most commonly reported TEAE. Combination therapy was statistically superior to mirabegron and solifenacin monotherapy for decreasing number of incontinence episodes (mirabegron, $p < 0.001$; solifenacin, $p = 0.002$) and micturitions (mirabegron, $p < 0.001$; solifenacin, $p = 0.004$).

Drake et al. (2016)¹¹ in the BESIDE trial evaluated the efficacy, safety, and tolerability of combination therapy (solifenacin 5 mg plus mirabegron 50 mg) versus monotherapy (solifenacin 5 or 10 mg) in a 1:1:1 randomized trial for OAB patients remaining incontinent after 4 weeks of solifenacin 5 mg. A total of 2,174 patients were randomized (83% women). At end of treatment, combination therapy was found to be superior to solifenacin 5 mg, with significant improvements in daily incontinence ($p = 0.001$), daily micturitions ($p < 0.001$), and incontinence noted in a 3-day diary ($p = 0.014$). Combination was non-inferior to solifenacin 10 mg for key secondary end points, including a change from baseline to end of treatment in the mean number of micturitions per 24 hours and number of incontinence episodes noted in a 3-day diary at end of treatment. Combination was superior to solifenacin 10 mg for improving daily micturitions.

One randomized controlled trial (RCT) by Kosilov et al. (2018)¹² and one prospective cohort study by Kosilov et al. (2013)¹³ evaluated combination solifenacin and trospium in women with OAB. The Panel notes that the doses of solifenacin and trospium utilized in the Kosilov et al. studies are higher than the standard recommended doses. The RCT randomized 312 women (60-83 years of age) to high dose solifenacin (20 mg/day) plus high dose trospium (60 mg/day), or a lower dose of solifenacin (10 mg/day) plus a lower dose trospium (30 mg/day), or placebo.¹² Following treatment, quality of life parameters in terms of the functional state of the lower urinary tract were improved compared with placebo, but with no differences between the higher

dose and lower dose combination groups ($p < 0.05$). The prospective cohort study was designed in two phases and included 229 women (65-77 years of age).¹³ In the first phase all women received 60 mg trospium and 40 mg solifenacin daily, while in the second phase, defined as the maintenance phase, women were allocated to additional trospium plus solifenacin treatment, electrical stimulation of detrusor muscle, laser puncture using a helium-neon laser applied to acupuncture points, or placebo for one month. The study reported that maintenance with the combination therapy resulted in effective maintenance of clinical and urodynamic results for at least seven months, while electrical stimulation was less effective, and laser puncture was inefficient.

Another RCT by Ellington et al. (2016) evaluated combination tolterodine and intravaginal estradiol cream in 58 menopausal women.¹⁴ Women were randomized to either oral tolterodine or estradiol cream for 12 weeks and then offered addition of the alternative therapy with follow-up at week 24 and week 52. Both monotherapies resulted in decreased symptom bother scores at 12 weeks when compared with baseline values. Following addition of the alternate therapy at the 12 week time-point, within group OAB symptom severity and health-related quality of life scores remained improved significantly at 24 and 52 weeks from baseline, though it should be noted that only addition of tolterodine at 12 weeks to the estradiol group resulted in further significant improvement in the OAB-q symptom bother score and the health-related quality of life scores above the single therapy effect noted at 12 weeks.

Finally, an RCT by Rovner et al. (2018)¹⁵ compared a 3 month combination of oral desmopressin 25 μ g plus 4 mg tolterodine with 4 mg tolterodine monotherapy in 106 women. When evaluating the overall population, combination therapy resulted in a non-significant reduction in nocturnal voids over monotherapy ($P = 0.112$). In a subgroup of patients with nocturnal polyuria, combination therapy resulted in improved nocturnal void volume ($P = 0.034$) and time to first nocturnal void ($P = 0.045$).

RESEARCH NEEDS AND FUTURE DIRECTIONS

Better Stratification of OAB. OAB is primarily a diagnosis of exclusion. Treatments are aimed at relieving symptoms and not necessarily at reversing pathophysiologic abnormalities. Understanding the pathophysiology and the risk factors for development of OAB is needed both

to treat the syndrome as well as to prevent it. Future research will need to address the entire spectrum of research endeavors including epidemiology, quality of life measurements, treatment modalities, and basic bladder physiology including sensory and motor signaling. Within the field of OAB, research is sometimes dichotomized between OAB/lower urinary tract symptoms (e.g., OAB-dry) versus OAB/urgency incontinence (OAB-wet). However, this type of compartmentalization highlights our lack of understanding of OAB. In addition, particularly in females, stress urinary incontinence symptoms may exist concomitantly with OAB symptoms. Further, isolated nocturia is a separate symptom entity, requiring different evaluation and management strategies.

Clinical Research. Several validated OAB symptom and OAB symptom bother tools have been developed. However, objective measures of the “cornerstone” OAB symptom of urgency¹⁶ remains poorly assessed. Investigators have tested urgency questionnaires to assess for validity and reliability;¹⁷⁻¹⁹ however, no single measure is used consistently across trials. Objective outcomes should include frequency, nocturia, urgency, incontinence episode frequency, and reporting of the variance for each of these measures.

Further research is needed focused on combination therapy utilizing other drug classes and dosing regimens looking at both efficacy and adverse effects. Additionally, the use of vaginal estrogen should be studied as a monotherapy for OAB as well as in combination with other therapies.

The effect of treatment of OAB on the elderly, the very frail, and those with pre-existing cognitive deficiencies needs further research. These include measures of cognitive side effects from anti-muscarinic treatments.

Diagnosis and treatment protocols for OAB can be expected to change as the evidence base continues to grow. As such, this document will undergo regular review to ensure currency of recommendations.

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ATTACHMENTS:

Table 1: AUA Nomenclature

Figure 1: Diagnosis & Treatment Algorithm

DISCLAIMER

This document was written by the Overactive Bladder Amendment Panel of the American Urological Association Education and Research, Inc., which was created in 2018. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the panel included specialists with specific expertise on this disorder. The mission of the panel was to review existing statements for currency and provide new statements that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the diagnosis and treatment of overactive bladder.

Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance

with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

DISCLOSURES

All panel members completed COI disclosures. Disclosures listed include both topic- and non-topic-related relationships. All unlisted authors have nothing to disclose.

Consultant/Advisor: Sandip P. Vasavada, Allergan, Axonics, Amphora, BlueWind

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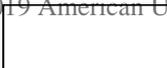
Scientific Study or Trial: Sandip P. Vasavada, Allergan

Investment Interest: Sandip P. Vasavada, NDI Medical LLC

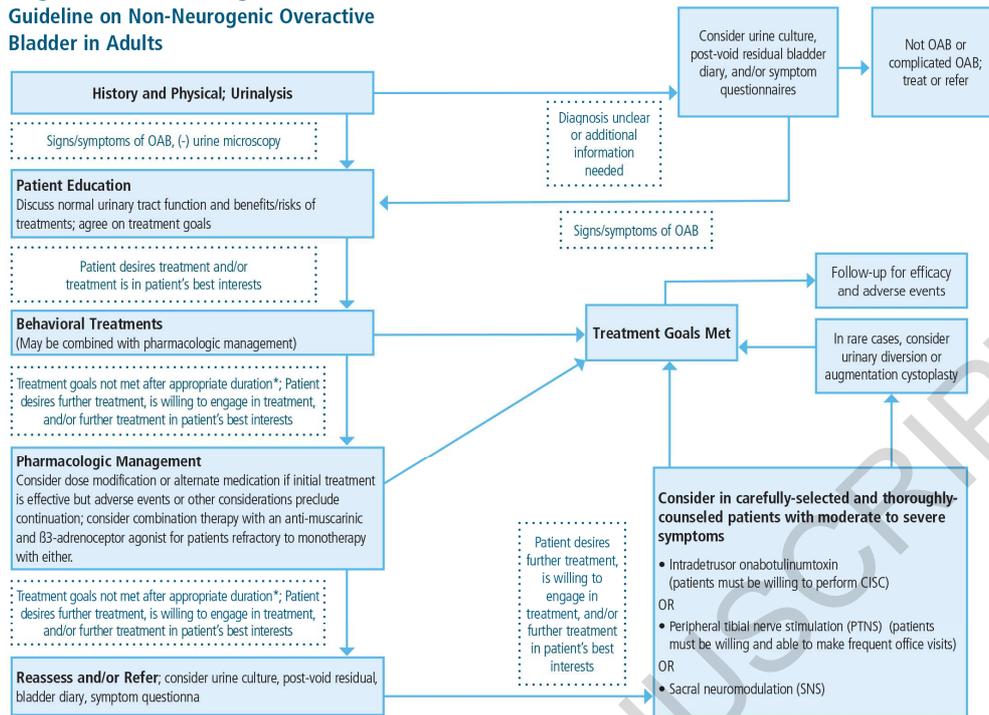
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Table 1: AUA Nomenclature Linking Statement Type to Level of Certainty and Evidence Strength
Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A (high quality; high certainty) or B (moderate quality; moderate certainty) evidence
Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C (low quality; low certainty) evidence
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A (high quality; high certainty), B (moderate quality; moderate certainty), or C (low quality; low certainty) evidence
Clinical Principle: a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature
Expert Opinion: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

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**Diagnosis & Treatment Algorithm: AUA/SUFU
Guideline on Non-Neurogenic Overactive
Bladder in Adults**



The complete OAB Guideline is available at AUA.net.org/Guidelines.
This clinical framework does not require that every patient go through each line of treatment in order as there are many factors to consider when identifying the best treatment for a particular patient.

*Appropriate duration is 8 to 12 weeks for behavioral therapies and 4 to 8 weeks for pharmacologic therapies
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