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Advances in pharmacotherapy for the treatment of overactive bladder

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Abstract

Purpose of review—To present the current literature on the pharmacologic management of overactive bladder, including combination therapies, agents still in clinical development, and special considerations related to individuals with cognitive decline, frailty and cardiovascular risk.

Recent Findings—Combination therapy is shown to be more effective than monotherapy, without additional side effects. Preliminary studies on novel treatment methods, including new medications, as well was novel use of established medications, demonstrates improved efficacy with a favorable side effect profile. Investigation into new target pathways may be an area for future pharmacologic development. Special consideration should be given when prescribing anti-muscarinic medication in the frail adult population. Overactive bladder has been associated with frailty and anti-muscarinic medications have been associated with the worsening cognitive decline.

Summary—Combination therapy is a safe and effective alternative to patients with refractory overactive bladder. Caution should be taken in prescribing medications for the frail older adult, and alternative first- and third-line treatments should be considered. Future studies should involve long term data on safety and outcomes stratified by age with objective measurements of cognition and frailty.

Keywords

overactive bladder; pharmacotherapy; anti-muscarinic; beta-agonist; frailty

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Conflict of Interest

Caitlyn Painter has no conflicts of interest.

Anne Suskind is a consultant for Acoustic Wave Cell Therapy, Inc.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Overactive bladder (OAB) is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence [1]. The overall prevalence of OAB in women is 16.9%, with women over the age of 65 being twice as likely to have overactive bladder symptoms [2]. Anti-muscarinic therapy has historically been the mainstay of pharmacologic treatment and continues to be recommended by the American Urologic Association and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (AUA/SUFU) guidelines for the treatment of non-neurogenic overactive bladder [3••]. In 2012 the United States Food and Drug Administration (FDA) approved a new pharmacologic agent called mirabegron, which is a β_3-adrenoreceptor agonist. This was soon followed by FDA approval for the use of intradetrusor onabotulinumtoxinA injections in 2013. Despite the addition of mirabegron and intradetrusor onabotulinumtoxinA injections to the OAB treatment armamentarium, there is still a proportion of patients in whom these therapies are not effective or are contraindicated. In addition, there is an established and growing body of evidence surrounding the side effect profile of anti-muscarinic medications. For these reasons, new treatments are needed and continue to be developed. This review aims to evaluate the recent literature on novel pharmacotherapy designed for the treatment of overactive bladder including combination therapy and pharmacotherapy currently in development. In addition, this review will investigate the OAB treatment considerations among special populations as related to cognition, frailty, and cardiovascular risk factors.

Combination therapy

Combination therapy is a promising new frontier for OAB pharmacological research. The most recent AUA/SUFU guidelines now suggest consideration for the use of a combination anti-muscarinic agent with a β_3-adrenoceptor agonist in those patients who fail monotherapy [3••]. Many combination therapies currently exist, including a muscarinic agonist and antagonist combination, an anti-muscarinic and β_3-adrenoceptor agonist combination, an anti-muscarinic and electrical stimulation combination, and an anti-muscarinic and vaginal estrogen combination [4•].

Muscarinic agonist plus antagonist

The combination of a muscarinic agonist plus antagonist pill, THVD-201, is a novel combination of tolterodine immediate release (IR) (2 mg) and pilocarpine extended release (ER) (9 mg). This therapy was designed to reduce the main side effects of anti-muscarinic drugs including: dry eye, dry mouth and constipation. In a double-blind, multiple-crossover phase 2 randomized controlled trial, THVD-201 was found to have equal efficacy compared to tolterodine IR, but with a significant reduction in dry mouth severity by 60% ($p<0.0001$) [5]. Side effects, including dry mouth, are a common reason for the discontinuation of anti-muscarinic medication. The addition of a muscarinic agonist to an anti-muscarinic medication may be a feasible alternative for patients who have relief of their OAB symptoms from an anti-muscarinic medication but cannot tolerate the dry mouth side effects.

Anti-muscarinic plus β_3-adrenoceptor agonist

The undesirable side effects of anti-muscarinic medications have been an ongoing challenge, which is one of the reasons why the addition of mirabegron, a β_3-adrenoceptor agonist, showed great promise. Mirabegron has similar efficacy as anti-muscarinic medications, with a lower side effect profile. Therefore, combining mirabegron with an anti-muscarinic medication may potentiate the therapeutic effect on OAB symptoms without increasing the side effect profile. There are several studies that have investigated this combination treatment. SYMPHONY, a double-blind, randomized, phase 2 trial, evaluated the use of solifenacin plus mirabegron compared to solifenacin alone for the treatment of OAB in men and women. A total of 1306 patients were randomized to 12 weeks of treatment in 1 of 12 groups, consisting of combination therapy, monotherapy and placebo. In this study, combination therapy with solifenacin/mirabegron significantly improved mean volume voided, micturition frequency, and urgency compared with solifenacin 5 mg monotherapy. In addition, all combinations were well tolerated, with no significant increase in adverse events when compared with monotherapy or placebo [6].

The SYMPHONY trial illustrates that the combination of mirabegron and solifenacin is superior to solifenacin monotherapy in the short term, however their study terminated at 12 weeks of treatment. In the SYNERGY II trial, the safety and efficacy of solifenacin 5 mg plus mirabegron 50 mg tablets (combination treatment) versus solifenacin or mirabegron monotherapy in patients with OAB was evaluated over 12 months. When compared to monotherapy, combination treatment significantly reduced the number of incontinence episodes and micturition episodes in a 24-hour period ($p < 0.05$). No clinically relevant differences across groups in the frequency of adverse events leading to permanent treatment discontinuation was noted [7••]. Collectively, these trials indicate that the use of combination solifenacin with mirabegron is not only safe, but has increased efficacy at up to 12 months, when compared to monotherapies.

In clinical practice, patients are often started on an anti-muscarinic medication and given a trial period of monotherapy. After several weeks, during re-evaluation, if there is not a significant improvement in symptoms, there is a consideration of adding on an additional medication to enhance the effectiveness of the first drug. The BESIDE trial, a randomized double-blind multicenter phase III study of 2174 participants, evaluated the efficacy and safety of mirabegron add-on therapy to solifenacin. Patients who remained incontinent after 4-weeks of solifenacin 5mg, were randomized to either: continuing current therapy of solifenacin 5 mg daily, solifenacin 10 mg daily, or add-on therapy of solifenacin 5 mg plus mirabegron 50 mg for 12 weeks. When comparing the addition of mirabegron 50 mg to solifenacin 5 mg, the addition of mirabegron was associated with significant improvements in daily incontinence episodes ($p=0.001$), daily micturitions ($p<0.001$) and incontinence episodes noted in a 3-day diary ($p=0.0014$). All treatments were well tolerated [8].

Both the SYMPHONY and SYNERGY II trials demonstrate improvement in OAB measures without an increase in adverse events when combining solifenacin with mirabegron. In addition, the BESIDE trial, shows that mirabegron add-on therapy to solifenacin is safe, with improvement in daily incontinence and daily micturitions. Overall, these studies show that

the combination of mirabegron and solifenacin is a safe drug regimen and may constitute a novel treatment option for overactive bladder.

Anti-muscarinic plus electrical stimulation

Neuromodulation, in the form of peripheral tibial nerve stimulation (PTNS) or sacral neuromodulation, is approved as a third-line therapy for the treatment of OAB [3]. PTNS has been studied for use in combination with solifenacin. In one randomized controlled trial, 105 women were randomized into three groups: solifenacin (5 mg once daily for 12 weeks), PTNS (30 minutes, weekly for 12 weeks), or combination therapy. Study participants were evaluated longitudinally, using validated questionnaires assessing symptoms and quality of life measures, with a maximum follow-up of 10 months. At the end of the study period, all treatment groups showed overall improvement, including symptoms and quality of life measures. However, combination therapy showed a significant improvement in urgency and urgency urinary incontinence episodes when compared to PTNS alone ($p=0.0015$). Combination therapy is more effective in improvement in quality of life than solifenacin or PTNS alone (p values: 0.0017; 0.0468 respectively). Although this study had small numbers of subjects, it demonstrated that the combination of solifenacin and PTNS may have significant improvements in the treatment of OAB symptoms compared to either treatment alone [9•].

One of the benefits of combining a pharmaceutical treatment with a non-drug therapy is the potential for decreased systemic side effects. Non-drug therapies that have been used in the treatment of OAB include: behavioral modifications, bladder training, PTNS, transcutaneous electrical nerve stimulation (TENS), and sacroneuromodulation (SNM). A meta-analysis of ten randomized controlled trials evaluated the therapeutic effects of combining anti-muscarinic medications with non-drug therapy. A total of 485 female patients were treated with combination therapy, which includes an anti-muscarinic plus electrical stimulation (PTNS, SNM or TENS) or anti-muscarinic plus bladder training. The control group included 497 women, that were treated with an anti-muscarinic alone. In a pooled analysis, combination anti-muscarinic plus electrical stimulation found a significant reduction in average frequency of urination, incontinence, and urgency when compared to anti-muscarinic alone [10]. Albeit these are small trials with a relatively low numbers, the use of combination anti-muscarinic medication with either PTNS or SNM is an innovative alternative treatment option in OAB. Future studies will need to be developed to assess the use of electric neuromodulation in larger populations and in combination with other medications, such as mirabegron. Furthermore, pharmacological therapy combined with intravesical chemodenervation (onabotulinumtoxinA) should be an area of future study as well.

Anti-muscarinic plus vaginal estrogen combination

In the sections above, we reviewed medications that are all approved therapies for the treatment of OAB. For women with OAB, vaginal estrogen is sometimes used to treat vulvovaginal atrophy as part of the overall treatment of lower urinary tract symptoms. There is increasing research to support the use of intravaginal estrogen for the improvement of OAB symptoms, however this is not currently an FDA approved indication for estrogen. A

recent systematic review concluded that compared with placebo, intravaginal estrogens improved urinary urgency, urinary frequency, and stress and urgency urinary incontinence [11]. Limited data exist that compares the use of vaginal estrogen with other treatments for OAB. One study compares the use of daily tolterodine ER 4 mg to low dose intravaginal estradiol cream 0.5 grams daily for 12 weeks, followed by the combination of tolterodine plus intravaginal estradiol cream. When comparing symptom bother score of study participants receiving tolterodine alone, intravaginal estradiol alone, or combination therapy, there was a statistically significant improvement in symptom bother score within the combination group (p=0.008) [12]. This study suggests a synergistic benefit between vaginal estrogen therapy and anti-muscarinic medications. Additional research and data are needed to further evaluate combination therapy in terms of efficacy, side effects, and patient compliance with these therapies.

Pharmacotherapy in Development

There are several pharmacologic agents currently in development that are showing promising results in decreasing OAB symptoms, while minimizing the side effect profile that has been associated with the standard anti-muscarinic pharmacotherapy. These medications include new agents that target known receptors (i.e., anti-muscarinic and β_3-adrenoceptor agonists), novel indications for already established medications (i.e., PDE5 inhibitors), and finally, investigation into new target pathways (i.e., P2X3 receptor antagonists and TRP channels).

Anti-muscarinic agents

Given the long history of proven efficacy, the study of anti-muscarinic medications remains at the forefront of pharmacologic research, with newer more specific formulations being an area for potential new treatments. Several novel compounds currently being studied include: Imidafenacin and Tarafenacin. Earlier anti-muscarinic medications, such as oxybutynin, act on multiple muscarinic receptors, including M_1, M_3, and M_4. Not only do these medications target the muscarinic receptors in the bladder, but also work on these receptors located in the eyes, mouth, bowel, and brain. The goal in developing newer medications is to make them more bladder specific. The bladder contains M_2 and M_3 receptors, however detrusor contractions are almost exclusively mediated via the M_3 receptor. M_1 receptors are located in the brain, and M_2 receptors are in the heart, which can account for the cognitive and cardiovascular side effects seen with the use of non-specific anti-muscarinic medications.

Imidafenacin is an antagonist of M_1/M_3 receptors with greater specificity for the M_3 receptor and has been available in Japan since 2007. A meta-analysis of five studies, involving 1,428 patients, compares the efficacy and safety of imidafenacin with propiverine and solifenacin. Imidafenacin demonstrates an improved side effect profile with lower rates of dry mouth and constipation, and no negative cognitive or cardiovascular side effects, compared to other anti-muscarinic medications. Additionally, imidafenacin was non-inferior to anti-muscarinic medications and statistically better than placebo in the reduction in number or urinary incontinence episodes per week [13].

Tarafenacin is a highly selective M_3 receptor antagonist currently in phase 2 trials. This medication has 200 times higher selectivity for M_3 than for M_2, with promising results compared to placebo and no reported cardiovascular events [14]. These experimental anti-muscarinic medications have so far shown to be of similar efficacy when compared to the older anti-muscarinic medications. They do, however, seem to have a lower side effect profile, which may increase their acceptability and ultimately patient compliance in clinical practice.

β_3-adrenoceptor agonists

While the safety and efficacy of mirabegron is now widely supported and accepted, the development of additional β_3-adrenoceptor agonists has just commenced. Three new drugs in this class include: vibegron, ritobegron and solabegron.

Vibegron is a potent, selective β_3-adrenoceptor agonist. In primate studies, this medication demonstrates a dose-dependent increase in bladder capacity, decreased micturition pressure and increased bladder compliance. Additionally, when combined with the nonspecific M_2/M_3 antimuscarinic tolterodine, bladder relaxation is enhanced [15].

Ritobegron and solabegron are currently undergoing phase II and III clinical trials. Solabegron was well tolerated in a randomized controlled trial consisting of 258 women, demonstrating a decrease in daily incontinence episodes when compared to placebo. Additionally, solabegron demonstrates similar rates of dry mouth and constipation, with acceptable rates of cardiovascular side effects, when compared to placebo at 8 weeks [16].

Overall, the discovery of the presence of the β_3-adrenoceptor in the bladder, and its role in detrusor muscle relaxation, led to a new direction of pharmacologic research and development in OAB. Preliminary studies demonstrate that these newer $\beta_3$adrenoceptor agonists may be a safe alternative among individuals who do not tolerate anti-muscarinic medicines.

Phosphodiesterase inhibitors

Phosphodiesterase 5 (PDE5) inhibitors, most notably tadalafil, have traditionally been used in the treatment of erectile dysfunction. These medications work by preventing the degradation of important mediators (i.e., cGMP and cAMP) involved in maintaining smooth muscle tone. More recently, these medications have been studied for use in treating OAB symptoms. In one study of 96 women in China, subjects were randomly assigned to daily tadalafil 5 mg or placebo. The treatment group showed significantly decreased overactive bladder symptom scores, decreased episodes of urinary frequency, urgency and urgency urinary incontinence compared to placebo at 3 months. Voided volume and total bladder capacity also increased in the treatment group [17•].

There are multiple clinical studies demonstrating favorable results for the use of PDE5 inhibitors in lower urinary tract symptoms (LUTS) in men, especially in relation to benign prostatic hyperplasia (BPH). In one study of 251 men 45 years or older, with a history of LUTS-BPH of 6 months or longer were randomly assigned to receive dose escalation of tadalafil or placebo. Tadalafil significantly improved obstructive and irritative symptoms and

there was no increase in adverse events [18]. The evidence for the use of PDE5 inhibitors in men with BPH is convincing, however more studies are needed to evaluate its use in men without BPH, and in larger more racially and ethnically diverse female patient populations. Currently tadalafil is approved by the FDA for the treatment of LUTS due to BPH with or without associated erectile dysfunction.

Alternate target pathways

There is ongoing research into different receptors on the bladder (other than muscarinic and β_3-adrenoceptors) for potential newly targeted mechanisms of action for the pharmacological treatment of OAB. While these pharmacotherapies are yet to reach phase II clinical trials, results of early animal studies are promising. One target is to block the ATP afferent pathway, using $P2X_3$ receptor antagonists. The P2X receptors are involved in sensing volume change and may aid in lowering the threshold for firing of afferent fibers in the micturition reflex during pathophysiologic conditions. In rat models, the $P2X_3$ receptor antagonist A-317491 produced a dose-dependent inhibition of non-micturition contractions, increased inter-micturition interval and increased bladder capacity, without changing the amplitude of voiding contractions. In-vitro pharmacologic studies of the $P2X_3$ receptor antagonist compound AF-353 demonstrates that this compound is highly selective, orally bioavailable, and specific, potentially making it a good candidate for future in vivo human studies [19–20].

The role of several transient receptor potential (TRP) channels expressed in the bladder is also being studied for its utility in OAB treatment. TRP channels are located primarily on afferent nerve fibers and are thought to act as sensors of stretch and/or chemical irritation in the bladder. The theory is that by inhibiting the TRP channels, there is a blockade of the afferent limb in the micturition signaling pathway. The inhibition of several TRP channels, including TRVP1, TRVP2, TRVP4, TRMP8 and TRPA1, has shown reduction in bladder activity. Currently, however, there are no commercially-available compounds being developed with this mechanism of action, but this is a potential area for future investigation [20].

Overall, investigation into these newer pharmacologic therapies shows potential for improved OAB treatments, with increased receptor specificity, reduction in bladder overactivity, and increase in bladder compliance. Future research, including phase II and phase III trials, is needed to establish the efficacy and safety of these medications.

Special Considerations in the Management of OAB

Pharmacotherapy is a mainstay of OAB treatment, with anti-muscarinic medications and β_3-adrenoceptor blockers being used for the longest amount of time. Aside from the main reported side effects of dry eye, dry mouth, and constipation, there is a growing body of research on the undesirable side effects of these medications in certain populations. Specifically, concerns for use of pharmacotherapy in individuals with deficits related to cognition, frailty, and cardiovascular risk factors exist and are discussed further herein.

Considerations on Cognition

Cognitive deficits, including difficulties with memory and dementia, have been reported in relation to the use of anti-muscarinic medications for OAB, particularly in the older adult population. A recent prospective observational study of adults ages 65 years and older without dementia, looked at the influence of anticholinergic medications on changes in cognition. A total of 350 adults were followed longitudinally for a mean follow up 3.2 years. The medication exposure was calculated as a total standard daily dose of anticholinergics. Cognitive diagnosis was categorized as: normal cognition, mild cognitive impairment (MCI), or dementia. Increased total standard dose of anticholinergics increased the odds of transition from normal cognition to MCI over the study period (odds ratio [OR] 1.15, 95% confidence interval [CI] 1.01–1.31, p = 0.0342) [21••]. This study suggests that there is an increase in rate of transition from normal cognition to mild cognitive impairment with higher daily dosages of anticholinergic medications. A prospective, two-year longitudinal study of 13,004 participants investigated the use of medications with anticholinergic activity and risk of cognitive impairment. Medications with definite anticholinergic effects were associated with a 0.33-point greater decline in mini mental status exam (MMSE) score (95% confidence interval (CI)=0.03–0.64, *P*=.03) when compared to those not using medications with anticholinergic activity [22]. While this large prospective study was not specifically designed for anti-muscarinic medications used for the treatment of OAB, these medications do have anticholinergic effects, and can cause decline in the MMSE. The other concern in relation to cognitive decline, is the risk of polypharmacy in the older adult population. In a meta-analysis of data pooled from ten double-blind, placebo-controlled trials using anti-muscarinic medication in the treatment of overactive bladder, there is a significant increase in the likelihood of reporting an adverse event in association with the number of coexistent medications (odds ratio (OR) = 1.028, 95% CI: 1.01431.044, P < 0.003) [23]. The AUA/SUFU guidelines recognize the risk of polypharmacy in the older adult population and recommend exercising caution in prescribing anti-muscarinic medications in patients who are using other medications with anticholinergic properties. To further quantify this risk, clinicians can consider use of an anti-muscarinic risk scale, or Beers Criteria, to assess the risk of concomitant anti-muscarinic use [24].

The American Urogynecologic Society (AUGS) issued a consensus statement in 2017 on the association of anti-muscarinic medication use and cognition in women with overactive bladder. This statement includes the following recommendation: “Given the available evidence, which has shown significant associations between anti-muscarinic medication use and increased risk of cognitive impairment and dementia, providers should counsel on the associated risks, prescribe the lowest effective dose, and consider alternative medications in patients at risk” [25••]. The AUA/SUFU guidelines agree and further state, “In dementia patients, anti-muscarinics should be used with extreme caution or may be contraindicated entirely depending on the level of cognitive impairment” [3]. Additional studies have recommended including performance of a mini mental status exam on all patients that may be at risk for cognitive impairment [24]. Maximizing first line behavioral therapy, and patient education as well as counseling patients about the potential adverse events related to anti-muscarinic medications, and potentially starting with third line therapies of

onabotulinumtoxinA injections, PTNS and sacroneuromodulation may be indicated in the older adult at risk for cognitive impairment.

Considerations on Frailty

Frailty, which is a measure of physiological vulnerability that is often manifested in older individuals as an increased susceptibility to disability, is another consideration when prescribing in the older adult population. There is increasing evidence that frailty is associated with a diagnosis of OAB in older adults. One study of individuals aged 65 and older presenting to a non-oncology academic urology practice demonstrated a significant association between frailty, measured via the Timed Up and Go Test (TUGT), and a diagnosis of OAB ($p<0.0001$). When controlling for other variables, such as age, a slower TUGT (indicative of frailty) was a significant predictor of a diagnosis of OAB (adjusted odds ratio: 3.0; 95% confidence interval: 2.0–4.8) [26••]. Due to this potential relationship, frailty should be considered when selecting OAB treatments. The and AUA/SUFU guidelines recommend exercising caution in prescribing these medications in the frail OAB population. Further research is required to determine whether frailty portents a poorer treatment outcome in these individuals.

Considerations on Cardiovascular risk

Cardiovascular risk has been a longstanding concern for the use of anti-muscarinic medications, however the true risk is not well established. Anti-muscarinic medications have been associated with increased heart rate and prolonged QT interval on electrocardiogram due to the blockade of the M_2 receptor on the heart. To assess the cardiovascular safety of anti-muscarinic drugs used in the treatment of OAB, a large Danish nationwide cohort study was conducted between 2004–2012. Date on 72,917 patients newly exposed to anti-muscarinic medications for the treatment of OAB was extracted using a Danish national registry. This study found no evidence of increased cardiovascular or mortality risk associated with use of any of the individual OAB medications. However, higher baseline prevalence of cardiovascular comorbidity, including hypertension, diabetes, ischemic heart disease, and cardiac conduction disorders, was found in patients with an OAB diagnosis [27•]. It is possible that cardiovascular disease is a confounding variable in prior studies linking anti-muscarinic medications with adverse cardiac outcomes, and it may be that patients with an OAB diagnosis may simply have higher baseline rates of concomitant cardiovascular disease. This is an area for future research, which may help to further specify and tailor OAB treatments to an individual patients' needs.

The use of mirabegron, the first β_3-adrenoceptor agonists, has also been associated with possible cardiovascular risks and side effects. A prospective observational study of 221 female patients receiving mirabegron for OAB found a 7.2% discontinuation rate because of any side effects. However, there was no significant associations between cardiovascular adverse events and pre-existing cardiac disease or pre-existing ECG abnormalities. There were no de novo cases of tachyarrhythmias and there was an overall decrease in mean systolic blood pressure, showing that mirabegron is associated with a satisfactory cardiovascular risk profile [28].

A Japanese study of 236 patients with pre-existing cardiovascular disease, also found mirabegron 25 or 50 mg to be well tolerated, with no unexpected cardiovascular safety concerns [29]. While the sympathomimetic effects of mirabegron on the other organ systems, aside for the bladder, are poorly understood, these studies are reassuring and indicate that the cardiovascular risk profile of mirabegron is favorable. Additional studies evaluating long term data is needed to corroborate these findings.

Conclusions

Overactive bladder is a common condition with a significant detrimental impact on quality of life for many individuals. Anti-muscarinic therapy has been the mainstay of treatment for many years, however the discontinuation rate is high, and the compliance rate is low. The side effect profile, in addition to the limited efficacy, has led to the need for additional therapeutic options. Combination medical therapy is a promising area of investigation, with studies showing improved or equal efficacy with decreased side effects. New innovative drugs and novel target pathways are currently in phase II and phase III clinical trials and may offer additional treatment options in the future. In the older adult population, considerations should be in place for evaluation of cognition, frailty, and economic burden, prior to and during administration of anti-muscarinic medications. The future of pharmacologic research for the treatment of OAB should focus on the utilizing the newer combination therapies and the development of treatments with lower anticholinergic burden, particularly for the frail, older adult populations.

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