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REVIEW

Cognitive Effects of Anticholinergic Load in Women with Overactive Bladder

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Abstract: Overactive bladder syndrome (OAB) is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology. The mainstay of treatment of OAB is anticholinergic/antimuscarinic medication. These drugs block muscarinic receptors throughout the body, not only the bladder, including in the brain, which may lead to cognitive side effects. Anticholinergic load or burden is the cumulative effect of taking drugs that are capable of producing anticholinergic adverse effects. The elderly are more susceptible to these effects, especially as there is increased permeability of the blood brain barrier. The anticholinergic drugs for OAB are able to enter the central nervous system and lead to central side effects. There is increasing evidence that a high anticholinergic load is linked to the development of cognitive impairment and even dementia. Some studies have found an increased risk of mortality. In view of this, care is needed when treating OAB in the elderly. Trospium chloride is a quaternary amine anticholinergic, which has a molecular structure, which theoretically means it is less likely to cross the blood brain barrier and exert central side effects. Alternatively, mirabegron can be used, which is a beta-3 adrenoceptor agonist, which does not add to the anticholinergic load or exert central nervous system side effects. Conservative therapy can be used as an alternative to pharmacological treatment in the form of behavioral modification, fluid management and bladder retraining. Neuromodulation or the use of botox can also be alternatives, but success may be less in the older adult and will require increased hospital attendances.

Keywords: anticholinergic burden, anticholinergic load, dementia, elderly, overactive bladder

Introduction

Overactive bladder syndrome (OAB) is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology.[1] The prevalence quoted in studies varies between 1%-38.8%.[2] OAB is projected to cost the United States $82.6 billion in 2020.[3] The mainstay of treatment of OAB is anticholinergic/antimuscarinic medication.

These drugs block muscarinic receptors irrespective of location in the body.[4] For the management of OAB, they block muscarinic receptors on the detrusor muscle of the bladder, reducing bladder contractions, decreasing urgency and increasing bladder capacity.[4] There are five muscarinic receptors, M1-5, with M2 and M3 present in the bladder.[5] Blockage of the other muscarinic receptors can lead to side effects which are common in those treated for OAB.[6] These side effects include

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accommodation paralysis, dry eyes, dry mouth, increased heart rate and constipation.[4]

Muscarinic receptors, M1-5, are present in the brain, with M1 and M2 important for higher cognitive processes.[6] Therefore, people taking anticholinergics for OAB have a risk of cognitive side effects, relating to learning, memory, somnolence and confusion.[6]

Anticholinergic Medication

Cognitive side effects occur if the drug can cross the blood brain barrier into the central nervous system.[5] Drugs that are more likely to cross the blood brain barrier are small (<400kDa), lipophilic, hydrophobic and have a neutral charge.[5] The anticholinergics used for OAB are either tertiary or quaternary amines.[4] The two groups are different, with tertiary amines having higher lipophilicity, neutral charge and smaller molecular size.[4] They are well absorbed by the gut and pass through the blood brain barrier into the central nervous system.[4] A quaternary amine has increased hydrophilicity, decreased lipophilicity and a positive charge.[5] Theoretically, this type of drug is less likely to cross the blood brain barrier and exert central nervous system side effects.

If a drug does cross the blood brain barrier, if it is a substrate of the permeability-glycoprotein (P-gp) system, it can be actively transported out of the brain.[5]

The following anticholinergics are tertiary amines, which are used in the treatment of OAB; darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin and tolterodine.[4] These drugs will have the molecular properties discussed above and will theoretically pass into the central nervous system. Darifenacin and fesoterodine are substrates for the P-gp system.[7] A study that looked at M1 and M3 receptor-binding affinities, to predict the risk of central nervous system affects, found that darifenacin and to a lesser extent solifenacin, were more selective of M3 receptors over M1.[8] Oxybutynin and tolterodine were less selective, meaning these drugs are more likely to exert central nervous system side effects compared to darifenacin and solifenacin.

Trospium chloride is a quaternary amine used in the treatment of OAB. It is also a substrate for the P-gp system.[5] Therefore, theoretically this is a drug that is least likely to cross the blood brain barrier and lead to cognitive side effects.

An animal study injected darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium chloride into rats.[7] One-hour post injection, blood, cerebrospinal fluid and brain samples were taken. Oxybutynin showed extensive central nervous system penetration, tolterodine and solifenacin showed significant penetration, whilst darifenacin, fesoterodine and trospium chloride showed poor penetration. The three drugs that performed best are also the drugs that are P-gp system substrates.

As mentioned earlier, if a drug is able to cross the blood brain barrier, it can exert cognitive side effects. The blood brain barrier is a barrier between the brain and the blood supply. It is formed of cerebrovascular endothelial cells that line the cerebral microvessels, forming tight junctions.[5] The drug concentration in the brain is based on passive diffusion across the blood brain barrier and active transportation through carriers out of the brain.[5] The permeability of the blood brain barrier can increase due to trauma, vascular dementia, Alzheimer's dementia, stress, diabetes, multiple sclerosis, hypertension, migraine, epilepsy, meningitis and Parkinson's disease.[5] Drugs have also been found to increase the permeability, such as bradykinin receptor agonists, 5-phosphodiesterase inhibitors and α-adrenoceptor agonists.[5] The elderly are more likely to have these risk factors and take medication.

Increasing age may also make the blood brain barrier more permeable, which may be an issue as 70% of those treated for OAB with anticholinergics are 61–80 years old.[9] Older adults may be prescribed or take over the counter medication, with over 600 drugs, which exert anticholinergic effects, increasing the risk of cognitive side effects.[10] Taking numerous medications is known as polypharmacy. Fifty percent of the elderly are prescribed at least one drug with anticholinergic effects.[11] In the elderly, there is also a reduction in renal and hepatic metabolism of drugs, which may allow drugs to continue to exert anticholinergic effects.[12]

Other drugs that patients take may also exaggerate the anticholinergic effects of anticholinergics used to treat OAB. Fluoxetine and macrolide antibiotics inhibit the hepatic cytochrome enzymes, CYP2D6 & CYP3A4, respectively, which metabolise anticholinergic drugs.[13] Ten percent of Caucasians and 3% of Africans and Asians are deficient in CYP2D6 enzyme.[13] Opioids may reduce the release of acetylcholine worsening the effects of anticholinergics.[14] Cholinesterase inhibitors for the treatment of dementia may decrease the effects of anticholinergics.[6] Some drugs may inhibit the P-gp system, such as common drugs like lansoprazole, omeprazole, loperamide, and simvastatin.[5] This will prevent active transport of the anticholinergic drug out of the brain.

Anticholinergic Load/Burden

Anticholinergic load or burden is the cumulative effect of taking drugs that are capable of producing anticholinergic adverse effects.[10] Therefore, for the elderly, this can increase the risk of cognitive side effects. It is important that healthcare professionals aim to reduce the anticholinergic load to reduce the risk of physical and cognitive impairment in the elderly population.[15] As there are so many drugs, both prescription and over the counter, that have anticholinergic effects, there are aids to help manage this.

Drug scales exist to determine the anticholinergic load. They are a list of medication with a score allocated to each drug.[16] The higher the score, the higher the load and potentially greater risk to the patient. A particular drug score may be different according to the drug scale used, as they have been validated to capture different elements of anticholinergic activity and drug characteristics.[17] Some scales take dosage into account, whilst others do not.[17] Route of administration is considered in some scales, whilst a drug found in one scale may not even be considered in another.[18] Scoring assumes that the effects of the different drugs with anticholinergic effects add up in a linear fashion. It is felt that these scales simplify pharmacodynamics and pharmacokinetics.[18] There is no ideal scale for both clinicians and researchers for all the different circumstances.[17]

A recent review article of published anticholinergic scales identified 16 in the literature.[17] The authors of this article demonstrated a long list of criteria to evaluate each scale. They felt only six were relevant and suitable for the quantification of anticholinergic exposure; Anticholinergic Activity Scale, Anticholinergic Burden Classification scale, Anticholinergic Cognitive Burden scale, Anticholinergic Drug Scale, Anticholinergic Loading Scale and the Anticholinergic Risk Scale. The association of anticholinergic burden with cognitive function has been investigated with all six scales. The number of drugs in each of these scales ranged from 27 to 520. Scoring was found to be different for the same drug, for example, paroxetine was in five of the scales and scored 1, 2 or 3. The greatest score similarity occurred between the Anticholinergic Cognitive Burden scale and Anticholinergic Drug Scale (ρ=0.82). The study felt that these two scales were well suited for implementation in observational studies where anticholinergic exposure needs to be quantified, as they consider the largest number of medications and were validated with adverse clinical outcomes. It concluded that methods to characterise anticholinergic burden through consideration of both anticholinergic dose and potency are needed.

Demonstration of a high score can allow medical professionals to think about the medication patients are using and whether any of these can be stopped to reduce the anticholinergic load. A systematic literature review and international consensus, known as LUTS-FORTA (Lower Urinary Tract Symptoms – Fit fOR The Aged), evaluated the efficacy, safety and tolerability of drugs used for treatment of OAB.[19] No drugs were labeled group A (absolutely), fesoterodine was labeled group B (beneficial), darifenacin, mirabegron, extended release oxybutynin, solifenacin, tolterodine and trospium chloride were labeled group C (careful) and immediate release oxybutynin and propiverine were labeled group D (do not). Care is needed with this as the pharmaceutical company Pfizer funded the meeting and the conduct of the systematic literature analysis, which at the time manufactured fesoterodine. The Beers criteria is updated and maintained by the American Geriatrics Society (AGS). It aims to improve care of elderly by reducing inappropriate drug use.[20] It involved a systematic literature review and consensus evaluation of evidence by a 13-member expert panel. It is recommended that anticholinergics should be avoided or the minimal number of anticholinergic drugs used. The Screening Tool of Older Persons potentially inappropriate Prescriptions (STOPP) and the Screening Tool to Alert doctors to the Right Treatment (START) was a second version developed with 13 European countries.[21] It advises stopping bladder anticholinergics in the elderly with dementia.

Importance of Anticholinergic Load

Reducing anticholinergic load is important because there is increasing evidence that it has detrimental effects especially on the older population. On the anticholinergic cognitive burden scale, which is described above to calculate anticholinergic load, the authors make three comments backed with evidence.[22] The first is that for each definite anticholinergic drug used, it may increase the risk of cognitive impairment by 46% over 6 years.[23] This was based on a longitudinal, observational study that evaluated 1652 patients over 70 years old. After adjusting for variables, they found that those using a drug with definite anticholinergic potential had a significantly increased risk for cognitive impairment (OR 1.46, p=0.02). The second

comment is that for each point increase in the anticholinergic burden scale, there is a decline in mini mental state examination score of 0.33 over two years.[11] This was based on a two year longitudinal study of 13,004 patients over 65 years of age. The final comment on the anticholinergic burden scale is that each one point increase in score has been correlated with a 26% increase in risk of death.[11] This was also based on the same study as the second comment.

A systematic review was performed investigating the effects of anticholinergic load on cognitive function, delirium, physical function and mortality.[24] Forty-six studies were eligible for this review, of which 38 were cohort studies, and six randomised controlled trials and two case control studies. There were 60,944 patients in these studies aged between 39.9 to 87.5 years, of which 32,543 were women. Of the 33 studies that reported on cognitive function, 23 found a significant decline. Of those that did not report a negative effect on cognitive function, the majority of the studies had shorter term follow-up and it is possible to speculate that they would have progressed to significant decline, if there was longer term follow-up. One of the five studies that assessed delirium found an association with the use of anticholinergics. Five out of eight studies showed a significant reduction in physical function. Nine studies investigated the effects on mortality, with only a third of these studies showing a significantly increased risk of death. This systematic review concluded that there was strong evidence that an increased anticholinergic load was associated with decline in cognition and that it may be associated with reduced physical function. Anticholinergic load was not proven to be a risk factor for delirium or mortality and the authors called for more evidence on these. A more recent systematic review found that 15 out of 27 studies reported a positive correlation between anticholinergic load and mortality and two studies showed mixed results. Of the 10 studies that did not find an association, eight of them had a follow-up of less than one year.[15]

A study examined brain samples of patients with Parkinson's disease with no evidence of dementia, who were taking anticholinergic medication.[25] Some of the patients were using oxybutynin for bladder dysfunction. Plaques suggestive of Alzheimer's dementia were found in significantly higher quantity in those using anticholinergics for greater than two years, compared to the control group (no anticholinergic use) (p=0.005) or those using the drug for less than two years (p=0.00005). An animal study found that ablation of the cholinergic neurons of the nucleus basalis magnocellularis in a rabbit led to deposition of amyloid around cerebral blood vessels.[26] The authors hypothesised that the loss of cholinergic innervation is involved in the pathogenesis of Alzheimer's.

A longitudinal study looked at cognitive and neuroimaging data of patients taking anticholinergics and compared it to those not taking the class of drug.[27] Both groups had the same mean age of 73.3 years. Those taking anticholinergics had significantly lower immediate recall memory scores (p=0.04) and lower executive function scores (p=0.04). Preprocessed fluorodeoxyglucose F 18–positron emission tomographic (FDG-PET) scans found that those using anticholinergic medication showed reduced glucose metabolism in the hippocampus. On magnetic resonance imaging (MRI), those on anticholinergics had reduced total cortical volume (p=0.02) and larger lateral ventricles volumes (p=0.01) and larger inferior lateral ventricle volumes (p<0.001). There were significantly reduced medial temporal lobe cortical thickness and thinner bilateral temporal lobe cortices. They concluded that anticholinergic drugs may be detrimental to brain structure and function.

A prospective population-based cohort study of 3434 patients aged over 65 years, with no evidence of dementia, were followed up every two years, to assess the development of dementia.[28] Bladder anticholinergics were the third most common anticholinergic drug, behind antidepressants and antihistamines. Oxybutynin was the most common in the treatment of OAB. Over 7.3 years, 23.2% developed dementia, with Alzheimer's being the most common (79.9%). Those taking oxybutynin 5mg per day or doxepin hydrochloride 10 mg per day (tricyclic antidepressant), for more than three years had the greatest risk of dementia. Those taking an anticholinergic primarily in the past had a risk of dementia similar to those with recent or continued use. Therefore, the risk of dementia may persist despite stopping the drug.

A United Kingdom based case controlled study of 40,770 patients aged over 65 years with dementia was compared with 283,933 control patients without dementia.[29] Anticholinergic drugs were scored according to the Anticholinergic Cognitive Burden scale. Increasing scale scores was associated with higher risk of dementia. Drugs used for OAB were significantly associated with increased risk of dementia. Oxybutynin and tolterodine were in the top five most commonly prescribed anticholinergics. When the drug was prescribed 4–10years, 10–15

years and 15–20 years prior to dementia diagnosis, there were OR of 1.23, 1.22 and 1.27 ($p<0.01$) respectively, for the development of dementia.

In the United States, an observational cohort study investigated 350 patients over the age of 65 years, with a mean follow up of 3.2 years.[30] The study found that increasing use of anticholinergics increased the risk of transitioning from normal cognition to mild impairment (OR 1.15, p=0.0342). Oxybutynin was the second most popular anticholinergic used with a maximum score of 3 on the Anticholinergic cognitive burden scale.

Considerations When Treating OAB

From the available data, it appears the strongest evidence is that anticholinergics increase the risk of cognitive impairment and potentially the development of dementia. Delaying the onset of dementia by only one year may prevent up to nine million cases of dementia by 2050.[31] This is not only an important medical issue but also a socioeconomic issue. Therefore, it is important to consider which medication to use for treatment of OAB in our older adults.

The National Institute for Health and Care Excellence (NICE) advises that health care provider should take into account; coexisting conditions (such as cognitive impairment), use of other drugs which affect anticholinergic load and the risk of adverse effects, including cognitive impairment.[32] It recommends discussing with the patient that long-term effects of anticholinergic medicines for overactive bladder on cognitive function are uncertain. It states that immediate release oxybutynin should not be offered to older women who may be at higher risk of a sudden deterioration in their physical or mental health.

In the United States, a population-based analysis of the 2009 National Ambulatory Medical Care Survey found that OAB medication users tended to be older and insured by Medicare, a national health insurance program provided by the US federal government for citizens aged over 65 years.[33] The most common drug prescribed was oxybutynin. The study feels this could be because the US Food and Drug Administration approved oxybutynin in 1988 and its drug patents last 20 years. Therefore after this time, they are available in generic formulation, which are less expensive and may contribute to its popularity by insurance companies. This therefore poses an issue for prescribing for the frail and elderly in the US.

Trospium Chloride

As mentioned earlier, trospium chloride is a quaternary amine and a substrate for the P-gp system, therefore, theoretically least likely to cross the blood brain barrier and lead to cognitive side effects. In a study of 12 patients with OAB and a mean age of 68 years without dementia, were given trospium chloride for 10 days.[34] Cerebral spinal fluid was tested at 0, 5 and 24 hours post dose. Trospium chloride was undetectable in cerebral spinal fluid, despite being present in plasma at the same time. Neurocognitive assessments found no significant effect on learning or recall.

A large Phase III study investigated the effects of trospium chloride and placebo on somnolence and daytime sleepiness.[35] In total 658 patients with OAB, with a mean age of 61 years, were blinded and randomised to either drug or placebo. There was no significant difference between groups in the Stanford Sleepiness Scale and in fact in those aged greater than 65 years, those in the trospium group did better than the placebo group. Central nervous system adverse events were also similar in both groups, 5.8% in the trospium chloride group and 5.2% in placebo group.

A study of 12 healthy young males were randomised to either trospium chloride or oxybutynin.[36] They had computer-aided topographical quantitative electroencephalometry performed to assess effects on the central nervous system. There was significant reduction in brain activity after oxybutynin, but not after administration of trospium chloride. The effects with the use of trospium chloride were not different to changes seen without any drug.

A prospective cohort study of 35 women with OAB with a mean age of 70 years, had cognitive function assessed.[37] There was an initial significant decline on day one and week one. These normalised by week four and remained stable until the end of the study at week 12. No patients reported subjective cognitive change. Another study by the same authors compared trospium chloride to placebo, over four weeks.[38] Forty-five patients completed the study with a mean age of 68 years. There was no significant difference between the two groups in the Hopkins Verbal Learning Test-Revised (p=0.29) or mini mental state examination (p=0.67) at the end of the study. There were also no differences based on the other cognitive tests.

Looking at persistence data, which is likely to be linked to bothersome adverse events,[39] a retrospective

analysis of a UK General Practice prescription database, found that trospium chloride was one of the best anticholinergics.[40] In treatment naïve patients, trospium chloride was the only anticholinergic which did not have a significant difference in persistence compared to mirabegron (p=0.068). The most recent Cochrane review comparing different anticholinergic drugs for OAB found a lack of data comparing trospium chloride with other drugs.[41] These data show that trospium chloride can be safely prescribed, with good persistence data, without fear of worse side effects compared to other anticholinergics.

Mirabegron

MIrabegron is a beta-3 adrenoceptor agonist used for the treatment of OAB in women. The beta-3 adrenoceptor is located in the bladder detrusor smooth muscle and stimulation of it leads to relaxation of the bladder muscle, leading to increased bladder capacity.[42] This drug is an alternative to anticholinergics without the common side effects associated with treatment of OAB. The most common side effects encountered in those over 65 years of age with mirabegron is hypertension (9.9%) and nasopharyngitis (4.1%), with dry mouth seldom seen.[43] There are few beta-3 adrenoceptors in the central nervous system and mirabegron is also a substrate for the P-gp system. The beta adrenoceptors are common in the cardiovascular system. In the trials, no patients over 65 years, had an increased heart rate. Hypertension was more frequent in those using tolterodine compared to mirabegron over one year, at 14.5% and 9.3%, respectively.[42]

A review article of the evidence suggested mirabegron as a suitable treatment for the older, complex patient due to its tolerability and not contributing to the anticholinergic load.[42]

A recent study assessed the efficacy, safety, and tolerability of mirabegron in patients aged 65 years or more, with OAB.[43] This was a Phase IV study comparing mirabegron with placebo over 12 weeks. Safety and tolerability were consistent with the known mirabegron safety profile. There were significant improvements in OAB symptoms in the mirabegron group compared to placebo. A pre-planned analysis of this study, investigated cognitive function between mirabegron and placebo using the Montreal Cognitive Assessment (MoCA), which is a screening tool for mild cognitive impairment.[44] Baseline scores and baseline cognitive impairment were similar between the mirabegron and placebo groups. There were no significant changes in adjusted mean scores from baseline to week 12, in either treatment group (p=0.471). Neither placebo nor mirabegron was favored over the other in regards to development of cognitive impairment (RR 0.923, 95% CI 0.512–1.662).

A sub analysis of the BESIDE study, which investigated the older adult population (>65 years), to assess the difference between using the combination of solifenacin 5mg plus mirabegron 50mg compared to solifenacin 5mg alone or solifenacin 10mg alone.[45] This study found that combination therapy had a greater benefit for OAB compared to the solifenacin at either dose alone. Adverse events were similar between combination treatment and solifenacin 5mg, whilst solifenacin 10mg was worse. The authors of the study suggested using combination treatment in the elderly, rather than increasing solifenacin from 5mg to 10mg, when OAB symptoms persist. This is because solifenacin 10mg may increase the anticholinergic load more than 5mg.

In a retrospective study of 50 patients with Parkinson's disease, using mirabegron, 11.4% had resolution and 50% improvement of OAB symptoms.[46] There were only two adverse events reported, dizziness and diaphoresis. At one, two and three years, 51.5%, 44.6% and 36.4%, respectively, continued with mirabegron. Further prospective randomised trials are needed to properly assess mirabegron in this group of patients. At the moment mirabegron can be used in these patients, who have a high risk of increased blood brain barrier permeability and risk of central nervous system side effects.

Alternative Treatments

Conservative treatment should never be forgotten for any medical problem. In OAB, conservative treatment is very important as this may improve successful toileting or increase the likelihood of continence.[47] Addressing a patient's mobility and functional impairment, for example, the use of a Zimmer frame or commode may help. Lifestyle techniques and bladder retraining, with education of fluid management and urgency suppression, may improve symptoms. A normal adult in a temperate climate only requires 24mL/kg of fluid intake per day.[48] Fluid reduction of 25% from baseline improves frequency, urgency and nocturia.[49] Caffeine may cause detrusor muscle contractions, worsening symptoms of OAB.[50] A prospective cohort study of 65,176 patients found a positive association between caffeine and urgency incontinence, with a risk of 25%.[51] Expectations of the patient, carer and their life expectancy, are also important when

managing these patients.[47] Failing that medical treatment may still be needed and alternatives to oral medication exist. These conservative measures should still be adopted in combination with other treatment options to improve success.

Up to 70% of women report that their urinary symptoms started around the menopause.[52] A cochrane review found that local vaginal oestrogens, improve frequency, urgency and incontinence.[53] A systematic review of 11 randomised trials found significant improvement in frequency, nocturia, urgency, incontinence episodes, first sensation and bladder capacity, with the use of local oestrogens.[54]

Posterior tibial nerve stimulation involves the use of electrical impulses and is a form of neuromodulation employed to improve urinary symptoms.[55] A retrospective review of 52 patients, with a mean age of 76 years, found a subjective success rate of 70%.[55] Overall success rates vary between 54–59%.[56] It has very few side effects but involves weekly attendances to hospital for treatment over 12 weeks and may require top-ups every few months, which may be difficult for an older adult.

Sacral neuromodulation involves a lead going into the sacrum and the device implanted into the subcutaneous tissue above, which needs replacing once the battery life expires. This may not be ideal for an older or frail adult. One study of 25 patients aged over 55 years found that 12 patients had a successful trial period and underwent permanent implantation.[57] Only 17% of the older adults achieved dryness after implantation, compared to 40% of younger patients. Another study found 90% of adults greater than 70 years, reported improvement, with no intraoperative or immediate postoperative complications.[58] Despite this, the elderly were significantly more likely to have the device removed compared to younger patients (p=0.018). A retrospective review of 356 patients found that age did not lead to worse clinical outcomes and should not negatively predict sacral nerve stimulation responses.[59] Patient selection is important as some patients in this group may not be able to assess efficacy during the trial phase and subsequently make necessary adjustments. They may also not be able to operate the device.[60]

Onabotulinumtoxin A (botox) is another successful treatment modality for OAB. It is injected under cystoscopic guidance into the detrusor muscle of the bladder. It can significantly increase a patient's post void residual, with up to 8.41% requiring self catheterisation.[61] Urinary tract infections are also more common when treated with botox, with a rate of 19.69%.[61] Being older than 68 years increases the risk of raised post void residuals and the need to perform self catheterisation.[62] With this in mind, it is important to consider whether the patient is able to be taught to self catheterise, which may be difficult in the old and frail. Also, with a high proportion of developing urinary tract infections in an already at-risk group, this could lead to renal dysfunction or cognitive impairment secondary to urosepsis.

Containment products such as pads can be used, but after all treatment options have been explored and with regular assessment of skin integrity.[32] An indwelling catheter is a potential option and may improve quality of life, but it should be made clear that it may not result in complete continence. The NICE guidelines recommend suprapubic catheters instead of urethral, due to lower risks of infection, "bypassing" and urethral complications.[32] Patient comfort, quality of life and satisfaction is good for suprapubic catheter compared to urethral.[63] The evidence regarding suprapubic catheters is based on use in the short term and there are no long-term data.[63]

The American Urological Association guideline states that third-line treatment such as neuromodulation or onabotulinumtoxin A should only be used if the patient has failed first or second-line OAB treatment.[64] This may make it more difficult to use these alternative treatments, which do not effect anticholinergic load, as first line. Though the guideline also states that caution should be used in prescribing anticholinergic medication in those using other drugs with anticholinergic properties or in the frail. Further clarification on using these third-line treatments, as alternatives to second line in this population may be helpful.

Should We Still Use Anticholinergics in Older Women with OAB?

A study which compared single dose solifenacin 10mg with oxybutynin immediate release 10mg and placebo, in elderly adults found no statistically significant cognitive deterioration with solifenacin versus placebo.[65] Oxybutynin was associated with statistically significant impairment in cognitive function. Another study compared healthy older adults who were randomised to darifenacin, oxybutynin or placebo.[66] Darifenacin had no significant

effects on memory compared to placebo, whilst oxybutynin caused significant memory deterioration. A pooled analysis of 4040 patients, aged 65 years and over in fesoterodine trials, found that central nervous system side effects were low.[67] Age and dose were not associated with increased risk of cognitive adverse events and they were low across all categories of medical and drug history. A study using propiverine found no significant change in mini mental state examination scores at 12 weeks for those with normal pre-study scores and those with mild cognitive impairment.[68] Tolterodine has not been found not to affect memory in a healthy, highly educated sample of adults, with a mean age of 63 years.[69]

In a randomised, double-blind, triple-crossover trial, 26 elderly volunteers with mild cognitive impairment were given solifenacin, oxybutynin and placebo, for 21 days each, separated by 21 days washout period.[70] Oxybutynin was associated with significant decreases in power and continuity of attention versus placebo, whilst solifenacin had no detectable effect on cognition.

The majority of studies for OAB have been on non-frail women for only 12 weeks duration.[71] A systematic review of the efficacy of pharmacological treatment for urinary incontinence in the elderly and frail elderly found that oxybutynin was the only drug that has been tested on the truly frail.[72]

In those with dementia, they may use cholinesterase inhibitors, which prevent the breakdown of acetylcholine, which in turn may increase the contractions of the bladder detrusor muscle. This may therefore worsen OAB. A systematic review investigated the use of a cholinesterase inhibitor for dementia with an anticholinergic for OAB.[73] Of the four studies that assessed cognition, three found no evidence of impairment using both drugs. One study found an improvement in cognition, but used donepezil at a higher dose than is currently approved. Three studies assessed functional outcomes, with one showing significant decline, another no significant difference and the last a significant improvement. Further research is needed in this group of patients.

Conclusion

OAB is a common problem, which affects the quality of life. Conservative treatment may help, but the majority need medical treatment. Anticholinergic medications are the most commonly used drugs. In the elderly population, this can add to an individual's anticholinergic load. Anticholinergic drugs have the potential to cross the blood brain barrier and cause cognitive side effects. There are increasing data that suggest that a high anticholinergic load increases the risk of cognitive adverse events, the development of dementia or potentially even death. Therefore, care is needed when treating elderly patients, especially the frail taking other medications, which contribute to their anticholinergic load. Trospium chloride which has different molecular properties to the other anticholinergics or mirabegron could be used instead. They are less likely to cross the blood brain barrier and evidence shows they are safe and do not have cognitive side effects. Each patient should be individually assessed and discussion regarding the risks and benefits, with the patient, family and carer. We do not want to deprive patients of treatment when they would value quality of life over the potential side effects.

Disclosure

GA reports no conflict of interests in this work. DR has worked with Allergan, Astellas, Femeda, Ferring, and Ixaltis and reports personal fees from Astellas, Allergan, Ixaltis, Ferring, and Pierre Fabre, outside the submitted work. LC has worked with Atlantic therapeutics, Boston scientific, DEKA, Fotona, Merck and has during the last year received funding for research, lecturing and/or advice/consultancies from the following organizations: Research consultancy and/or advisory work for Boston Scientific, Contura, ConvaTech DEKA, Fotona, Merck, Shionogi. The authors report no other potential conflicts of interest for this work.

References

1. Haylen BT, De Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn*. 2010;29(1):4–20. doi:10.1002/nau.20798
2. Milsom I, Coyne KS, Nicholson S, Kvasz M, Chen CI, Wein AJ. Global prevalence and economic burden of urgency urinary incontinence: a systematic review. *Eur Urol*. 2014;65(1):79–95. doi:10.1016/j.eururo.2013.08.031
3. Coyne KS, Wein A, Nicholson S, Kvasz M, Chen CI, Milsom I. Economic burden of urgency urinary incontinence in the United States: a systematic review. *J Managed Care Pharm*. 2014;20(2):130–140. doi:10.18553/jmcp.2014.20.2.130
4. Andersson KE, Cardozo L, Cruz F, Lee KS, Sahai A, Wein AJ. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Wagg A, Wein A, editors. *Incontinence 6th edition*. 2017:805–957.
5. Chancellor MB, Staskin DR, Kay GG, Sandage BW, Oefelein MG, Tsao JW. Blood–brain barrier permeation and efflux exclusion of anticholinergics used in the treatment of overactive bladder. *Drugs Aging*. 2012;29(4):259–273. doi:10.2165/11597530-000000000-00000

6. Kay GG, Granville LJ. Antimuscarinic agents: implications and concerns in the management of overactive bladder in the elderly. *Clin Ther*. 2005;27(1):127–138. doi:10.1016/j.clinthera.2005.01.006
7. Callegari E, Malhotra B, Bungay PJ, et al. A comprehensive non-clinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder. *Br J Clin Pharmacol*. 2011;72(2):235–246. doi:10.1111/j.1365-2125.2011.03961.x
8. Zinner N, Tuttle J, Marks L. Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder. *World J Urol*. 2005;23(4):248–252. doi:10.1007/s00345-005-0507-3
9. Wolters Kluwer Pharma Solutions. Source Lx Managed Care Database. 2010.
10. Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry*. 2001;62(Suppl 21):11–14.
11. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011;59(8):1477–1483. doi:10.1111/j.1532-5415.2011.03491.x
12. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab*. 2011;12(7):601–610. doi:10.2174/138920011796504527
13. Chancellor M, Boone T. Anticholinergics for overactive bladder therapy: central nervous system effects. *CNS Neurosci Ther*. 2012;18(2):167–174. doi:10.1111/j.1755-5949.2011.00248.x
14. Hustveit O. Interaction between opioid and muscarinic receptors in the guineapig ileum preparation: a mathematical model. *Pharmacol Toxicol*. 1996;78(3):167–173. doi:10.1111/j.1600-0773.1996.tb00199.x
15. Ali S, Peterson GM, Bereznicki LR, Salahudeen MS. Association between anticholinergic drug burden and mortality in older people: a systematic review. *Eur J Clin Pharmacol*. 2019;Dec:1–7.
16. Villalba-Moreno AM, Alfaro-Lara ER, Pérez-Guerrero MC, Nieto-Martín MD, Santos-Ramos B. Systematic review on the use of anticholinergic scales in poly pathological patients. *Arch Gerontol Geriatr*. 2016;62:1–8. doi:10.1016/j.archger.2015.10.002
17. Lozano-Ortega G, Johnston KM, Cheung A, et al. A review of published anticholinergic scales and measures and their applicability in database analyses. *Arch Gerontol Geriatr*. 2020;87:103885. doi:10.1016/j.archger.2019.05.010
18. Kersten H, Wyller TB. Anticholinergic drug burden in older people's brain – how well is it measured? *Basic Clin Pharmacol Toxicol*. 2014;114(2):151–159. doi:10.1111/bcpt.12140
19. Oelke M, Becher K, Castro-Diaz D, et al. Appropriateness of oral drugs for long-term treatment of lower urinary tract symptoms in older persons: results of a systematic literature review and international consensus validation process (LUTS-FORTA 2014). *Age Ageing*. 2015;44(5):745–755. doi:10.1093/ageing/afv077
20. Fick DM, Semla TP, Beizer J. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227–2246. doi:10.1111/jgs.13702
21. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44(2):213–218. doi:10.1093/ageing/afu145
22. http://www.agingbraincare.org/tools/abc-anticholinergic-cognitive-burden-scale. Accessed August 13, 2020.
23. Campbell NL, Boustani MA, Lane KA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. *Neurology*. 2010;75(2):152–159. doi:10.1212/WNL.0b013e3181e7f2ab
24. Fox C, Smith T, Maidment I, et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age Ageing*. 2014;43(5):604–615. doi:10.1093/ageing/afu096
25. Perry EK, Kilford L, Lees AJ, Burn DJ, Perry RH. Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. *Ann Neurol*. 2003;54(2):235–238. doi:10.1002/ana.10639
26. Roher AE, Kuo YM, Potter PE, et al. Cortical cholinergic denervation elicits vascular Aβ deposition. *Ann N Y Acad Sci*. 2000;903(1):366–373. doi:10.1111/j.1749-6632.2000.tb06388.x
27. Risacher SL, McDonald BC, Tallman EF, et al. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol*. 2016;73(6):721–732. doi:10.1001/jamaneurol.2016.0580
28. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015;175(3):401–407. doi:10.1001/jamainternmed.2014.7663
29. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ*. 2018;25(361):k1315. doi:10.1136/bmj.k1315
30. Campbell NL, Lane KA, Gao S, Boustani MA, Unverzagt F. Anticholinergics influence transition from normal cognition to mild cognitive impairment in older adults in primary care. *Pharmacotherapy*. 2018;38(5):511–519. doi:10.1002/phar.2106
31. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimer's Dementia*. 2007;3(3):186–191. doi:10.1016/j.jalz.2007.04.381
32. National Institute for Health and Care Excellence: Urinary incontinence and pelvic organ prolapse in women: management.NICE Guideline [NG123].2019.
33. Ju R, Garrett J, Wu JM. Anticholinergic medication use for female overactive bladder in the ambulatory setting in the United States. *Int Urogynecol J*. 2014;25(4):479–484. doi:10.1007/s00192-013-2246-0
34. Staskin D, Kay G, Tannenbaum C, et al. Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. *Int J Clin Pract*. 2010;64(9):1294–1300. doi:10.1111/j.1742-1241.2010.02433.x
35. Staskin DR, Harnett MD. Effect of trospium chloride on somnolence and sleepiness in patients with overactive bladder. *Curr Urol Rep*. 2004;5(6):423–426. doi:10.1007/s11934-004-0064-0
36. Pietzko A, Dimpfel W, Schwantes U, Topfmeier P. Influences of trospium chloride and oxybutynin on quantitative EEG in healthy volunteers. *Eur J Clin Pharmacol*. 1994;47(4):337–343. doi:10.1007/BF00191165
37. Geller EJ, Crane AK, Wells EC, et al. Effect of anticholinergic use for the treatment of overactive bladder on cognitive function in postmenopausal women. *Clin Drug Investig*. 2012;32(10):697–705. doi:10.1007/BF03261923
38. Geller EJ, Dumond JB, Bowling JM, et al. Effect of trospium chloride on cognitive function in women aged 50 and older: a randomized trial. *Female Pelvic Med Reconstr Surg*. 2017;23(2):118–123. doi:10.1097/SPV.0000000000000374
39. Yeowell G, Smith P, Nazir J, Hakimi Z, Siddiqui E, Fatoye F. Real-world persistence and adherence to oral antimuscarinics and mirabegron in patients with overactive bladder (OAB): a systematic literature review. *BMJ Open*. 2018;8(11):e021889. doi:10.1136/bmjopen-2018-021889
40. Wagg AS, Foley S, Peters J, Nazir J, Kool-Houweling L, Scrine L. Persistence and adherence with mirabegron vs antimuscarinics in overactive bladder: retrospective analysis of a UK general practice prescription database. *Int J Clin Pract*. 2017;71(10):e12996. doi:10.1111/ijcp.12996
41. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJC. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Sys Rev*. 2012. doi:10.1002/14651858.CD005429.pub2

42. Wagg A, Nitti VW, Kelleher C, Castro-Diaz D, Siddiqui E, Berner T. Oral pharmacotherapy for overactive bladder in older patients: mirabegron as a potential alternative to antimuscarinics. *Curr Med Res Opin*. 2016;32(4):621–638. doi:10.1185/03007995.2016.1149806
43. Wagg A, Staskin D, Engel E, Herschorn S, Kristy RM, Schermer CR. Efficacy, safety, and tolerability of mirabegron in patients aged ≥65 yr with overactive bladder wet: a Phase IV, double-blind, randomised, placebo-controlled study (PILLAR). *Eur Urol*. 2020;77(2):211–220. doi:10.1016/j.eururo.2019.10.002
44. Griebling TL, Campbell NL, Mangel J, et al. Effect of mirabegron on cognitive function in elderly patients with overactive bladder: moCA results from a Phase 4 randomized, placebo-controlled study (PILLAR). *BMC Geriatr*. 2020;20(1):1. doi:10.1186/s12877-020-1474-7
45. Gibson W, MacDiarmid S, Huang M, et al. Treating overactive bladder in older patients with a combination of mirabegron and solifenacin: a prespecified analysis from the BESIDE study. *Eur Urol Focus*. 2017;3(6):629–638. doi:10.1016/j.euf.2017.08.008
46. Peyronnet B, Vurture G, Palma JA, et al. Mirabegron in patients with Parkinson disease and overactive bladder symptoms: a retrospective cohort. *Parkinsonism Relat Disord*. 2018;1(57):22–26. doi:10.1016/j.parkreldis.2018.07.005
47. Wagg A. Anticholinergics for overactive bladder in frail and medically complex older people: the case for. *Drugs Aging*. 2018;35(9):777–780. doi:10.1007/s40266-018-0577-8
48. Hashim H, Al Mousa R. Management of fluid intake in patients with overactive bladder. *Curr Urol Rep*. 2009;10(6):428–433. doi:10.1007/s11934-009-0068-x
49. Hashim H, Abrams P. How should patients with an overactive bladder manipulate their fluid intake? *BJU Int*. 2008;102(1):62–66. doi:10.1111/j.1464-410X.2008.07463.x
50. Lee JG, Wein AJ, Levin RM. The effect of caffeine on the contractile response of the rabbit urinary bladder to field stimulation. *Gen Pharmacol*. 1993;24(4):1007–1011. doi:10.1016/0306-3623(93)90180-6
51. Jura YH, Townsend MK, Curhan GC, Resnick NM, Grodstein F. Caffeine intake, and the risk of stress, urgency and mixed urinary incontinence. *J Urol*. 2011;185(5):1775–1780. doi:10.1016/j.juro.2011.01.003
52. Iosif C, Bekassy Z. Prevalence of genitourinary symptoms in the late menopause. *Acta Obstet Gynaecol Scan*. 1984;63(3):257–260. doi:10.3109/00016348409155509
53. Cody JD, Jacobs ML, Richardson K, et al. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev*. 2012;10:CD001405.
54. Cardozo L, Lose G, McClish D, et al. A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. Acta Obstet Gynecol Scand. 2004 Oct 1; 83(10):892–897. Bhide AA, Tailor V, Fernando R, Khullar V, Digesu GA. Posterior tibial nerve stimulation for overactive bladder—techniques and efficacy. *Int Urogynecol J*. 2019;18:1–6.
55. Palmer C, Farhan B, Nguyen N, Ghoniem G. Clinical outcomes of percutaneous tibial nerve stimulation in elderly patients with overactive bladder. *Arab J Urology*. 2019;17(1):10–13. doi:10.1080/2090598X.2019.1590032
56. Tutolo M, Ammirati E, Heesakkers J, et al. Efficacy and safety of sacral and percutaneous tibial neuromodulation in non-neurogenic lower urinary tract dysfunction and chronic pelvic pain: a systematic review of the literature. *Eur Urol*. 2018;73(3):406–418. doi:10.1016/j.eururo.2017.11.002
57. Amundsen CL, Webster GD. Sacral neuromodulation in an older, urge-incontinent population. *Am J Obstet Gynecol*. 2002;187(6):1462–1465. doi:10.1067/mob.2002.130004
58. White WM, Mobley III JD, Doggweiler R, Dobmeyer-Dittrich C, Klein FA. Sacral nerve stimulation for refractory overactive bladder in the elderly population. *J Urol*. 2009;182(4):1449–1452. doi:10.1016/j.juro.2009.06.049
59. Faris AE, Gill BC, Pizarro-Berdichevsky J, et al. Impact of age and comorbidities on use of sacral neuromodulation. *J Urol*. 2017;198(1):161–166. doi:10.1016/j.juro.2017.02.020
60. Pratt TS, Suskind AM. Management of overactive bladder in older women. *Curr Urol Rep*. 2018;19(11):92. doi:10.1007/s11934-018-0845-5
61. Cui Y, Zhou X, Zong H, Yan H, Zhang Y. The efficacy and safety of onabotulinumtoxinA in treating idiopathic OAB: a systematic review and meta-analysis. *Neurourol Urodyn*. 2015;34(5):413–419. doi:10.1002/nau.22598
62. Miotla P, Cartwright R, Skorupska K, et al. Urinary retention in female OAB after intravesical Botox injection: who is really at risk? *Int Urogynecol J*. 2017;28(6):845–850. doi:10.1007/s00192-016-3212-4
63. Cottenden A, Fader M, Beeckman BB, et al. Management using continence products. In:Abrams P, Cardozo L, Wagg A, Wein A, editors. *Incontinence 6th edition* 2017:2303–2402.
64. American Urological Association. *Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults: An AUA/SUFU Guideline (2019)*. American Urological Association; 2019.
65. Wesnes KA, Edgar C, Tretter RN, Bolodeoku J. Exploratory pilot study assessing the risk of cognitive impairment or sedation in the elderly following single doses of solifenacin 10 mg. *Expert Opin Drug Saf*. 2009;8(6):615–626. doi:10.1517/14740330903260790
66. Kay G, Crook T, Rekeda L, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. *Eur Urol*. 2006;50(2):317–326. doi:10.1016/j.eururo.2006.03.057
67. Wagg A, Arumi D, Herschorn S, et al. A pooled analysis of the efficacy of fesoterodine for the treatment of overactive bladder, and the relationship between safety, co-morbidity and polypharmacy in patients aged 65 years or older. *Age Ageing*. 2017;46(4):620–626. doi:10.1093/ageing/afw252
68. Oelke M, Murgas S, Schneider T, Heßdörfer E. Influence of propiverine ER 30 mg once daily on cognitive function in elderly female and male patients with overactive bladder: a non-interventional study to assess real life data. *Neurourol Urodyn*. 2013;32(6):800–802.
69. Kay G, Kardiasmenos K, Crook T. Differential effects of the antimuscarinic agents tolterodine tartrate ER and oxybutynin chloride ER on recent memory in older subjects. *InProc 36th Meeting Int Continence Soc*. 2006;25(6):P087.
70. Wagg A, Dale M, Tretter R, Stow B, Compion G. Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study. *Eur Urol*. 2013;64(1):74–81. doi:10.1016/j.eururo.2013.01.002
71. Woodford HJ. Anticholinergic drugs for overactive bladder in frail older patients: the case against. *Drugs Aging*. 2018;35(9):773–776. doi:10.1007/s40266-018-0575-x
72. Samuelsson E, Odeberg J, Stenzelius K, et al. Effect of pharmacological treatment for urinary incontinence in the elderly and frail elderly: a systematic review. *Geriatr Gerontol Int*. 2015;15(5):521–534. doi:10.1111/ggi.12451
73. Triantafylidis LK, Clemons JS, Peron EP, Roefaro J, Zimmerman KM. Brain over bladder: a systematic review of dual cholinesterase inhibitor and urinary anticholinergic use. *Drugs Aging*. 2018;35(1):27–41. doi:10.1007/s40266-017-0510-6