International Journal of Women's Health

Dovepress
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REVIEW

Adherence to Overactive Bladder Syndrome Treatments Recent Developments and Future Perspectives

Dudley Robinson, Miriam O'Kane, Linda Cardozo

Department of Urogynaecology, King's College Hospital, London, UK

Correspondence: Dudley Robinson, Department of Urogynaecology, King's College Hospital, Suite 8, Level 3, Golden Jubilee Wing, London, SE5 9RS, UK, Tel +447966485503, Email dudley.robinson@nhs.net

Abstract: Overactive bladder (OAB) is a common and distressing condition which is known to have a significant effect on Health-Related Quality of Life (HRQoL). Whilst all patients complaining of overactive bladder symptoms will, in theory, initially benefit from conservative measures, many will require pharmacological therapy. Antimuscarinics currently remain the most commonly used drugs to treat OAB although compliance and persistence can be poor due to concerns regarding adverse events and lack of efficacy. This review will explore the common management strategies for OAB with a particular focus on patient adherence to therapy including compliance and persistence. The role of antimuscarinics and the B3-agonist, mirabegron, will be considered along with barriers to their efficacy and adoption. For those patients in whom conservative and pharmacological treatment proves ineffective or is unsuitable, the management of refractory OAB will also be considered. In addition, the role of current and future developments will be examined.

Keywords: OAB, adherence, compliance, persistence, antimuscarinics, β_3 agonists

Introduction

Overactive bladder (OAB) is defined as urinary urgency, usually in association with frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.[1]

According to North American epidemiological studies, the prevalence of OAB in women has been reported to be 16.9%, but rises with increasing age, to 30.9% in those over the age of 65 years.[2]

Pathophysiology

The symptoms of OAB are presumed to be due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions are termed detrusor overactivity[1] and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors.[3] However the diagnoses are not synonymous, as OAB is a symptom-based diagnosis, whilst detrusor overactivity is a urodynamic one. It has been estimated that urodynamically-proven detrusor overactivity is found in only 64% of patients with OAB and that symptoms suggestive of OAB, are reported by only 83% of patients with detrusor overactivity.[4]

OAB: Clinical Management

Although OAB is a symptomatic diagnosis, all patients require a basic clinical assessment in order to exclude any alternative cause for lower urinary tract dysfunction. Such an assessment should include a midstream urine specimen, to identify a lower urinary tract infection, alongside measurement of a post void residual urine volume to exclude voiding dysfunction.

Women with a complex presentation often benefit from further specialised investigation including uroflowmetry, filling cystometry and pressure/flow voiding studies. Videocystourethrography or ambulatory urodynamics may further improve diagnostic accuracy in patients with refractory symptoms.

Received: 20 January 2023
Accepted: 5 May 2023
Published: 23 May 2023

Evaluating OAB Treatments

Persistence with the long-term medication required to manage chronic disease is typically low, and OAB is no exception.[5] This is a contributory factor in rising healthcare costs and avoidable morbidity and mortality.[6] Therefore, when evaluating treatment strategies in the management of OAB it is imperative to consider how patients are likely to comply with therapy and how long they are likely to continue with treatment.

Adherence and compliance are interchangeable terms referring to the degree or extent of patient conformity to the provider's recommendations regarding timing, dosage and frequency of medication. Consequently, it may be best defined as "the extent to which a patient acts in accordance with the prescribing interval and dose of a dosing regimen".

Conversely persistence refers to the act of continuing the treatment for the prescribed duration and is defined as "the duration of time from initiation to discontinuation of therapy".[7] In addition, adherence may also be measured using the medication possession ratio (MPR) which is defined as the proportion of a time period where a medication supply is available.[8]

Methods

A search of the English language literature was performed using the PubMed database with no date limitations. The search terms used included "urinary bladder, overactive" AND "medication adherence" OR "patient compliance" OR "barriers". Search results were initially screened to exclude those papers that were not relevant. In addition, the reference lists of identified studies were reviewed and assessed to identify further relevant papers.

Conservative Management

Advice regarding the introduction of several simple lifestyle measures which have the potential to alleviate OAB symptoms, will provide an initial benefit for all women troubled by the condition. These include reducing their total daily fluid intake to between 1 and 1.5 litres per day,[9] as well as avoiding caffeine containing food and drink, white and sparkling wine and artificial sweeteners if these exacerbate their problem. In addition, there is increasing evidence to suggest that urinary incontinence symptoms may improve with weight loss.[10]

The efficacy of lifestyle interventions are well documented[11] although, given human nature, may often be difficult to maintain in the longer term. A prospective trial assessing compliance with lifestyle advice to restrict coffee, tea, alcohol, carbonated and artificially sweetened drinks demonstrated an improvement in the urinary symptoms of urgency and frequency although found that adherence to the study protocol was poor. By the end of the study intake of the restricted fluids was close to baseline and the authors concluded that the elimination of fluids known to cause bladder irritation was difficult to achieve and maintain.[12]

Whilst "old habits" may be difficult to modify with regard to patient care the same may also be true of the clinicians caring for them. A mixed methods qualitative study has investigated the patient perspective on care provided for OAB in the primary care setting. Medication nonadherence was found to be associated with lack of efficacy and adverse effects as well as poor communication between patient and physician. The use of investigations was variable and only 29% and 31% of patients were offered bladder retraining and pelvic floor muscle training (PFMT) respectively. Overall patients who reported more frequent communication with clinicians had higher levels of adherence than those with less frequent communication.[13] Consequently improving education and communication in primary care may lead to an improvement in adherence.

Adherence with PFMT may also be challenging in women with lower urinary tract symptoms. A multicentre randomised trial comparing continence pessaries, behavioural therapy and combined therapy also looked at persistence rates and potential barriers. At 12 months only 32% of patients were still performing self-directed PFMT and barriers to adherence included illness, travel, fatigue, work/personal conflicts and boredom.[14] A further smaller qualitative study of 31 women has demonstrated that adherence to self-instructed PFMT was dependent on the type of exercise programme, the efficacy of the programme and their own beliefs and previous experience with conservative therapy. The authors conclude that adherence could be improved by better education about pelvic floor dysfunction, mutually agreeing a course of training and the potential risk of worsening dysfunction if PFMT is not performed.[15]

The available evidence would suggest that the major barriers associated with poor adherence to conservative therapy are lack of awareness and poor communication as well as more patient led factors such as time constraints and recognising the importance of behavioural therapy. The use of mobile applications could possibly lead to an improvement in patient adherence[16] although the quality of the technology available remains mixed and of 20 applications reviewed only one was evidence based and clinically investigated.[17]

Pharmacotherapy

Whilst conservative measures provide initial benefit, drug therapy remains integral in the management of women with OAB. Antimuscarinics have been the mainstay of OAB drug treatment for many years. As a result, there are several antimuscarinic drugs available, but more recently the β3 agonist, mirabegron, has offered an alternative. Whilst the efficacy of drug therapy has been clearly demonstrated adherence with therapy remains a therapeutic challenge.

Barriers to patient adherence and persistence with treatment have a significant effect on the way patients view their use of medication for OAB. Patient reported reasons for discontinuing OAB medication have been investigated in a large screening survey of 260,000 households in the USA. Overall 168,298 responses were available for analysis. Most respondents (89%) reported discontinuing OAB medication primarily due to lack of efficacy and unmet treatment expectations or tolerability. In addition, a much smaller number (11%) indicated a general aversion to taking medication. Interestingly age, sex, race, income and history of incontinence were not predictive of discontinuation. The authors concluded that expectations regarding treatment efficacy and side effects are the most important interventions to improve adherence to therapy.[18]

A qualitative analysis performed in a study of 33 women supports these findings. The majority of respondents reported only a partial response to medication and therefore developed their own personalised strategies to improve their symptoms including fluid restriction, preventive toileting and the use of incontinence pads. The study concluded that, using a chronic care model, rather than attempting to cure the condition, may be the best way to optimise outcomes and improve health related quality of life (HRQoL).[19] These finding would suggest that a holistic package of care involving patient support, behavioural intervention and pharmacotherapy may be the best approach to improving adherence.

Antimuscarinic Drug Therapy

Traditionally, the effectiveness of antimuscarinic agents has been limited by issues with tolerability, compliance and persistence, although with the introduction of newer bladder selective drugs, once daily dosing and variable routes of administration, it is possible that the impact of these factors may decrease. Prescription data from the United Kingdom has reported a range of persistence from 23 days for darifenacin to 1758 days for tolterodine. The longest mean persistence was reported for solifenacin; 187 days as compared to 77–157 days for the other antimuscarinic drugs. At three months 58% of patients continued to take solifenacin compared to 47% taking tolterodine. By 12 months this fell to 35% and 28% respectively. Subgroup analysis revealed that patients over 60 years old were more likely to persist with treatment.[20] Interestingly there was no difference in adherence between once daily dosing and multiple dosing regimens.

Currently there are several different licensed antimuscarinic drugs available, all of which have recently been reviewed by the International Consultation on Incontinence[21] [Table 1]. All have Level 1 evidence[22] and a Grade A recommendation.[23]

Support for antimuscarinic therapy as effective management of OAB is attested by the results of a systematic review and meta-analysis. This comprised 83 studies examining six different drugs (oxybutynin, propiverine, fesoterodine, solifenacin, tolterodine and trospium) and included 30,699 patients. Active treatment was associated with a higher return to continence overall, compared to placebo; the pooled RR being 1.3–3.5 ($p<0.01$). Antimuscarinic therapy was also shown to be statistically significantly more effective in reducing the number of incontinence and urgency episodes, as well as micturitions, per day.[24]

While medication efficacy may be a common reason for discontinuation, adverse effects of treatment and tolerability is also an important factor in patient adherence. A systematic review and meta-analysis explored the role of adverse events (AEs) in treatment discontinuations of antimuscarinics for the treatment of OAB in adults over 65 years.[25] A total of 16 studies, where patients received either an antimuscarinic (oxybutynin, tolterodine, trospium, solifenacin, darifenacin, fesoterodine) or placebo, were included in the review. Eighty AEs were identified, including dry mouth, constipation,

Table 1 Antimuscarinic Drugs Used in the Treatment of Overactive Bladder

	Level of Evidence	Grade of Recommendation
Antimuscarinic drugs		
Darifenacin	I	A
Fesoterodine	I	A
Oxybutynin	I	A
Propiverine	I	A
Solifenacin	I	A
Tolterodine	I	A
Trospium	I	A

gastrointestinal upset, dizziness, urinary retention and headache. Overall treatment discontinuation due to AEs was higher in the antimuscarinic group (7.1%) compared to placebo (5.0%).

A more recent updated systematic review has also assessed efficacy and harm profiles in a further 20 trials published since 2012 including 16,478 patients. Overall efficacy outcomes were improved in favour of combined treatment with solifenacin and mirabegron over monotherapy with either drug, but the rate of constipation and dry mouth increased significantly when compared to solifenacin and mirabegron respectively. Solifenacin was shown to reduce incontinence in comparison to mirabegron or tolterodine, as well as urgency episodes over tolterodine. In addition to an overall similar efficacy to tolterodine, the incidence of dry mouth was reduced among patients taking mirabegron. Fesoterodine was shown to have similar efficacy and similar adverse effects when compared to tolterodine. The authors concluded that there is evidence to suggest small, but clinically uncertain differences amongst antimuscarinic monotherapies and between combination therapy and monotherapy.[26]

All the evidence would therefore suggest that antimuscarinic therapy offers an improvement in OAB symptoms and that there may be a difference in terms of efficacy although whether this is a real clinically important difference remains unclear.

A recent systematic review has also investigated persistence and adherence in the treatment of overactive bladder. The study reviewed 147 papers and identified discontinuation rates ranging from 4% to 31% in treatment groups and 5% to 20% in placebo groups. Among medical claims studies, discontinuation rates were substantially higher; within the first 30 days of treatment between 43% and 83% of patients discontinued medication, and this rate increased with time. Furthermore, these studies suggest that more than 50% of patients never refill their initial prescription and the mean Medical Possession Ratio (MPR) ranged from 0.30–0.83. Given the low levels of persistence and adherence the authors conclude that new drugs and non-pharmacological alternatives with good efficacy and minimal adverse effects should be explored.[27]

Adherence with OAB medication, as one may expect, is associated with improved outcomes. A study of medication adherence has been reported using the Medication Adherence Self-Report Inventory (MARSI). Overall, 62.5% of women were adherent and 37.5% were non adherent. Adherent women were more likely to report overall improvement in symptoms when compared to non-adherent women. In addition, adherent women were more likely to report a greater improvement in HRQoL.[28]

Anticholinergic Burden

Whilst highly effective and indispensable in the management of women with OAB, antimuscarinic drugs act on the central nervous system and there is increasing evidence that long-term use may negatively affect cognitive function and lead to an increased risk of dementia.[29] This clearly has implications in terms of adherence with therapy particularly in more elderly populations.

46 studies, comprising 60,944 participants, were included in a systematic review, which demonstrated an association between increasing anticholinergic load and decline in cognition, and although not statistically significant, an increasing trend in mortality.[30] Similar results were reported in a longitudinal study of 13,004 participants over the age of 65 years

taking anticholinergic medication for two years. 2-year mortality risk was increased (OR = 1.68; 95% CI: 1.30–2.16; p<0.001) and Mini Mental State Examination (MMSE) scores significantly reduced, among those using drugs with an anticholinergic effect.[31]

Further support for a causal relationship between anticholinergic burden and cognitive decline is evidenced in the results of a North American prospective cohort study which sought to examine the relationship between the onset of dementia or Alzheimer's disease and the Total Standardised Daily Dose (TSDD) of anticholinergic medication. A 10-year dose response relationship was observed for both conditions, (test for trend p<0.001), with the highest adjusted hazard ratio of 1.54 (95% CI: 1.21–1.96) for dementia, being associated with higher cumulative anticholinergic use.[32]

A more recent systematic review has reported on 14 longitudinal and case-control studies with a total of 1,564,181 patients. Overall antimuscarinic therapy was associated with an increased risk of all cause dementia and Alzheimer's disease. Interestingly both low and high anticholinergic load burdens were associated with an increased risk and a dose dependent relationship was demonstrated.[33]

Consequently, whilst increasing age may not represent an absolute contraindication to the use of antimuscarinic medication, one must be mindful of the risk of polypharmacy when initiating OAB treatment in patients with comorbidities. Many medications have an anticholinergic effect and therefore the overall anticholinergic burden must be considered; this may be assessed clinically using an anticholinergic burden scale.[34] Alternatively, avoiding antimuscarinic therapy in those patients at a higher risk of cognitive decline may offer a rationale for improving drug adherence.

β-Adrenoceptors and OAB

The adrenoceptor family is comprised of seven transmembrane receptors, with two main groups; α and β, each of which contains several subtypes. β1-, 2- and 3-adrenoceptors can be found in human urothelium and detrusor muscle, but it is the particularly high expression of β3 in the urinary bladder which has rendered it the target for new therapies for OAB treatment.[35,36] During in vitro studies dose-dependent detrusor relaxation during the storage phase of the micturition cycle and inhibition of neuropathic detrusor overactivity has been mediated by agonists of B3-adrenoceptors.[37,38]

Mirabegron: Efficacy

Mirabegron was the first commercially available selective β3-agonist for the treatment of OAB. A large multicentre randomised double blind, parallel group, placebo- and tolterodine-controlled Phase III trial assessed the efficacy and tolerability of mirabegron.[39] With respect to the co-primary endpoints of incontinence episodes and micturition frequency, mirabegron demonstrated significant superiority. Furthermore, patients in the mirabegron arm reported significant improvement in QoL, whilst rates of dry mouth and constipation were no different to placebo.

Low rates of dry mouth and constipation were also reported by a 12-month randomized double blind Phase III study in 2444 patients, supporting the long-term safety of mirabegron. In addition, longer term use of mirabegron was not associated with significant cardiovascular changes in terms of pulse rate and blood pressure.

Mirabegron: Adherence

The different tolerability profile of mirabegron compared to antimuscarinic treatment may improve patient adherence and persistence. Three recent studies have shown that patients taking mirabegron have lower discontinuation rates (defined as a break in therapy of at least 30 days or changing therapy) and improved treatment adherence (calculated using the MPR) compared to those receiving antimuscarinic therapy.[40–42]

In a retrospective analysis of 19,485 patients, 12-month persistence was higher among treatment-experienced patients receiving mirabegron (39%) in comparison to patients prescribed solifenacin (35%; HR 1.220; CI: 1.013–1.469; p = 0.037), oxybutynin ER (17%; HR 1.838; CI: 1.409–2.398; p < 0.001) and oxybutynin IR (14%; HR 2.160; CI: 1.759–2.652; p < 0.001). In the treatment-naïve cohort, again persistence rates at 12 months were highest among mirabegron users (30%) compared to those receiving antimuscarinics (13.8–21.0%), with those taking oxybutynin demonstrating the lowest persistence rates (14%; HR 1.786; CI: 1.663–1.997; p < 0.001).[43,44] Age was a factor in discontinuation rates in the treatment-naïve group, with older patients (over 65 years) less likely to discontinue treatment than their younger (under 46 years) counterparts. Significantly better adherence rates were seen among patients taking mirabegron compared to antimuscarinics (64.5% vs 18.6–49.2%, P < 0.001). Adherence

also was greater in treatment-experienced patients than treatment-naïve, with patients under 46 years old being the least adherent. However, a further study found that persistence was higher for those taking mirabegron versus antimuscarinics only once age, sex and prior medication use had been adjusted for, but not between unadjusted cohorts.[43]

Long-term persistence with mirabegron has also been investigated in a real-world prospective case series of 354 women; of these 25% were still taking mirabegron at 1 year.[44] Side effects and lack of efficacy were the most frequently reported reasons for discontinuing treatment, and continuation rates were similar for mirabegron and antimuscarinics.

A further review of hospital prescription data for mirabegron supports these findings. Out of 197 patients, 69% were still taking treatment at 3 months, but this fell to 48% at 6 months; both sexes demonstrated similar persistence rates and discontinuation was most often attributed to ineffectiveness and adverse events.[45] As with other studies the majority of participants were treatment-experienced, and mirabegron was prescribed as a first-line treatment in only 19% of patients.

In addition, in PREFER, an eight-week crossover, double-blind, Phase IV study investigating tolerability, mirabegron was significantly superior compared with tolterodine.[46] This study involved randomising 358 patients experiencing OAB symptoms, to one of four treatment sequences: mirabegron/tolterodine, tolterodine/mirabegron, mirabegron/mirabegron, or tolterodine/tolterodine. The mean OAB-S Medication Tolerability score of 83.40 for tolterodine (CI: 80.59, 86.20) was significantly lower than 86.29 for mirabegron (CI: 83.50, 89.08; $p < 0.004$) and because the "period-by-treatment" interaction did not reach statistical significance (p=0.955), the possibility of tolerability scores being affected by medication sequence was excluded. Clinically meaningful benefit is defined as a minimal important difference (MID) of ≥90 in OAB-S Medication Tolerability score or a ≥10-point improvement in OABq scale. In this study, 52.5% of mirabegron users achieved a clinically meaningful benefit from treatment vs 48.5% for those taking tolterodine ER. However, improvements in OAB symptoms and Patient Reported Outcomes (OAB Satisfaction, OABq and PPBC), as well as patient preference, were comparable between the groups.[47] Whilst this study shows a preference for mirabegron over tolterodine it is interesting that there was no difference in terms of patient reported outcome (PRO) measures and therefore any effect on adherence may be difficult to predict.

Another large systematic review and network meta-analysis has afforded additional support for better persistence and adherence rates with mirabegron. Trials involving 237,602 patients demonstrated that antimuscarinics are inferior to mirabegron with respect to persistence. In trials examining adherence, with 46,731 participants, at 12 months rates were highest among those patients taking mirabegron, although the difference in adherence rates compared to all other anticholinergics did not reach statistical significance.[48]

The available evidence would suggest that adherence with mirabegron is better than that with the antimuscarinic drugs which are currently available. This is likely due to the fact that the efficacy of mirabegron is similar to the most commonly used antimuscarinic drugs although the adverse effect profile is more favourable.

Combination Therapy; Mirabegron and Solifenacin

The BESIDE study investigated the efficacy and safety of combination therapy in patients with an inadequate response to solifenacin monotherapy.[49] In this prospective randomized double blind study, 2174 patients were randomised to receive either solifenacin alone (5 mg or 10 mg) or combination therapy (solifenacin 5 mg and mirabegron 50 mg). Overall the efficacy of combination therapy was superior to solifenacin 5 mg, and non-inferior to solifenacin 10 mg, for micturition frequency and incontinence episodes. Whilst increasing efficacy with no significant increase in adverse events should lead to improved adherence at present there are no available data to demonstrate if combination therapy has an effect in the longer term.

Management of Refractory Overactive Bladder

Although there is no formal definition of refractory overactive bladder in clinical terms this applies to women whose symptoms have failed to improve with behavioural intervention and drug therapy. This may be because patients' individual interpretation of treatment success is defined by different expectations and perceptions, or because of a previously undetected underlying pathology.[50] Such pathologies include occult neurogenic bladder, undetected bladder outlet obstruction secondary to pelvic organ prolapse, urethral strictures and dysfunctional voiding, urothelial dysfunction

with aging, chronic bladder ischemia, chronic bladder inflammation, and central sensitization, where OAB is associated with other somatic symptoms disorders such as irritable bowel syndrome and fibromyalgia.[51]

After conservative measures have failed the recent NICE guidelines recommend botulinum toxin, if the patient is willing and able to self-catheterise, or alternatively sacral neuromodulation in those patients who are unable to do so. As an alternative percutaneous Posterior Tibial Nerve Stimulation (PTNS) may also be considered.[52]

A recent cross-sectional web survey has investigated patient preferences for refractory OAB treatment in the UK. Overall 80% of patients were willing to try therapy with 57%, 34% and 9% favouring PTNS, sacral neuromodulation and botulinum toxin respectively.[53] However in real life practice only 4.7% of patients received more advanced treatment for OAB and this is dependent on ethnicity, age, gender, education level and geographical location[54] with higher rates of usage of 10% and 14.1% occurring in more specialist urology and female pelvic medicine and reconstructive surgery centres respectively.[55] This would suggest that lack of awareness may be the greatest challenge when considering adoption of refractory OAB treatments.

Botulinum Toxin

Intravesical botulinum toxin is generally regarded as first line therapy in patients with refractory OAB who are willing, and able, to self-catheterise. A study of 100 patients from a single centre has shown high rates of satisfaction with adherence rates of 68%. Of those who chose to discontinue 44% were using conservative measures or had restarted taking drug therapy.[56]

Adherence rates in patients receiving botulinum toxin for refractory OAB have also been reported in a study of 128 women treated over a five-year period with a mean follow up of 97 (60–125) months. Of all the patients 30% were still receiving botulinum toxin at the last follow up visit. Of the 70% who discontinued 27% complained of insufficient efficacy and 43% complained of problems with tolerability. Of those who discontinued; 79% discontinued after the first injection, and 19% after the second. Interestingly only 2% discontinued after more than two injections.[57] A further long-term study conducted over seven years in 268 patients has revealed similar results with 61.3% of patients discontinuing therapy at 36 months and 63.8% at 60 months. The main reasons for discontinuation were tolerability issues related to recurrent lower urinary tract infection and the need for self-catheterisation.[58]

The available evidence would suggest that those patients who gain sufficient efficacy with treatment whilst experiencing minimal adverse effects will adhere to treatment whilst those who have insufficient improvement or suffer with significant side effects discontinue. It is interesting to note that the need for repeat injections every nine to twelve months does not seem to influence patient decision-making with regard to adherence.

Percutaneous Posterior Tibial Nerve Stimulation (PTNS)

Percutaneous Posterior Tibial Nerve Stimulation (PTNS) offers an alternative approach to the management of refractory OAB symptoms in women who are unable, or unwilling, to self-catheterise. The treatment regimen consists of 12 weekly treatments initially and then maintenance therapy once a month. Consequently, PTNS treatment is a considerable commitment in terms of time and therefore this may well have an impact on patient adherence.

Long term adherence with PTNS therapy has been reported in a series of 402 patients for a single centre in the Netherlands. Only 57% of patients completed the initial treatment phase and commenced maintenance therapy. Of these, over 40% stopped treatment due to logistical reasons and physical strain over a six-year period.[59] These results are supported by a smaller series of 42 from the same centre which has shown the median treatment persistence was 16 (1–112) months. Reasons for discontinuation included loss of efficacy (55%) and preference for another type of neuromodulation (24%). The authors concluded that PTNS was effective in the short term although not effective in the longer term.[60]

Similar discontinuation rates have been reported in a further study of 141 women with 53.2% discontinuing treatment at one year. When considering those women who discontinued treatment as treatment failures the overall success rate of maintenance therapy at one year was 30.7% to 42.9%. The need for repeat maintenance visits means that realistically this may only be a treatment for a minority of patients who are able to invest the time to have treatment.[61]

Sacral Neuromodulation

Given that repeated maintenance visits are required for PTNS then an implantable neurostimulation device may offer improved adherence in the management of women with refractory OAB. Whilst there are no specific studies that have reported adherence rates with sacral neuromodulation there are several which have reported long-term success and explantation rates.

A five year follow up study in 17 centres involving 163 patients with refractory OAB has reported successful outcomes in 68% of patients with urgency incontinence and 56% with urinary frequency and urgency. Explantation rates were 6% and 37% of patients who experienced device related adverse effects.[62] A further study of 340 patients, 272 of which received a permanent implant, reported device related adverse effects in 50% of cases and explantation rates of 19.1%.[63]

A more recent multicentre French study of 320 patients, of which 247 received a permanent implant has reported a significant reduction in symptoms of urgency urinary incontinence with a corresponding improvement in HRQoL. Overall, 20% of patients required implant revision and 9% required explantation.[64]

Since a number of patients may choose not to have a non-efficacious implant removed the reported explantation rates may not accurately reflect adherence rates and a five-year study of 60 women has reported that the implant was still in use in 80% of women but 20% retained their implants without benefit rather than having them removed.[65]

Future Perspectives: Improving Adherence

Despite all the recent developments in the management of OAB adherence to treatment, both conservative and interventional, remains problematic and is likely to be related to a number of factors. Whilst lack of efficacy and adverse effects may be the drivers behind poor treatment adherence in patient's taking drug therapy other factors including treatment regimens and the need for repeated hospital appointments may be the main obstacles when considering the treatment of refractory OAB.

Central, however, to all these causes is the need for greater disease awareness, better education and improved communication allowing a more patient centered approach.

Improving Patient Centered Care

Barriers to adherence in OAB therapy may be patient or clinician centered. Patient specific barriers include limits on personal time available for keeping appointments, previous negative experiences with OAB treatments and lack of disease awareness and the potential benefits of treatment.[66] In addition poor communication and difficulty reporting symptoms due to embarrassment have also been found to have a significant effect on treatment compliance.[13]

The role of primary care has also been shown to be important. In a large database study of 1.4 million OAB patients in North America only 37% were treated with antimuscarinics, 5% with β3 agonists, 7% with topical oestrogens and 2% with PFMT. Only 26% were referred to a specialist and just 3% had third line therapy. The median time to cessation of therapy for β3 agonists was 4.1 months (IQR 1–5) and antimuscarinics was 3.6 months (IQR 1–10).[67] Consequently improving disease awareness in the primary care setting is likely to improve management decision-making and drive referrals into the secondary care setting so the appropriate care can be provided.

In secondary care patient, provider and clinical consultation level factors have been shown to be opportunities to individualise care, patient satisfaction and adherence with treatment.[68] In addition better education and information giving regarding disease awareness is likely to improve adherence with treatment[69] as well as a greater understanding of bladder physiology and the interpretation of lower urinary tract investigations.[70]

The evidence would suggest that improved awareness of OAB and the treatment options available are likely to improve adherence with therapy. In addition, improved communication and patient referral pathways should ensure that OAB patients receive the most appropriate treatment for them based on their symptoms, beliefs and patient reported goals.

Advances in Pharmacotherapy

Antimuscarinic therapy remains integral in the management of women with OAB although adherence remains a significant challenge despite the introduction of newer, more bladder specific agents and once daily dosing. Whilst

transdermal drug delivery systems are now available for oxybutynin in the form of a patch[71] or gel[72] this has had little real effect on adherence to therapy.

More recently imidafenacin has been launched in a number of countries although is not yet available in Europe, the USA or the UK. A recent systematic review including 1428 patients has indicated that imidafenacin has similar efficacy to solifenacin and propiverine although was better tolerated.[73] A further systematic review of 1430 patients has also reported improved tolerability with reduced adverse events and lower discontinuation rates when compared to antimuscarinic therapy supporting the possibility of improved adherence with imidafenacin.[74]

Whilst new antimuscarinic agents may improve adherence novel β3 agonist drugs remain under development and may offer a better balance of efficacy and adverse effects. Solabegron was initially investigated in Phase II and III clinical trials[75] although has not yet been launched and it remains unclear whether there are any plans to develop the drug commercially.

Conversely the use of vibegron has recently been investigated in a large Phase III randomised, double blind, placebo-controlled study in 1518 patients with tolterodine as an active comparator. When compared to tolterodine vibegron was found to have a similar improvement in frequency of micturition and was significantly superior to placebo in terms of reduction of urgency episodes and urgency incontinence episodes. Overall vibegron was well tolerated with a discontinuation rate of 1.7% compared to 3.3% for tolterodine and 1.1% for placebo.[76] Vibegron has recently been launched in the USA and whilst the data suggest that this may improve adherence with drug therapy[77] there are no specific studies to support this at present.

Advances in the Treatment of Refractory OAB

For those patients who fail to achieve an adequate therapeutic response with conservative measures and pharmacotherapy more invasive third line procedures such as botulinum toxin, PTNS and sacral neuromodulation offer therapeutic benefit. However, the time constraints associated with repeat appointments to have maintenance therapy is known to have an impact on patient adherence.

Unfortunately, the effects of intravesical botulinum toxin are only temporary and last approximately nine to twelve months on average. Whilst the majority of procedures were initially performed as a day case procedure under general anaesthetic there has now been a move to perform this under local anaesthetic in the ambulatory setting reducing costs and time and also improving patient safety. At present it remains unclear whether this will improve overall patient compliance and whilst other less invasive forms of botulinum administration have been investigated[78] it is unlikely that any will be clinically available in the foreseeable future.

Time constraints have also been shown to limit long-term adherence to PTNS therapy although trials of an implantable stimulation device may lead to an increase in patient acceptability and compliance. A battery free stimulation device (Renova, Bluewind Medical) designed for posterior tibial nerve stimulation was first described in a small study of 15 patients and was shown to be efficacious in terms of symptom improvement and to have a good safety profile.[79] These promising initial results are supported by a three year follow up study in 34 patients that has shown a success rate of 75% with no technical failures or explantations.[80] The device can be charged using Bluetooth technology and should therefore remove the need for repeat follow up appointments. Theoretically this should lead to an improvement in adherence although at present there are no longer term data.

Rechargeable technology may also mean that sacral neuromodulation also becomes less expensive and more accessible. A prospective multicentre trial of a novel rechargeable sacral neuromodulation system (Axionics r-SNM System) has recently been reported in 51 patients with a 12 month follow up.[81] At the 12 month follow up 94% of patients continued to respond to treatment and 98% found the recharging acceptable Overall 21% of patients complained of device related adverse events with discomfort due to stimulation occurring in 20% of subjects. These adverse events all resolved with reprogramming of the stimulator. Whilst a rechargeable stimulator avoids the need for regular battery replacement there are no available data at present to suggest whether this will lead to any meaningful improvement in treatment adherence.

Conclusions

Overactive bladder is a common and distressing condition which is known to have a significant effect on HRQoL although adherence to therapy remains a clinical challenge.

Whilst the majority of women will benefit from conservative measures in the first instance many fail to continue, and the evidence would suggest that this may be due to poor awareness of the condition and the need for long-term treatment. Consequently, educating patients and clinicians as well as improving clinical guidelines may facilitate referral and ensure appropriate treatment is provided.

Should conservative measures fail, many women will eventually require drug therapy. At present antimuscarinics are the most commonly used drugs for OAB although their usage is limited by the common anticholinergic side effects of dry mouth, constipation, somnolence and blurred vision. For those with refractory symptoms switching to an alternative class of therapy, such as a β3 agonist, may be useful and there is now considerable evidence to support the use of combination therapy in those women with persistent symptoms. Choice of drug, in addition to being able to offer different classes of drug, should improve clinical decision-making and ultimately patient adherence to therapy.

For the minority of patients who fail to gain sufficient improvement with pharmacotherapy botulinum toxin and neuromodulation may offer an alternative. Whilst all these third line treatments require increased resources in terms of cost and time the newer devices with rechargeable batteries may improve patient acceptability and therefore adherence to therapy.

In conclusion, empowering our patients with information regarding the causes and consequences of OAB, in addition to the available management options, should be able to facilitate patient driven decision-making and allow a tailored treatment regimen based around patient expectations and personal goals. This should lead to improved acceptability and ultimately improved compliance.

Disclosure

Mr Dudley Robinson reports personal fees from Allergan, outside the submitted work; Professor Linda Cardozo is a Consultant for ConvaTech and Merck, outside the submitted work. The authors report no other conflict of interest in this work.

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