Therapeutics and Clinical Risk Management

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REVIEW

Assessing Quality-of-Life of Patients Taking Mirabegron for Overactive Bladder

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Abstract: Lower urinary tract symptoms (LUTS), including urgency, frequency, and urgency incontinence, are highly prevalent in the general population and increase in prevalence with increasing age. All LUTS, but notable urgency and urgency incontinence, are associated with negative impact on quality-of-life (QoL), with multiple aspects of QoL affected. Urgency and urgency incontinence are most commonly caused by overactive bladder (OAB), the clinical syndrome of urinary urgency, usually accompanied by increased daytime frequency and/or nocturia in the absence of infection or other obvious etiology, which may be treated with conservative and lifestyle interventions, bladder antimuscarinic drugs, and, more recently, by mirabegron, a β3 agonist. This narrative review describes the impact of OAB on QoL, quantifies this impact, and outlines the evidence for the use of mirabegron in the treatment of, and improvement in QoL in, people with OAB.

Keywords: lower urinary tract symptoms, incontinence, quality-of-life, health-related quality-of-life, mirabegron

Introduction

It is well recognized that lower urinary tract symptoms (LUTS) including urgency, frequency, and urinary incontinence (UI) are highly prevalent in the general population and increase in prevalence in association with increasing age.[1,2] Urgency, defined by the International Continence Society as the complaint of a sudden, compelling desire to void which is difficult to defer,[3] is a particularly bothersome symptom, even in the absence of incontinence.[4] The syndrome of urinary urgency, usually accompanied by increased daytime frequency and/or nocturia in the absence of infection or other obvious etiology, is termed overactive bladder (OAB) and may be associated with UI (termed OAB-wet) or without (OAB-dry),[5] is a common cause of incontinence in both men and women and is associated with a significant negative impact on quality-of-life (QoL).[6] Beliefs that LUTS and UI are a normal part of aging, as well as the stigma associated with them lead patients to not seek care.[7]

Multiple guidelines for the treatment of LUTS and UI in older adults stress the importance of conservative management, including the treatment of constipation, fluid intake normalization, treatment of underlying conditions and polypharmacy, and bladder training prior to pharmacotherapy,[8,9] with bladder antimuscarinics and beta-3 agonists being available options.

While anticholinergic agents for the treatment of OAB have been available for many years,[10] concerns around anticholinergic side-effects and the tolerability of these agents led to the beta-3 agonist mirabegron being developed in the mid-2000s, and it was first licenced in the early 2010s.[11]

This review will examine the evidence on mirabegron's effect on QoL in patients with OAB, with and without associated urgency incontinence.

Overactive Bladder

Epidemiology

As with most LUTS, prevalence rates of OAB are difficult to estimate due to few population-based studies. In those that have been done significant heterogeneity exists regarding definitions used, inclusion and exclusion criteria, and how symptoms are

Received: 2 November 2022
Accepted: 14 December 2022
Published: 10 January 2023

assessed/measured. Prevalence estimates range between 2% and 53%, with most studies estimating between 10% and 20%.[12] The EPIC study found the prevalence of OAB was 11.8% using data from five European countries.[1] In EpiLUTS, 35.7% of women and 22.4% of men experienced urgency.[13] A recent epidemiology study in Canada found that OAB was experienced by 12.3% of respondents, in a nationally representative adult sample.[14] Urgency UI was endorsed by 5.3% of respondents. Prevalence estimates change when the degree of bother is reported.[13,15] In the EPIC study, of those with OAB nearly half endorsed UI, and there was an increased level of bother seen in the incontinent group.[1]

Pathophysiology

The pathophysiology of the symptom complex of OAB is not yet well understood. While once thought to be synonymous with detrusor overactivity (DO), there is only a moderate correlation between OAB symptoms and the presence of DO on multichannel subtracted cystometry.[16] In older adults, LUTS including OAB and UI are most often multifactorial, and the role of abnormalities in the neural control of the bladder cannot be understated.[17] Functional brain imaging, including functional magnetic resonance imaging (fMRI) and single-photon emission computed tomography (PET), have demonstrated periaqueductal gray matter, pons, and the ventral and dorsal portions of the pontine tegmentum are activated during the filling phase of voiding and may be involved in suppressing the voiding reflex. Damage to these areas, such as the development of white matter hyperintensities, may impair the ability to suppress the voiding reflex.[18] A recent study in Japanese older adults showed that participants with OAB showed a higher volume of WMH than those without OAB.[19] OAB in older adults is, at least in part, a "brain disease".[20]

Quality-of-Life

LUTS are highly stigmatizing symptoms[21] which impact an individual's QoL in numerous interacting ways. QoL data are most robust with UI, studies consistently showing UI to be associated with a lower QoL and poor self rated health.[22,23] A systematic review in 2010 including both UI and OAB demonstrated that OAB-dry impairs QoL.[24] However, QoL has been shown to be worse in those with UI.[25] When further categorizing UI, urgency UI (as associated with OAB-wet) is often seen to be the most impairing,[26] along with mixed UI, though in mixed it is the urgency component that has the biggest effect.[27] Data have suggested that it is the symptom severity, rather than type of incontinence that is most associated with impaired QoL.[25,28] Similarly, the degree of impact of OAB appears to be related to both the presence of urgency UI and the overall severity of the condition.[24] This opens the door for action, for if lifestyle or pharmacological interventions can reduce the severity of symptoms, even without cure, it may significantly improve QoL.

While UI may be considered the most bothersome symptom of OAB, other LUTS such as urgency also impact QoL. A study of Spanish men found that the frequency of urgency episodes was inversely proportional to health-related quality-of-life (HRQoL).[29] Urgency is the LUTS with the greatest population level burden, at the individual level the LUTS with the greatest bother is urgency UI.[4] A nested study within the EPIC cohort demonstrated that men and women with OAB equally reported symptom bother; more bother was associated with urgency than stress incontinence.[30]

UI has consistently been associated with shame,[31] depressive symptoms,[32] poor self-rated health,[33] falls,[34] and high expense.[35] Similarly, OAB has been found to be associated with feelings of depression and stress, worry and shame, and feeling uncomfortable in social situations.[36] While it is well recognized that people with LUTS will often not seek healthcare,[37] the level of bother of LUTS impacts the likelihood of health care seeking, with patients with high bother being more likely to initiate a conversation with a healthcare provider, even with the same frequency and severity of symptoms.[30]

A population-based study of OAB and urgency UI in the US, UK, and Sweden of adults aged 40–65 demonstrated decreased work productivity in men and women with OAB, most pronounced among those with UI.[38] Patients with OAB-wet may worry about interrupting meetings and often consider their urinary symptoms in decisions about work hours and location. Urgency accompanied by a fear of leaking and perceived daytime frequency were most strongly associated with work productivity impairment in both men and women. Associations were also seen with storage, voiding, and micturition symptoms. EPIC found similar findings, with the addition that men with OAB were more likely to be retired than those without OAB, and also showed that those with OAB demonstrated less work productivity and sexual satisfaction, higher rates of depressive symptoms and erectile dysfunction, and lower levels of overall health.[30]

Care partners of those experiencing LUTS are also affected by their partner's symptoms. Providing continence care is considered burdensome, requiring significant time and energy expenditure. In addition to physical burden, LUTS and UI affect psychological well-being by causing worry, sleep deprivation, and burnout.[39–41] UI is an independent predictor of institutionalization in those with dementia, as it is often the symptom for which caregivers are no longer able to provide care at home.[42–44]

QoL Tools

Numerous validated tools have been developed to assess and quantify the impact of LUTS on QoL. For both sexes, the International Consultation on Incontinence Questionnaire – Quality of Life (ICIQ LUTS-QoL) is a validated questionnaire assessing the impact of a variety of LUTS on QoL.[45–47] It is a 22-item questionnaire with possible scores of 19–76, with higher scores indicating increased impact on QoL. Many domains are assessed, including household tasks, relationships, activity, and mental health. Bother is also assessed for each included domain.

Several scales have been validated specifically for OAB: the overactive bladder questionnaire (OAB-q),[48] the patient perception of bladder condition (PPBC),[49] and the treatment satisfaction visual analog scale (TS-VAS).[50] These tools also assess symptom bother in OAB, which is an important consideration for how OAB is impacting QoL. The ICIQ-Cog was developed to assess how LUTS impact QoL in cognitively impaired individuals.[51] The minimally important difference (MID), the smallest change in response outcome that is perceived as meaningful by the patient, has been estimated as 10 points for all OAB-q subscales.[52]

Mirabegron

Safety, Efficacy, Tolerability

Mirabegron was the first beta-3 adrenoceptor agonist to enter the market. It was approved for use initially in the United States and the European Union. Mirabegron was developed to target the beta-3 adrenoceptors that make up the majority of beta-adrenoceptors in the detrusor muscle and urothelium.[53] Available dosage forms are 25 mg, 50 mg, and 100 mg tablets. Metabolism occurs in the liver with involvement of the cytochrome P450 system. Excretion is via urine and feces.

Phase II and III randomized controlled trials (RCTs) (BLOSSOM, DRAGON, SCORPIO, ARIES, CAPRICORN, TAURUS) demonstrated mirabegron to be superior to placebo in a number of micturitions and incontinence episodes in 24 hours.[54–59] Pooled analysis from three trials also demonstrates a statistically significant dry rate as well as a decrease in incontinence episodes by 50%.[60] Participants across all studies were adult men and women over 18 years with OAB symptoms for over 3 months. An assessment of pooled data showed improvement in incontinence episodes and micturitions per day in older adults over 65 years.[61] Evidence of benefit was seen early and was maintained throughout treatment. A placebo-controlled trial of older adults over age 65 (PILLAR) also demonstrated improvement in the number of micturition and incontinence episodes per day.[62]

Discussions around the safety of mirabegron have predominantly focused on cardiovascular safety, given the presence of beta-3 adrenoceptors in cardiac and vascular tissue. In one healthy volunteer study, supratherapeutic doses of mirabegron was associated with QTc prolongation in women, and also with a dose-dependent increase in heart rate (6.7, 11, and 17 bpm for the 50, 100, and 200 mg dose groups, respectively).[63] These cardiovascular effects have not been seen in any other trial. Pulse increases in the clinical trials were more modest (1–5 bpm, depending on dosage and time of day). Blood pressure effects were similarly modest in the clinical studies, with only a 1 mmHg increase in systolic or diastolic blood pressure. A Canadian population-based cohort study did not find increased incidence of arrhythmia, tachycardia, myocardial infarction, or stroke within 1 year from initiation when compared to other OAB drugs.[64] Few other adverse effects have been reported. Pooled safety data from three trials looked at post-void residuals (PVR) and found unremarkable change in mirabegron 50 mg and 100 mg doses, as well as tolterodine and placebo groups, and the number of patients with PVR over 150 mL was lower in both mirabegron groups.[60] In that population, the number of patients who experienced acute urinary retention was less than 1%, and was lower than the tolterodine or placebo groups.

The most common adverse effects (AE) reported in the RCTs were hypertension, nasopharyngitis, urinary tract infection, headache, pruritis, constipation, diarrhea, and dry mouth.[42–47] Across all studies, the majority of AE were mild

or moderate, and discontinuation rates were low. AE were similar between anticholinergic (tolterodine), mirabegron, and placebo groups, except dry mouth and pruritis which were 5-times higher in the anticholinergic groups. In PILLAR, there was a slightly higher incidence of AE in the over 75 years age group compared to the less than 75 years age group, but no meaningful differences in HR or BP were seen in either group.[62] A meta-analysis of trials comparing mirabegron to solifenacin demonstrated similar efficacy with greater tolerability in the mirabegron group due to the lack of anticholinergic side-effects.[65]

Quality-of-Life

As with many trials of medications for OAB, the primary endpoints of trials of mirabegron were usually objective and easily measured parameters such as voids per day or occurrences of incontinence. Several trials of mirabegron have used patient-reported measures or HRQoL as secondary endpoints.[55–58] These phase II and III trials used OAB-specific QoL scales. In those studies that utilized the OAB-q, all domains exceeded the MID, except for the OAB-q Social Interaction domain in three trials.[57–59] Using the PBC, in two trials, there was a minimally important difference in QoL scales between mirabegron and placebo.[56,57] Another trial also demonstrated this but the result was not statistically significant.[57] DRAGON used ICIQ-OABqol and demonstrated improved QoL scores with increased dosages.[55]

A large European observational study (BELIEVE) demonstrated improved symptom bother and HR-QoL scores at 2–4 and 10–12 month follow-ups.[66] More patients achieved MID at 10–12 months than 2–4 months (symptom bother 71.2% vs 43.8%, HRQoL 63.1% vs 37.2%), with a greater improvement in women than men. At 10–12 months, 53.8% of patients were still receiving mirabegron, the remainder having discontinued treatment entirely or switched to a different agent. However, another observational study in the UK demonstrated only a 38% 12-month persistence rate.[67] Secondary analysis of BELIEVE participants only age 65 and over demonstrated that older adults' symptom bother scores improved similarly to younger patients, and proportions of older patients with improvement were similar to younger patients.[68]

Few studies have assessed the effect of mirabegron on caregivers of those with OAB. One prospective, non-randomized study[69] of 186 caregivers of older women with urgency or mixed incontinence in Greece found that the caregivers of those women treated with mirabegron, compared to conservative management, had significant reductions in the Zarit Burden Scale after 3 months of treatment.

Conclusion

OAB, a symptom complex characterized by urgency, nocturia, and sometimes urgency UI, is a condition that has significant and deleterious impact on QoL, as the symptoms are often associated with significant bother. In younger people, it has significant implications for work and employment, and in older people it also affects the QoL of caregivers and increases the likelihood of institutionalization. Mirabegron has been shown to be safe, tolerable, and efficacious in patients with OAB. It may be more tolerable to patients than the available anticholinergic medications due to a lower burden of anticholinergic side-effects. Use of mirabegron has been associated with improved QoL scores of patients in randomized-controlled trials and real-world observational studies. Decreased burden has also been demonstrated in caregivers of patients on mirabegron for OAB. Patient-reported outcome measures and measures of quality-of-life impacts should be included and prioritized in future research into treatments for OAB.

Disclosure

Dr William Gibson reports grants from Pfizer Canada, outside the submitted work. The authors report no other conflicts of interest in this work.

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