Introduction

Overactive bladder (OAB) affects 12-16% adults across Europe, North America and Japan. Its prevalence increases with age, affecting ~30% of elderly over the age of 65. It significantly affects the quality of life and increase the likelihood of sleep deprivation, depression, falls & fractures.

According to the 2014 amended Guideline on Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults by the American Urological Association (AUA) and Society for Urodynamics Female Urology (ASFU) [1], behavioral therapies (bladder training, bladder control strategies, pelvic floor training, fluid management) should be offered to all patients with OAB as first-line treatment. Second-line treatment is pharmacological treatment which should be initiated if there is failure of response or only partial response to behavioral therapies. Third-line treatments included intra-detrusor botulinum toxin A injection, peripheral tibial nerve stimulation (PTNS), sacral neuromodulation (SNS) which may be considered after thorough counselling of patients who has been refractory to first and second line treatments and remained problematic.

For the second line pharmacological treatment, anti-muscarinic drugs are the mainstay of treatment. They block muscarinic M2/M3 receptors located on the urothelium, interstitial and detrusor muscle cells, and afferent nerves. Meta-analysis of RCTs has shown that anti-muscarinics significantly improve OAB symptoms. However, over 60% patients discontinue anti-muscarinic therapy over a 12-month period either due to inadequate symptom control and/or intolerable side effects such as dry mouth or constipation. In the 2014 amended guideline, a new class of drug, B3-adrenoceptor agonists, is added as an alternative to anti-muscarinics. Mirabegron represent the first approved drug in this new class. It acts by direct relaxation of detrusor smooth muscle via stimulation of bladder B3-adrenoreceptors.

In USA and Canada, the recommended starting dose of Mirabegron is 25mg daily, with an option to increase to 50mg daily. In Europe and Japan, the recommended dose is 50mg daily (25mg daily for those with renal or liver impairment and taking concomitant drug with strong CYP3A inhibitory effects (e.g. Itraconazole, Ketoconazole, Ritonavir, Clarithromycin, etc.) In Hong Kong, the recommended dose of Mirabegron (Betmiga®) for adults aged over 18 is same as that in Europe & Japan. It is in the form of prolonged release tablet. It is swallowed in whole piece and is not to be chewed, divided or crushed. It can be taken with or without food.
Mode of Action & Pharmacological Properties of Mirabegron

The activation of the micturition reflex is distension of the bladder, an activity mediated by the stimulation of myelinated Aδ fibres and unmyelinated C-fibres. There are 3 β-adrenoceptor subtypes (β1, β2 and β3) identified in the human detrusor muscle & urothelium. The B3-adrenoceptor is found to be the predominant subtype in the human urinary bladder [2, 3]. Studies showed that B3-adrenoceptor agonist directly relaxes the detrusor muscle during the storage phase and inhibit bladder afferent activity with a consequence increase in bladder volume [4, 5]. On the other hand, it does not affect the voiding phase parameters, including the maximum urinary flow rate (Qmax), detrusor pressure at Qmax and residual volume [6, 7].

Mirabegron is rapidly absorbed after oral administration, the time to maximum plasma concentration (Tmax) being ~3 hours. It is highly lipophilic, and is metabolised in the liver via multiple pathways, but mainly by cytochrome P450 (especially CYP3A4). It circulates in plasma as the uncharged active form and as inactive metabolites. Most of an administered dose is excreted in the urine, mainly as the unchanged form, and one-third is recovered in faeces, almost entirely as the unchanged form. The terminal elimination half-life is about 23-25hrs. Mirabegron exhibited a greater reduction in plasma exposure after a low-fat meal compared with a high-fat meal. However, the effects of food seen do not warrant a dose adjustment in clinical practice.

Efficacy & Safety Studies

Two Phase II studies [8, 9] showed significant reduction in micturition episodes/24hr, increase in mean volume voided, reduction in incontinence episodes/24hr, urgency episodes/24hr and urge incontinence episodes/24hr when compared with placebo. The most promising dose for clinical use was 50mg daily.

There are five Phase III RCTs reported so far. The first study by Nitti et al [10] is a double-blinded, placebo-controlled trial in USA randomizing 1,329 patients with OAB into 3 groups: Mirabegron 50mg daily, Mirabegron 100mg daily or placebo for 12 weeks. There was significant reduction of incontinence episodes [-1.47 & -1.63 vs -1.13 for placebo] and micturition episodes [-1.66 & -1.75 vs -1.05 for placebo] at 4 weeks after treatment for Mirabegron 50mg and 100mg groups compared with placebo and there was further improvement up to 12 weeks. There was also significant improvement in secondary endpoints including mean voided volume, urgency episodes, urge incontinence episodes and nocturia episodes in the active treatment groups. The incidence of frequently reported treatment emergent adverse events (HT, UTI, headache, nasopharyngitis) was similar in the Mirabegron and placebo groups. Dry mouth was reported for 0.5%, 2.1% and 1.5% of patients in the 50 mg, 100 mg and placebo groups respectively.

In the SCOPRIO trial [11], Khullar et al randomized 1,987 patients in Europe and Australia with OAB symptoms for >3 months into 4 groups: Placebo, Mirabegron 50mg, Mirabegron 100mg, Tolterodine ER 4mg daily for 12 weeks. Primary endpoints showed that Mirabegron significantly reduced incontinence episodes [-1.57 & -1.46 vs -1.17 for placebo] and micturition episodes [-1.93 & -1.77 vs -1.34 for placebo]. Comparison between Mirabegron and Tolterodine ER was only a secondary endpoint and did not showed significant difference but is under-powered. The prevalence of AEs were not significantly different across the 4 groups. Hypertension was the most common AE (7.7%, 5.9%, 5.4% & 8.1% respectively). Dry mouth was most common in the Tolterodine group (2.6%, 2.85%, 2.8% & 10.1%). Khullar et al published a post hoc analysis of this RCT evaluating separately the results in patients who had not received any prior anti-muscarinic drugs and those who had received prior anti-muscarinic drugs. The latter group was further subdivided in 2 subgroups according to the cause of discontinuation: inadequate efficacy or poor tolerability. Mirabegron showed significant improvement of primary endpoints in patients who were anti-muscarinic naive and who had discontinued prior anti-muscarinics.

Herschorn et al published another Phase III study [12] comparing Mirabegron 25mg daily, 50mg daily or placebo for 12 weeks in 1,306 patients with OAB in Canada. Primary endpoints also showed significant reductions in incontinence episodes [-1.36 & -1.38 vs -0.96 for placebo] and micturition episodes [-1.65 & -1.60 vs -1.18 for placebo] for the 2 active treatment groups. Mirabegron was well tolerated and the incidence of AEs were similar.
The trial by Yamaguchi et al. [13] randomized 1,139 Japanese patients with OAB into 3 groups: Placebo, Mirabegron 50mg daily, Tolterodine 4mg daily for 16 weeks. Mirabegron showed significant improvement vs placebo in micturition episodes [-1.67 vs -0.86 for placebo], urgency episodes [-1.85 vs -1.37], incontinence episodes [-1.12 vs -0.66], urgency incontinence episodes [-1.01 vs -0.6] and mean voided volume [24.3ml vs 9.71ml]. The overall incidence of treatment-related AEs were 24%, 24.5% & 34.9% respectively. Constipation (2.9%, 2.6% & 3.5%) and dry mouth (2.9%, 2.6% & 13.3%) were the most common treatment-emergent AEs. For cardiovascular-related AE, the prevalence was low and similar in all 3 groups.

Long-term safety and efficacy evaluation was studied in a Phase III RCT, TAURUS study, by Chapple et al. [14] where 2,452 patients were randomized into 3 groups: Mirabegron 50mg daily, Mirabegron 100mg daily or Tolterodine ER 4mg daily for 52 weeks. The improvement in OAB symptoms were similar among the 3 groups and were maintained over the 52 weeks. The prevalence of AEs was ~60% in each group and most AEs were mild or moderate in severity. Prevalence of hypertension (9.2%, 9.8% & 9.6%), constipation (2.8%, 3% & 2.7%) and headache (4.1%, 3.2% & 2.5%) were similar among the 3 groups. Dry mouth was significantly more prevalent in the Tolterodine group (2.8%, 2.3% & 8.6%). Drug discontinuation rate was low and similar among the 3 groups. Hence, the efficacy of Mirabegron was non-inferior to anti-muscarinic but have a better toxicity profile.

Anti-muscarinic or β3-adrenoreceptor agonist?

So far there was no study designed and powered to show the non-inferiority or superiority of Mirabegron compared with other anti-muscarinic agents. However, tolerability data especially dry mouth problem seems to be in favor of β3-adrenoreceptor agonist. There will also be an advantage for β3-adrenoreceptor agonist in specific group of patients like patients with glaucoma or dementia. Since the mechanism of action of β3-adrenoreceptor agonist is different from that of anti-muscarinics, it might prove to be a useful treatment in patients experiencing intolerable side-effects to anti-muscarinics. There is yet no recommendation on whether anti-muscarinic or β3-adrenoreceptor agonist should be the first line pharmacological treatment. There is also no recommendation on combination therapy or as an “Add-on” therapy at the moment.

Combination Therapy or Add-on Therapy Studies

Since the β3-adrenoreceptor agonists and anti-muscarinics work by different mechanisms of action, combining the two drugs is theoretically plausible and may have synergistic effects. A number of studies recently confirmed this synergistic effect while there is no increase in adverse events.

The “SYMPHONY” study [15] by Paul Abrams et al. randomized 1,306 patients with OAB to 12 week of treatment in 1 of 12 groups: 6 combination groups (Solifenacin 2.5mg, 5mg, 10mg plus Mirabegron 25mg or 50mg daily), 5 monotherapy groups (Solifenacin 2.5mg, 5mg, 10mg or Mirabegron 25mg or 50mg daily, or Placebo. Results showed that all combination groups with Solifenacin 5 or 10mg significantly improved mean voided volume when compared with monotherapy with Solifenacin 5mg daily. 3 combination groups significantly reduced micturition frequency compared with Solifenacin 5mg. 5 combination groups significantly reduced urgency episodes compared with Solifenacin 5mg. No dose-related trends in treatment-emergent adverse events (TEAEs), blood pressure, pulse rate, ECG parameters were observed although the incidence of constipation was slightly increased with the combination groups.

The Russian trial by Kirill et al. [16] randomized 239 elderly patients (age >65) with severe OAB symptoms (incontinence episodes >3/day) into 4 groups: Mirabegron 50mg daily, Solifenacin 10mg daily, Combined Mirabegron & Solifenacin, and Placebo. Results after 6 weeks treatment showed all active treatment groups had significant improvement in micturition episodes [-3.7, -3.6, -3.8 vs -1.2 for placebo] and incontinence episodes [-2.3, -2.2, -3.5 vs -0.4 for placebo]. The combined treatment group showed significantly greater reduction in incontinence episodes and micturition episodes than monotherapy groups. The percentage of side effects did not significantly different from the monotherapy group.
In the “MILAI” study [17] by Yamaguchi et al which was a multi-centre, open-labelled Phase IV study on 223 adult patients with OABSS total score ≥3 and Question 3 of OABSS score ≥2 while already on Solifenacin at stable dose of 2.5mg or 5mg daily for at least 4 weeks. All patients were given “Add-on” therapy with Mirabegron 25mg daily for 16 weeks. At 8 weeks, Mirabegron dose could be increased to 50mg daily if there was insufficient response and there was no safety concern. ~60% patients were required to step up to the 50mg dose. Results showed that “Add-on” therapy significantly improved OAB symptoms and were well tolerated.

Another double-blinded RCT, SYNERGY Study, to assess the efficacy and safety of the “Add-on” therapy with Mirabegron in patients treated with Solifenacin is in progress. Initial results showed that “Add-on” therapy significantly improved OAB symptoms. The “Add-on” group reported a lower incidence of dry mouth than the Solifenacin 10mg group and a similar incidence as the Solifenacin 5mg group.

Another double-blinded RCT, “BESIDE” study, comparing “Add-on” therapy with Mirabegron and Solifenacin alone, is currently under way.

Summary

A new class of drugs is now available for the pharmacological treatment of OAB. The β3-adrenoreceptor agonist acts by direct muscle relaxation of the detrusor muscle during the storage phase without affecting the voiding mechanism. Mirabegron is the first approved drug in this new class. Initial studies showed that the efficacy of Mirabegron is comparable to anti-muscarinics though these studies are not specifically designed for the direct comparison. The safety profile is comparable to placebo and has less dry mouth and constipation than anti-muscarinics. It can be used as monotherapy at the first instance or when patient does not respond or intolerable to anti-muscarinics. It can also be used in combination treatment with anti-muscarinic to achieve greater synergistic effect and minimize the side effect of anti-muscarinic at higher dose.

References


Urinary Incontinence (UI) is a common health problem and creates a tremendous negative effect of different aspects to our clients. One of the common scenarios for our local Chinese is that lots of clients do not seek medical advice of UI because of the embarrassing feeling.

Due to the rapid development of medical technology such as latest surgical techniques and tools and effective evidence based treatment including both pharmacological and other means of treatments, most of the conditions can be treated or at least have some improvement after appropriate management.

As we know, UI will induce a lot of impacts to the clients as well as family. It creates a lot of psychological issues like poor self-esteem, shamefulness because of the wet pants incident and the odor of the clothing or furniture afterwards. The impact is also found in relationships including both friendship and between family members.

In view of those negative impacts to the clients, as a health care professional, we have great responsibility to help our cases to overcome the problems caused by UI and help them to regain their dignity and change their life. As an Occupational Therapist, we will provide functional training, home assessment and modification, assistive device prescription, clothing design and modification and carer training to those cases who suffer from UI problems. The goals for those training are to enhance both physical and psychological functions, facilitate independent living, improve Quality of Life (QOL) of people with disabilities or special needs, and promote their reintegration into home, work & community.

Behavioral therapy is one of the major treatments for UI patients by multi-disciplinary professional like Nurses, Physiotherapy colleagues and Occupational Therapy colleagues. Voiding diary is usually used to monitor the voiding habit of our clients which includes urinary frequency, urgency and incontinence episodes. Some of our clients suffer from frequent voiding with small amount of urine that severely affected their normal daily routine. Besides, bladder training is designed to help the patients to regain control, increase bladder capacity and reduce the number of episodes of incontinence. The ultimate goal for this behavioral treatment is to delay the time of toilet visit and enhance urgency control. The deferment techniques include pelvic floor muscle contraction, mental distraction, penile compression and other techniques. However, most patients show poor competence to extend the voiding time with target over one hour because they feel not achievable for their condition. In this situation, we can ask the clients to start from a short duration like few minutes and then gradually increase the time interval and also they can be advised to use the build-in timer function of their mobile phone as an assistive tool to monitor the progress.

Using mobile phone as a treatment modality is very common now, even clients aged over 70 will use smartphone. There are some very useful applications suitable for them and are able to increase the effectiveness of the treatment. In this article, two applications will be suggested for our clients like toilet finder and drug management which are practical in daily life.

In Hong Kong, it is not easy to find restroom in the community and they may not be user-friendly to our clients even so. Nowadays in Hong Kong, it is not easy to find a toilet nearby with satisfactory and hygiene environment and fully equipped with toilet paper. Due to this inconvenience, clients with urinary problems will prefer idling at home and become asocial. The “TOILET FINDER” is a very friendly application as it can be used in both online and offline mode, easy to be downloaded and the information covers most of the big cities around the world.
The on-line mode uses the Global Position System (GPS) for the real time location and then spots out the nearest toilet nearby. The information includes distance, service hours, facilities and with comments by other users for the clients to consider. The off-line mode allows the user to search the relevant restroom information in the desired location. This application is good for clients who are reluctant to join outdoor activity because of UI problem and allows them to make a good route planning and source out the nearby toilet if necessary.

Apart from the “TOILET FINDER”, “MEDICATION MANAGEMENT” is another useful application to our clients. Good medication adherence is one of the keys to success in disease management. Although the application is not only for urological patient, it can be applied to all population who need to take medication especially for those who need poly-medication but with fair cognitive function. It allows the users to choose the shape, color of the medications and set the time according to the prescription regime. The system will alert them by sound and vibration and will show the picture of drug that needs to be taken. The alert can also be the voice of the family members by its recording function. It is really helpful in drug management especially for those who have borderline cognitive function and clients who are living alone.

Sexual function and satisfaction is also a major concern for male urological patients. It is about 50 % of UI patients suffer from erectile dysfunction (ED). There are many treatment alternatives for clients who suffer ED such as medication (Viagra, Cialis, Levitra), various wave therapy and surgical treatment such as implants. Obviously the suitability of the treatment depends on medical advice and patients’ choice. As a sex therapist, we will try to explore the possible causes away from physical condition. Some patients are actually having psychological or social problems more than the real physical dysfunction. After analyzing the cause, we will suggest some home exercises for clients to practice in order to help them to achieve a more satisfactory intimacy life. Some urological clients also feel enjoyable sexual life even the erection function is not really good enough for penetration. Suggestion to use sex toys for enjoyment enhancement will be also given.

In Hong Kong, there are different organizations which can provide sex therapy for people in need. Within Hospital Authority (HA), clients can be referred to Rehabaid Center for a comprehensive assessment and treatment. If the cases do not prefer HA service, they can also seek service from Family Planning Association and other non-government organizations like Caritas which will also provide sex therapy service. In addition, the Hong Kong Polytechnic University Rehabilitation Clinic also provides sex therapy consultation and training to those cases having problem in intimacy life.

To conclude, UI is a treatable condition which advanced medical and surgical treatment, various aids, techniques, advice and modern tips can help. The key is to make our clients understand more about the disease and various treatment options, leading to possible positive changes of UI conditions.

*You can search “Toilet finder” and “medication management” or “drug management” at Android market or App store by Smartphone to source suitable applications for trial.

References

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Merry Christmas