MEDICATIONS UPDATE

Mirabegron - a new option for OAB?

What is Mirabegron?

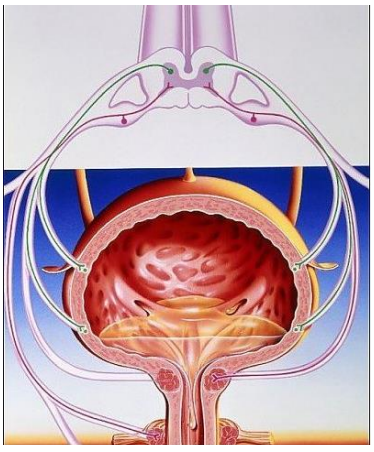
Mirabegron (trademark "Myrbetriq" to the public) is the first in an entirely new class of drug now being marketed for the management of OAB. It is already approved in some parts of Europe and the USA, and is likely to *hit the Australian market in the next 6-12months*.

How is Mirabegron different to previous OAB Drugs?

Unlike all previous drugs for OAB, Mirabegron is **NOT** an **antimuscarinic**. Mirabegron is a **β3 Adreno-Receptor Agonist (β3-AR)**. To fully understand this difference we need to first review the normal neurological control of the LUT.

LUT PHYSIOLOGY REVIEW

The lower urinary tract (LUT) obviously consists of the **Bladder** (designed to store urine) and the **Urethra** (designed to release urine at a convenient time).



The bladder wall is largely made up of a ***smooth muscle*** layer known as the ***detrusor*** which is designed to remain relaxed during storage and contract during voiding. The urethra is also partially controlled by smooth muscle. The ***internal urethral sphincter*** consists of smooth muscle fibres that begin as extensions of the smooth muscle detrusor fibres at the bladder neck and extend down the length of the urethra.

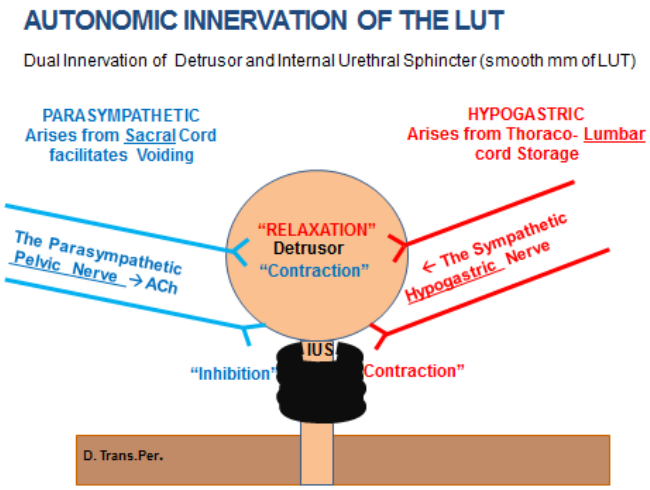
THE SMOOTH MUSCLE COMPONENTS OF THE LOWER URINARY TRACT –

Detrusor and Internal Urethral Sphincter

Being smooth muscles, both the detrusor and internal urethral sphincter are under the influence of the autonomic nerves. The two autonomic nerves that co-ordinate the actions of the detrusor and internal urethral sphincter are the:

1. **Pelvic Splanchnic Nerve** – a **parasympathetic nn**
   I. Originates from the sacral spine
   II. Sends motor efferents to facilitate **voiding**.
   III. → *Detrusor Contractoin and IUS relaxation*

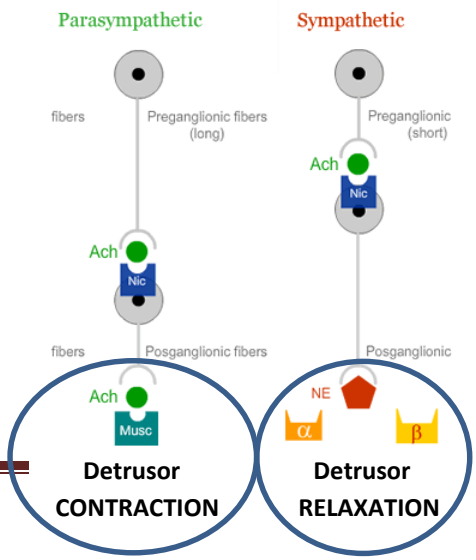
2. **Hypogastric Nerve** – a **sympathetic nn**
   a. Originates from T10-L2
   b. Sends motor efferents to facilitate storage.
   c. → *Detrusor Relaxation and IUS relaxation*



The two nerves work in different ways because they release different neurotransmitters into different receptors on the detrusor cells:

- Activation of the **Parasympathetic Pelvic** nerve facilitates voiding by releasing AcetylCholine into **muscarinic** receptors on the detrusor cells that facilitate **contraction**

- Activation of the **Sympathetic Hypogastric** Nerve facilitates storage by releasing Nor-Epinephrine (Nor-Adrenaline) into α & β Receptors on the detrusor cells that induce **relaxation**.



So how is Mirabegron different??

All previous drugs for overactive bladder could be grouped under the term "antimuscarinics" (historically also termed 'anticholinergics'). They were all designed *to block the muscarinic receptors* in the bladder, thereby preventing the neurotransmitter Ach binding to smooth muscle cells. They worked by **stopping the detrusor contraction mechanisms.**

Mirabegron is a β3 adrenergic receptor (β3-AR) agonist. It improves the symptoms of OAB by instead *activating the ß3 receptors* thereby **facilitating the detrusor relaxation mechanisms**.

Is this clinically relevant???..... The Side Effect Profile

Probably the main difference is not going to be in the outcome for OAB symptoms. The main difference will be in the side effect profile. Any drug that alters the activation of sympathetic and parasympathetic nerves will often do so not just in the LUT, but in multiple areas of the body.

The Antimuscarinic Side Effects

The antimuscarinics worked by blocking parasympathetic muscarinic receptors. Parasympathetics normally also cause production of saliva, production of lubrication to the eye, colonic peristalsis etc

The side effects of antimuscarinics were therefore dry eyes, dry mouth, constipation, dizziness etc.

The β3-AR Agonist Side Effects

The β3 Agonists work by enhancing sympathetic actions. Therefore, the side effects will be enhancement of normal sympathetic mechanisms. These include increasing blood pressure, headache, nasopharyngitis (cold like symptoms such as runny nose etc), dizziness and nausea.

Main Clinical Relevance for Physiotherapists

There will soon be a new drug on the market for OAB. This new class of drugs will have different side effects and different precautions. They work via a very different mechanism to the anti-muscarinics. Being aware of this option is important when working with the multidisciplinary team and being able to support our patients in understanding all the options available to them to manage their urinary disorders.

NEXT PAGE..... QUICK SUMMARY OF THE MAIN POINTS ABOUT MIRABEGRON .....

Mirabegron – Summary

Public Name **Myrbetriq**

Company Astellas

Appearance: Tablet - oval
Light Brown / Yellow
Not scored (cannot be broken)
Astellas Logo and either "325" or "355" printed.

Dosage: 25mg / 50mg x 1 daily with or without food

1. start with 25mg and then increase to 50mg if needed
2. active ingredient is slow release so only once daily

Time to Full Benefit: ~8 weeks

Duration of Treatment Not curative (needs long term use)

Efficacy 3 x High Quality Randomised Controlled Trials

Contra-Indications None

Main Warnings Risk of increasing blood pressure in people with uncontrolled hypertension

Risk of urinary retention in patients with either bladder outlet obstruction or those already taking an Antimuscarinic.

Pregnancy / BF: There are no adequate studies at this time on Mirabegrons effects during pregnancy in humans. In animals there were no toxicities / adverse effects at 6x the standard 50mg equivalent dose. Bone changes and decreased fetal body weight were seen when levels 14-22x the standard dose were used.

No human trials. Mirabegron has been found in the milk of rats at concentrations twice that of maternal plasma levels. It is therefore predicted that Mirabegron is excreted in breastmilk and so not advised during BF.