



MIRTAZAPINE AND SLEEP

Sleep problems are common among older people in residential aged care. Older people without dementia spend less time on the restorative stages of sleep and more time in the lighter stages. These lighter stages are often interrupted by periods of wakefulness. Total sleep time decreases with normal ageing by about 27 minutes per decade from mid-life until the 8th decade. People with dementia including Alzheimer's disease, can have a reversal of normal sleep patterns, sleep fragmentation, poor sleep quality and shallow sleep.

A comprehensive review of underlying problems is necessary before medication therapy is considered. Conditions including sleep apnoea, nocturia, COPD, depression, anxiety, pain, gastro-oesophageal reflux (GORD) and restless legs syndrome all have a negative impact on sleep.

Medicines that can disrupt sleep can be identified by Residential Medication Management Reviews (RMMRs). These include beta-blockers, prednisone or prednisolone, SSRI antidepressants, venlafaxine, and diuretics, as well as caffeine and alcohol.

Non-drug strategies including sleep hygiene, cognitive behavioural therapy for insomnia (CBTi), relaxation techniques and behavioural interventions should always be first-line management. NPS MedicineWise website has lots of useful information of non-drug strategies including a sleep diary.

Medication therapy can be used for short-term management of insomnia, as an adjunct to non-drug treatment. They have limited benefit, making only small improvements in sleep latency (4 minutes) and sleep duration (60 minutes) when used for 14 days or less. Benzodiazepines (temazepam, oxazepam) may be considered for short-term use only (less than 2 weeks), as tolerance quickly develops. Dependence may lead to withdrawal symptoms. Long-acting benzodiazepines such as diazepam and nitrazepam should be avoided in older persons. Zopiclone (Imovane) and zolpidem (Stilnox) are also used for insomnia but are no more effective or safer than benzodiazepines. Adverse effects associated with the use of these medicines include confusion, memory and other cognitive impairment, falls, and incontinence.

Other options include melatonin, which may reduce sleep onset latency and improve sleep quality. Controlled-release melatonin (Circadin) in a dose of 2mg is administered 1 to 2 hours before bedtime for up to 13 weeks.

Suvorexant (Belsomra) may be effective in people who have difficulty staying asleep but is probably not useful for people with difficulty falling asleep. A 20mg dose is administered at night 30 minutes before bed with at least 7 hours remaining before planned awakening time.

Use of other medications which cause sedation are not recommended unless indicated for treating other coexisting conditions. These include sedating antihistamines, tricyclic antidepressants, antipsychotics (e.g., quetiapine) and mirtazapine.

Herbal medicines such as valerian, chamomile, catnip, lavender and Passiflora have limited evidence of benefit.

Mirtazapine

Mirtazapine (Avanza, Axit, Mirtanza, Milivin) is an antidepressant commonly used in aged care for depression where insomnia is a feature. Mirtazapine is approved for major depression including prevention of relapses. It is also effective for anxiety symptoms associated with depression. Mirtazapine may have an earlier onset of action for anxiety symptoms associated with major depression compared to paroxetine. SSRI antidepressants such as paroxetine may cause an initial transient increase in anxiety symptoms including agitation.

Mirtazapine is also used for prevention of tension-type headaches and itch in palliative care.

Product information recommends a starting dose for treatment of depression of 15mg/day, with usual maintenance dose of 30-45mg/day, and a maximum of 60mg daily. It is recommended to administer mirtazapine as a single night-time dose before going to bed.

The medication is available as a tablet in multiple strengths (15mg, 30mg, 45mg) and as an oral disintegrating tablet which may be useful for residents with swallowing problems.

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Actions

Mirtazapine is called a tetracyclic antidepressant, with a unique dual mode of action. Antidepressant efficacy is similar to other commonly prescribed antidepressants. However, individual responses may vary markedly with any antidepressant. Adding mirtazapine to other antidepressants does not improve efficacy but increases the risk of harm.

Mirtazapine has interesting actions, being sedating at low doses but not at higher doses. At lower doses, mirtazapine increases slow-wave sleep and decreases wakefulness; whereas, at higher doses rapid-eye-movement (REM) sleep is suppressed and slow-wave sleep increases.

At low doses (7.5 - 15mg daily) mirtazapine has an antihistamine effect, causing sedation. The sedating effect is most noticeable in the first few weeks of therapy, sometimes after as little as 2 days use, and often diminishes with time. However, at low doses mirtazapine may not be as effective for treating depression.

Mirtazapine's effects on sleep quality include:

- Shortened time-to-onset of sleep
- Reduced stage 1 sleep
- Increased deep sleep
- Increased latency of REM sleep
- Reduced night-time awakening
- Improved sleep continuity

These sleep-promoting effects need to be balanced against the risk of excessive sedation, and increased risk of falls and fractures.

At higher doses, the sedating effect is reduced, and in fact may be over-stimulating in older persons. For example, 45mg administered at bedtime may cause insomnia. Morning administration of higher doses is less likely to interfere with sleep. However, in doses exceeding 30mg daily, the benefits decrease, and risk of harm markedly increases.

Adverse effects

Common adverse effects such as increased appetite, weight gain, and sedation are often considered a benefit in frail older residents who lack appetite or have anorexia, with unexplained weight loss and for sleep problems. Mirtazapine has some anticholinergic activity so may cause a dry mouth.

Weight loss is a frequent symptom of depression. Compared to other antidepressants, mirtazapine has the greatest potential to cause weight gain.

It also has fewer sexual side effects compared with SSRI and SNRI (e.g., venlafaxine) antidepressants.

Other common adverse effects include weakness, dizziness and peripheral oedema.

Drug interactions

Serotonin toxicity can rarely occur in combination with SSRI antidepressants and venlafaxine.

Summary

Mirtazapine is an antidepressant with unusual dose-dependent effects on sleep. Mirtazapine may help residents fall asleep and improve their sleep architecture. Sedation may be excessive at low starting doses of 7.5mg daily, and therefore a higher starting dose of 15mg daily is suggested. At higher doses such as 30mg to 45mg daily, mirtazapine may interfere with sleep and should be administered as a morning dose. Use of mirtazapine for people with major depression with anxiety and/or insomnia has the potential to reduce polypharmacy.

References

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