Graylands Hospital
Drug Bulletin

Psychostimulants in Psychiatry

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Introduction

Psychostimulants – dexamphetamine, methylphenidate, and modafinil – reduce fatigue, promote alertness and wakefulness and have possible mood enhancing properties.[1] Currently these medications are indicated for attention deficit hyperactivity disorder (ADHD) and/or narcolepsy, however use in general psychiatry continues, particularly in the treatment of depression and fatigue.[1] Atomoxetine is a non-stimulant medication that is also indicated for the treatment of ADHD.

Despite the limited evidence to support their use in general psychiatry, some benefits have been seen in regards to treating a range of affective, cognitive and somatic symptoms.[1] Research into these areas continues, but currently there is not enough evidence to routinely recommend their use.[1]

Doctors who prescribe dexamphetamine and methylphenidate in Western Australia require a stimulant prescriber number, which can be obtained from the Department of Health. No such authorisation is required for prescribing modafinil and atomoxetine.

Pharmacology & kinetics

Dexamphetamine

Dexamphetamine is rapidly absorbed from the gastrointestinal tract and readily crosses the blood-brain barrier.[1] It produces central nervous system (CNS) stimulation by enhancing dopaminergic and noradrenergic neurotransmission and is indicated for the treatment of ADHD and narcolepsy.[2]

Dexamphetamine is immediate acting, having some effect within 30 minutes and a peak after 1 to 3 hours.[3]

Methylphenidate

Methylphenidate's mode of action is not completely understood,[4] but it is likely that that it stops the reuptake of noradrenaline and dopamine. It is indicated for the treatment of ADHD and narcolepsy.

Methylphenidate is available in immediate release tablets as well as long-acting capsules and tablets. The extended release tablets (Concerta®) release some drug rapidly, followed by slow release of the remaining medication over the next few hours. The long-acting capsules (Ritalin LA®) release the medication in two phases, producing two distinct peaks in concentration approximately four hours apart.[4]

When switching to a long-acting formulation, establish a daily dose using conventional tablets then convert this to the nearest strength of long-acting tablet or capsule.[2]

Modafinil

Modafinil is a non-amphetamine psychostimulant whose exact mode of action is unknown.[2] It is indicated for the treatment of narcolepsy and excessive sleepiness associated with shift work and in obstructive sleep apnoea as an adjunct to continuous positive airways pressure (CPAP).[2] It can be given as a once daily dose in the morning, or dosed twice daily in the morning and at noon.[4]

Modafinil may have less potential for misuse and dependence than amphetamine stimulants[2] but is not indicated for ADHD.

Atomoxetine

Atomoxetine is a noradrenaline reuptake inhibitor (NRI) indicated for the treatment of ADHD.[3] It is a non-stimulant medication, has low abuse potential and is not a controlled drug.[5]

Another NRI is licensed for use in Australia, reboxetine, but this is only indicated for the treatment of depression.

Atomoxetine is administered as a single daily dose in the morning.[5] However, if side effects are troublesome the patient may benefit from taking half their dose in the morning and the other half in the afternoon.[5]

Atomoxetine carries a warning regarding an increased risk of suicidal thoughts and behaviours in children. Patients started on atomoxetine must be closely monitored for suicidality.[4]

Dexamphetamine, methylphenidate, modafinil and atomoxetine can all cause insomnia if taken later in the day. If multiple daily dosing is required, ensure that no doses are taken in the late afternoon or evening as this may result in sleep disturbances.

Adverse effects

Common adverse effects of the psychostimulants include insomnia, agitation, anxiety and confusion.[1] These tend to be short-lived, however most evidence surrounding these adverse effects is related to children and adolescents who were being treated for

ADHD.[1] Information regarding adverse effects in adults and those treated for other conditions is limited.

Increased heart rate and blood pressure have been noted with psychostimulants, but they are typically described as mild, of short duration, and they usually respond to dosing and timing changes.[6]

The psychostimulants also have the potential to be misused, particularly dexamphetamine and methylphenidate which carry black box warnings in their product information relating to the potential for misuse.[4]

Table 1: Approved Australian indications for the psychostimulants[4]

Stimulant	Approved Australian Indication
Dexamphetamine	ADHD Narcolepsy
Methylphenidate	ADHD Narcolepsy
Atomoxetine	ADHD in people aged >6 years
Modafinil	Narcolepsy Excessive sleepiness associated with chronic shift work sleep disorder Adjunct to CPAP in obstructive sleep apnoea/ hypopnoea

Attention Deficit Hyperactivity Disorder

ADHD is characterised by inattention, impulsivity and hyperactivity.[7] Dexamphetamine and methylphenidate are first line treatment options for ADHD, and there is little evidence to suggest that one is better than the other.[3] If a patient does not respond to or is intolerant to one of these they may benefit from switching to the other agent.[3] Before switching to other alternative agents, dexamphetamine and methylphenidate should both be trialled by the patient.[3]

Atomoxetine is considered second-line treatment for ADHD. It should be used when psychostimulants are contraindicated, have resulted in adverse effects, and when there is a history of substance abuse or misuse, co-morbid motor tics or Tourette syndrome, or severe anxiety disorders.[3]

Narcolepsy

Narcolepsy is characterised by chronic daytime sleepiness, which may lead to sudden uncontrollable sleep attacks.[3] It is classically associated with disturbed nocturnal sleep and abnormal manifestations of rapid eye movement (REM) sleep–like behaviour during waking.[3]

Treatment of narcolepsy is symptomatic with dexamphetamine, methylphenidate and modafinil being first line treatment options.[3]

Modafinil has been studied in a double-blind, placebo-controlled trial and shown to be efficacious in the treatment of narcolepsy.[8] Dexamphetamine and methylphenidate may have better efficacy compared to modafinil[8] but also have a higher abuse potential.

Cataplexy is characterised by a sudden drop in muscle tone, and occurs commonly in patients with narcolepsy.[8] Cataplectic attacks can involve facial muscles, arms, legs, jaw dropping and unlocking of the knees.[8] Antidepressants, including selective serotonin reuptake inhibitors, tricyclic antidepressants, and serotonin and noradrenaline reuptake inhibitors have been used to treat cataplexy.[8] Psychostimulants have no effect on cataplexy.

Narcolepsy sufferers often have disrupted night-time sleep, as they are unable to stay awake or asleep for long periods.[8] Treatment of disturbed nocturnal sleep may be alleviated with benzodiazepines or related hypnotics (zolpidem, zopiclone), but the benefit of this must be balanced with the possibility of increasing daytime sleepiness.[8]

Major Depression

Psychostimulants have euphoric and alerting properties which could be beneficial when treating depressive disorders.[9] Whilst current antidepressants still remain treatment of choice, psychostimulants have some advantages over these including their short onset of action (within 24 hours), and that they reduce fatigue which can be problematic in some patients.[10] Issues with tolerance and dependence, as well as limited supporting data has meant their use in the treatment of depressive disorders is not widely used.[9]

There have been several reviews of psychostimulants used as monotherapy in the treatment of depression.[1] Most of these trials are more than 20 years old, and compare dexamphetamine and methylphenidate to older antidepressants such as imipramine and phenelzine.[1]

There have been no reports of manic switching when using dexamphetamine and methylphenidate for bipolar depression, however they must still be used with caution in bipolar affective disorder as amphetamine-like drugs and modafinil have been linked to a manic switch.[10]

A Cochrane review found no statistically significant difference in depression symptoms between modafinil and placebo.[11] There have been several case reports,

however, where improvement was noted when modafinil was used to augment other antidepressant agents.[12]

There are limited studies examining the long-term use of psychostimulants in the treatment of depression.

Schizophrenia

Cognitive dysfunction in schizophrenia is associated with impaired social and occupational function as well as deficits in executive functions including memory and planning.

There have been several studies focussing on cognition and functioning in patients with schizophrenia taking modafinil 100-200mg daily.[13] Most of these studies included patients with primarily negative symptoms. Improvements in executive functioning and day-to-day functioning were noted in a majority of the trials,[13] however one trial found no benefit of modafinil over placebo.[14] There have also been reports of modafinil exacerbating positive symptoms in some patients with schizophrenia, therefore modafinil should not be used in individuals experiencing such symptoms.[13]

Other stimulants

Caffeine

Caffeine is a very popular over-the-counter drug, which is also popular in many energy drinks. Caffeine's mode of action is now thought to be by antagonising neurotransmitters called purines at purine receptors.[15] Certain purines are functionally coupled with dopamine receptors. When caffeine binds to the purine receptors, it subsequently enhances dopaminergic actions in the CNS.[15]

Whilst there is no conclusive data that caffeine exacerbates mental illness, there are case reports of hospitalisation in patients with a psychiatric illness following large consumption of energy drinks.[16] Increased caffeine intake should be limited in patients with a history of mental illness.

Gamma hydroxybutyrate

Gamma hydroxybutyrate, also known as GHB or sodium oxybate, is an approved treatment for excessive daytime sleepiness and cataplexy associated with narcolepsy in some countries including the United States.[15] It promotes wakefulness due to its CNS depressant actions[17] on slow-wave sleep, making the patient more rested and therefore more alert the next day.[15]

The use of GHB in Australia is prohibited due to its abuse potential, and it remains an illicit drug. In the United states it is scheduled as a controlled substance and its supplies are tightly regulated.[15]

Conclusion

Clinical research is continuing into the use of psychostimulants in general psychiatry, but there is currently not enough evidence to recommend their routine use for these conditions.[1] Most of the trials have been short with very little maintenance and follow-up data.[1]

The evidence to date suggests that these agents could be considered for specific symptoms such as depression, fatigue and sleepiness in some mental health conditions, but should not be trialled until traditional agents have been ineffective or are contraindicated.[1]

Agomelatine (Valdoxan®)

Agomelatine is a novel antidepressant agent with melatonergic MT_1/MT_2 receptor agonist and serotonin 5-HT_{2C} receptor antagonist activity.[18] It is indicated for the treatment of major depressive disorder (MDD) in adults including the prevention of relapse. At the time of writing this bulletin it is not listed on the Pharmaceutical Benefits Scheme.

Mode of Action

Agomelatine is an antidepressant that is a powerful agonist of melatonin, whilst also having antagonistic properties at the 5-HT_{2C} receptor.[19] Melatonin is an endogenous synchronizer of biological rhythms in mammals. Its secretion and actions are tightly related to seasonal and light/dark cycles.[20] Agomelatine has shown to have an effect on resynchronization of circadian rhythms.[21]

The antidepressant effect is related both to activation of melatonin receptors and inhibition of 5-HT_{2C} receptors, and putatively to increased levels of extracellular noradrenaline and dopamine.[21]

Pharmacokinetics

Agomelatine is rapidly and well absorbed after oral administration, reaching a peak plasma concentration within 1 to 2 hours.[4] The absolute bioavailability is low (approximately 1%), and is highly variable due to the first pass effect and inter-individual differences in cytochrome (CYP) 1A2 activity. Bioavailability is also increased in women compared to men.[4]

Agomelatine is metabolised by CYP1A2 (90%) and CYP2C9/2C19 (10%), and the major metabolites are not pharmacologically active.[4] Agomelatine is contraindicated in people also taking potent CPY1A2 inhibitors such as fluvoxamine and ciprofloxacin.[4]

The mean half life is 1 to 2 hours, and excretion is mainly urinary and corresponds to metabolites.[4]

Efficacy

Placebo-controlled trials

There have been six, short-term, placebo-controlled trials involving 2605 patients evaluating antidepressant efficacy of agomelatine in the treatment of major depression.[18, 22-24] Four of these studies also included a reference selective serotonin reuptake inhibitor (paroxetine or fluoxetine) as an active control to assess assay sensitivity.[18]

Three of these trials, all of which were published, demonstrated an improvement in depressive symptoms after treatment with agomelatine when compared to placebo.[22-24]

Of the three unpublished trials, one trial showed no significant difference between agomelatine and placebo, and two trials were considered to be "failed" trials as the active control did not separate from placebo.[18]

Two relapse-prevention trials have provided varying information.[18] The first trial demonstrated no significant difference between relapse rates for agomelatine and placebo, whilst the second trial showed the incidence of relapse was significantly lower with agomelatine compared with placebo.[18, 25]

Active Comparator Trials

Agomelatine has been compared to venlafaxine, venlafaxine XR, sertraline and fluoxetine in active comparator trials.[18, 26]

A 6-week study comparing agomelatine 25-50mg/day and venlafaxine 75-150mg/day showed similar antidepressant efficacy between the two agents.[27] This study also reported that agomelatine improved sleep more than venlafaxine[27], but venlafaxine was taken twice daily and is known to cause insomnia when taken at night.

In a 12-week study, venlafaxine XR 150mg daily was compared to agomelatine 50mg at night.[28] Sexual functioning was the primary focus of this study, but effects on depression were also recorded. The results of this study indicate that agomelatine has a favourable sexual side effect profile in the treatment of major depressive disorder and has comparable antidepressant efficacy to venlafaxine XR. [28]

Agomelatine and sertraline were compared in a 6-week, randomised, double-blind study in patients with MDD.[29] The primary outcome was improvement in the circadian rest-activity cycle, while efficacy on depressive and anxiety symptoms was a secondary outcome. Agomelatine significantly improved sleep parameters in this study, but agomelatine and sertraline were both taken at night which is not recommended for sertraline.[29]

A randomised, double-blind, 8-week study compared agomelatine and fluoxetine for the treatment of MDD. This study showed a superiority of agomelatine 25-50mg/day versus fluoxetine 20-40mg/day.[26]

Adverse effects

In studies for agomelatine, the safety profile of agomelatine did not differ significantly from that of placebo, except for dizziness.[18] Preliminary findings also suggest that agomelatine does not affect bodyweight and sexual dysfunction occurs less frequently in agomelatine users compared to those taking venlafaxine and paroxetine.[18] Current available evidence also suggests that there are no significant cardiovascular concerns with agomelatine.[18]

It has been reported that agomelatine does not cause discontinuation symptoms upon abrupt withdrawal of the medication.[30] This was based on a study involving 88 patients who received agomelatine 25mg/day for 12 weeks and sustained remission.[30] 27 of these patients then discontinued agomelatine abruptly and were given placebo.[30] There was no statistically significant difference between the groups when evaluated for discontinuation symptoms.[30] This study used the lower dose range of 25mg/day, whilst the recommended dose in Australia is 25-50mg/day.

Dose

The recommended dose of agomelatine is 25mg taken orally at night, which may be increased after two weeks to 50mg at night if required.[4] It should be taken as a single dose at bedtime, and may be taken with or without food.[4] Agomelatine is available in 25mg tablets.

No dose adjustment is required in renal impairment, but agomelatine is contraindicated in patients with hepatic impairment. Even in mild hepatic impairment there is a significant increase in the half life and maximum plasma concentration.[4]

Conclusion

Evidence from clinical trials involving agomelatine indicates that it may be an effective treatment for MDD whilst also having a low adverse-effect burden. There have been differing results from the placebo-controlled trials, therefore further confirmatory information from studies would be beneficial.

This Drug Bulletin was written by Katie Walker and was reviewed by the Graylands Pharmacy Department and Dr Babu Mathew

References available on request

Comments are welcome at the email address: DrugInformation.Graylands@health.wa.gov.au