Graylands Hospital

DRUG BULLETIN

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Atomoxetine – how useful is it in the treatment of ADHD?

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- **Atomoxetine appears to show an improvement in the symptoms of attention deficit hyperactivity disorder (ADHD) compared to placebo and is generally well tolerated.**
- **There is no evidence that it has greater efficacy or a better safety profile than existing therapy for ADHD.**
- **It is difficult to establish its place amongst existing therapy for ADHD due to limited comparative data and lack of long-term safety and efficacy data.**
- **It does offer the advantage of being a non-stimulant medication and can be given once daily.**

Atomoxetine (Strattera®) is a nor-adrenaline reuptake inhibitor registered in Australia for the treatment of ADHD in children over 6 years and adults.

- It is a highly selective noradrenaline re-uptake inhibitor, with minimal affinity for and no functional activity at other receptors[1].
- Although noradrenaline abnormalities have been associated with the presentation of ADHD[2], the exact mechanism of action of atomoxetine is not known[1].
- It is the only non-stimulant medication available that is specifically indicated for ADHD.

Seven randomised, double blind, controlled trials in children, adolescents and adults have shown atomoxetine to improve symptoms of ADHD compared to placebo.

- All seven trials were funded by the manufacturer.
- The trials only ranged in length from three to twelve weeks. Further trials will be needed to assess atomoxetine's long term effectiveness.
- Four randomised, double blind, placebo-controlled trials were conducted to assess the efficacy of atomoxetine in children and adolescents, aged 6 to 17, with ADHD (n=171, n=297, n=147, n=144)[3,4,5,6]. In all four studies, atomoxetine showed significant improvement in ADHD symptoms compared to placebo.
- Three randomised, double blind, placebo controlled trials have been conducted in adults with ADHD (n=280, n=256, n=21)[7,8]. All three trials found statistically significant decreases in ADHD symptoms in patients on atomoxetine compared to placebo.
- However, an independent review of the evidence found that the placebo response in children, using the ADHD Rating Scale as the primary outcome, was high, ranging from 39 to 59%[9].

There is one trial suggesting it is as effective as methylphenidate, but there is no evidence as yet to suggest it is more effective or safer than current treatments.

- Although two of the manufacturer-funded studies randomised some patients to methylphenidate, the results of the methylphenidate group were not reported and no comparisons with atomoxetine were made.
- A separate trial comparing atomoxetine to methylphenidate (atomoxetine n=184, methylphenidate n=44), found preliminary evidence that atomoxetine's therapeutic

effects are comparable to those of methylphenidate[10].

It is a non-stimulant medication that may be less liable to abuse.

- A study has been conducted looking at the abuse potential of atomoxetine by comparing the effects of atomoxetine, placebo and methylphenidate in recreational drug users (n=16)[11].
- The results suggested that atomoxetine did not induce subjective effects, unlike methylphenidate, and that atomoxetine is therefore unlikely to have abuse liability.
- These findings are limited by the small sample size of the study.

As atomoxetine can be taken once or twice daily, children will not have to take medication to school.

- Although atomoxetine has a relatively short half life of approximately 4 hours (in most individuals), it can be administered once a day, or if preferred in divided doses[3,4].
- Atomoxetine is metabolised primarily via cytochrome P450 2D6 (CYP2D6). Approximately 5-10% of the population are poor metabolisers of this enzyme and may experience higher concentrations of atomoxetine and a longer half-life (around 21 hours), due to slower elimination. However, adjustment of atomoxetine dosage in these individuals is not necessary[1].
- Once a day dosing for ADHD medication is not unique to atomoxetine. There are long-acting formulations of methylphenidate available in Australia that can be given once daily.

The incidence of insomnia is no different from that of placebo in children and adolescents.

- Insomnia was reported more frequently with atomoxetine than with placebo in adults. Other adverse effects reported in adults included decreased appetite, dry mouth, nausea, constipation, decreased libido and sexual disturbances.
- Adverse events that were reported more frequently with atomoxetine than with placebo in children or adolescents included, decreased appetite, dizziness, vomiting, diarrhoea, abdominal pain and headache.

Increases in blood pressure are not listed as an adverse event in the product information.

- Although not listed in the product information, a trial found that atomoxetine was associated with small but significant increases in mean systolic blood pressure in adults (n=612) and diastolic blood pressure in children (n=169)[12]. Mean pulse rate in both groups was also increased[12]. The clinical significance of these results is not known.
- Care should be taken with any drugs to be given concomitantly, which may increase blood pressure or affect the cardiovascular system, such as beta- adrenergic receptor agonists (eg. salbutamol).

Atomoxetine can interact with antidepressant medications.

- Fluoxetine and paroxetine inhibit CYP2D6 and thereby can increase the plasma levels of atomoxetine.
- Tricyclic antidepressants, mirtazapine, venlafaxine and reboxetine affect nor-adrenaline levels, so should be used cautiously due to possible additive side effects.
- Atomoxetine use with monoamine oxidase inhibitors (MAOIs) or within 2 weeks of discontinuing MAOI therapy, is contraindicated.

No human studies to date have looked at atomoxetine in pregnancy or lactation.

- Atomoxetine is pregnancy category B3 – animal studies showed an increased occurrence of foetal damage.

Atomoxetine has been available in Australia since April 2004. It is not currently covered by the Pharmaceutical Benefits Scheme (PBS) and is only available by private prescription.

- Atomoxetine has not yet been assessed by the West Australian Drug Evaluation Panel, therefore it is not known whether it will be available on public hospital formularies.
- Atomoxetine was registered for use in the United States in late 2002, and has just been registered in the United Kingdom.

Presentation and Dosage

- Atomoxetine (Strattera®) is manufactured by Eli Lilly and is available as capsules only

in the following strengths: 10mg, 18mg, 25mg, 40mg and 60mg.

	STARTING DOSE	TARGET DAILY DOSE	MAXIMUM DAILY DOSE
Children/ adolescents under 70 kg	0.5 mg/kg/d	1.2 mg/kg/d	1.4 mg/kg/d or 100mg, whichever is less
Adults/ adolescents over 70 kg	40 mg/d	80 mg/d	100 mg/d

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Note: Atomoxetine was originally called tomoxetine, but was changed to avoid any confusion with the drug tamoxifen that may lead to errors.

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Antidepressant Induced Hyponatraemia

✪ Hyponatraemia has been reported in connection with <u>all</u> classes of psychotropic drugs (antipsychotics, antidepressants, lithium, other mood stabilisers and benzodiazepines). Of the various psychotropic agents, antidepressants and carbamazepine are the most frequently associated[1].

Mechanism

The syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) is thought to be the most likely mechanism for psychotropic-induced hyponatraemia and is generally characterised by decreased plasma osmolality and a high urine sodium level[2].

Symptoms

Hyponatraemia is arbitrarily defined as plasma sodium of <135mmol/L, however, symptoms may not develop until the sodium level is lower (generally <125mmol/L). Hyponatraemia may easily go undetected in psychiatric patients as symptoms may mimic those of depression or psychosis.

Mild hyponatraemia is frequently asymptomatic and early symptoms are vague and non-specific. Common symptoms include lethargy, fatigue, sleep disturbance, muscle cramps and headaches. This may progress as the hyponatraemia worsens to include nausea and vomiting, confusion, seizures, coma and ultimately death. The rate of fall in plasma sodium is more significant in producing the neurological symptoms than the absolute magnitude of the fall[2].

The incidence of hyponatraemia seems to be highest in the first few weeks of treatment and is currently not thought to be dose-related. Upon stopping the drug, most patients' serum sodium levels return to normal within days but can sometimes be delayed for weeks[2]. A few cases of successful selective serotonin reuptake inhibitor (SSRI)-rechallenge, and normalising of sodium concentration whilst continuing the drug indicate that hyponatraemia may sometimes be a transient effect, with tolerance developing over time[3].

Are all antidepressants implicated?

No antidepressant has been shown to not be associated with hyponatraemia and most have been implicated in the literature. Various post-marketing surveillance sources have found that SSRIs seem to have a stronger association than non-SSRIs (though this may be a reflection of their preferential use)[3,4].

A recent Australian bulletin by ADRAC (Adverse Drug Reactions Advisory Committee) concerning hyponatraemia, stated that as a group, the SSRIs accounted for about a quarter of all reports received and were second only to diuretics as the group most commonly associated with hyponatraemia[4]. The characteristics of these ADRAC reports mirrored those in the literature, suggesting risk factors for the development of hyponatraemia include those given in the table below. Symptoms such as agitation, delirium, hallucinations and behavioural changes also featured in the reports received by ADRAC.

The literature does not identify any clear differences between the various SSRIs and venlafaxine, in their propensity to cause hyponatraemia[5]. A small study (N=74), found hyponatraemia in more venlafaxine-treated patients than SSRI-treated patients[5], however larger studies would be required to confirm a difference in risk of hyponatraemia.

Risk Factors[3,4]

- Older age (>65yo)
- Female gender
- Low body weight
- Concomitant medications linked to hyponatraemia eg. diuretics (esp thiazides)
- Certain co-morbidities (eg. diabetes mellitus, renal damage, hypertension)

Hyponatraemia is not unique to elderly patients[3], however they certainly appear to be at increased risk. A study in elderly psychiatric patients found that patients treated with SSRIs or venlafaxine were 3.5 times more likely to develop hyponatraemia than those who did not receive those drugs (after controlling for confounding factors)[5].

A 12-week study of elderly patients treated for depression with paroxetine, found a 12% incidence of hyponatraemia. The risk for development of hyponatraemia was found to be highest in the first two weeks of treatment. The authors go on to recommend that monitoring of sodium levels be carried out at baseline and weeks 1 and 2 of therapy[6].

Management

Management of hyponatraemia should begin with prompt identification of potential causes. Further management is dependant on the degree of hyponatraemia and the rapidity at which it develops, and should be individualised to the patient and their condition.

Psychotropic drug-induced hyponatraemia and SIADH generally respond swiftly and completely to discontinuation of the offending drug[1]. Fluid restriction may be required and if hyponatraemia is severe (<125mmol/L), correction with saline is indiciated[1].

An algorithim for the recommended management of hyponatraemia has been suggested by Yeates et al, published recently in the Canadian Medical Association Journal[7].

Summary

Psychiatric patients appear to be at risk of hyponatraemia by virtue of their medications and the psychiatric disorder itself[2].

Periodic monitoring of electrolytes, though not routine in patients on antidepressants is advisable. Suggested intervals at baseline, 2 weeks and 4 weeks[5,6] should detect most cases, then perhaps quarterly thereafter, especially in patients at high risk.

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