The Medicine Cabinet: Atomoxetine.

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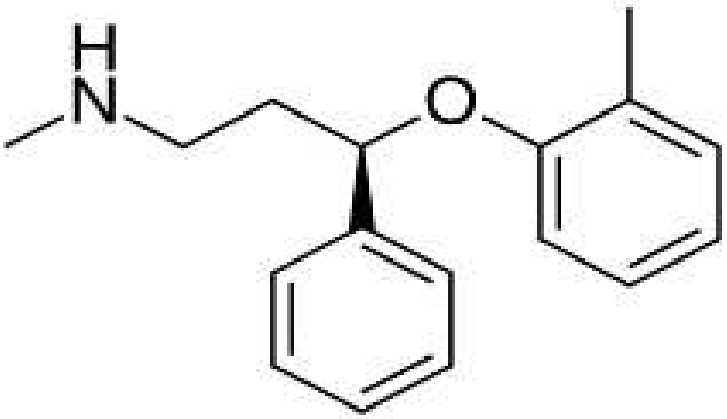
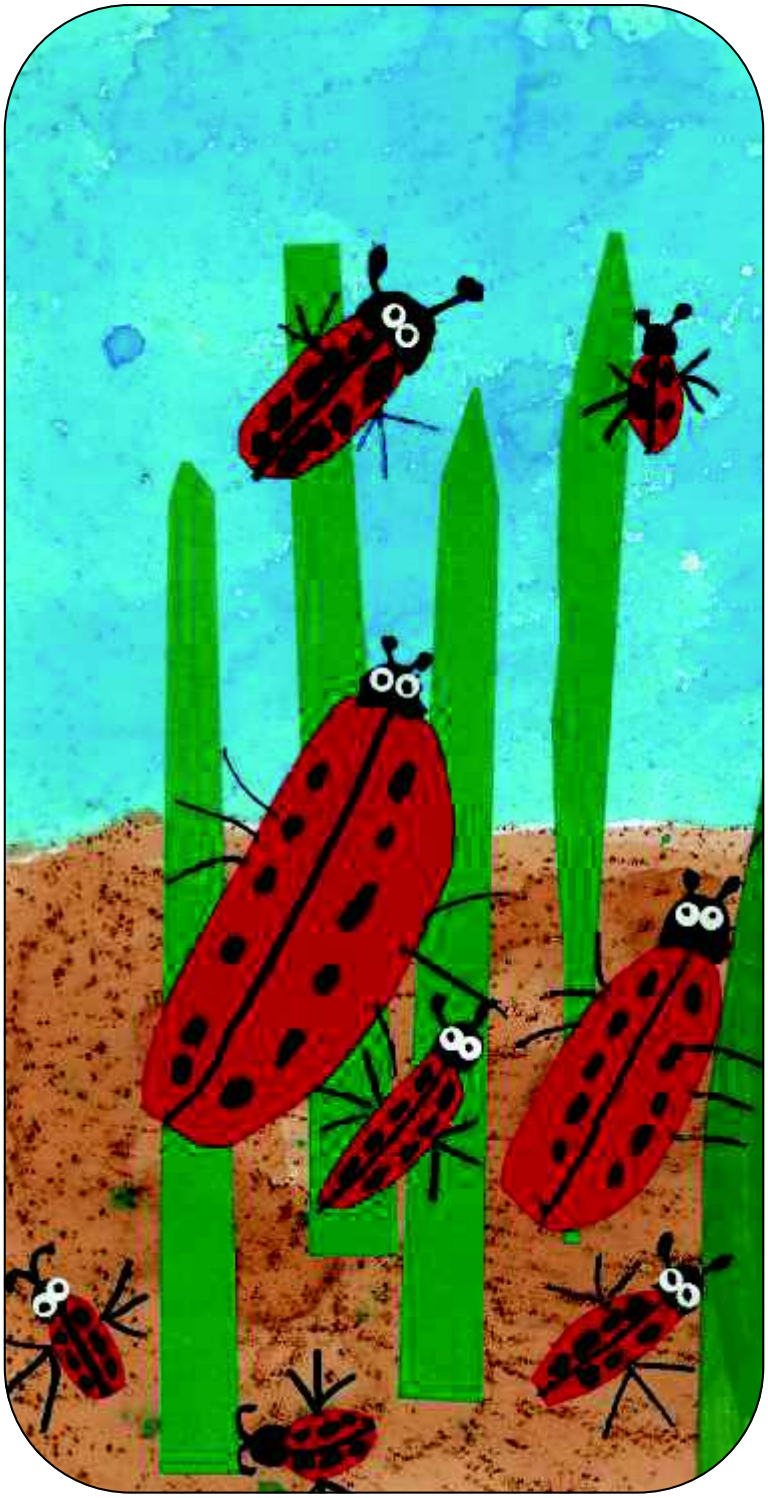


Atomoxetine was originally developed as an antidepressant (tomoxetine) by Eli Lilly in 1990s but not found to be very efficacious whilst undergoing phase III clinical trials for depression. As a noradrenaline (norepinephrine) reuptake inhibitor had potential in ADHD and thus further clinical trials were performed from 1996 and finally released onto the Australian market in 2004 under the brand name of Strattera® and now there are generic versions also available such as Atomoxetine Amneal®.

When treating ADHD the psychostimulants (dexamphetamine and methylphenidate) are the first line agents and then atomoxetine is considered.

Atomoxetine clinical trials have included children and adolescents as well as adults with ADHD and smaller number of case studies has been reported in the developmental disability populations.

Some studies suggest that it's because of dopamine and noradrenaline dysregulation in the prefrontal cortex activation that ADHD patients have poor response to cognitive tasks of attention and executive functioning. It has also been shown hypothetically that low to moderate levels of dopamine and noradrenaline stimulation lead to better working memory and to reinforce learning and reward conditioning. Deficient dopamine and noradrenaline input will theoretically lead to increased noise and decreased signal, thus preventing a coherent signal from being sent. Hypothetically this causes ADHD symptoms such as inattention, hyperactivity, impulsivity and in some a combination. Strengthening prefrontal cortical output is hypothesised to be beneficial in restoring patient's ability to tease out important signals from unimportant ones, and to manage to sit still and focus. Adding stress from environment can further affect the noise and signal leading to noradrenaline and dopamine release thus inefficient information processing. With chronicity this can lead to a difficulty in treating as the patients present with dopamine and noradrenaline depletion.



Atomoxetine is a selective noradrenaline reuptake inhibitor or selective NRI or NET inhibitor. The mechanism of therapeutic action in ADHD, since the prefrontal cortex lacks high concentrations of DAT (dopamine transporter) dopamine is inactivated in this part of the brain by NET (noradrenaline transporter) thus, inhibiting NET increases both dopamine and noradrenaline in prefrontal cortex. In ADHD patient with weak noradrenaline and dopamine signals in prefrontal cortex, atomoxetine increases both noradrenaline and dopamine in the prefrontal cortex. As there is no effect on the noradrenaline and dopamine levels in the nucleus accumbens there is no abuse potential.

“Adverse effects are mostly dose related but can include insomnia...”

Atomoxetine clinical trials enabled atomoxetine to be licensed for use in children over the age of 6 years. Atomoxetine is available in Australia in 18mg, 25mg, 40mg, 60mg and 80mg capsules. It has a slow onset of action and response can take up to 4 weeks and the dose needs to be titrated slowly to minimise adverse effects and to see full optimization of the drug. It is not a controlled substance so unlike the psychostimulants has not shown any potential for abuse. Care should be taken in prescribing for poor metabolisers of CYP450 2D6 about 10% of the population as there could be increase in the adverse effects and only require a smaller dose as well as when given concurrently with fluoxetine or paroxetine – potent inhibitors of CYP450 2D6.

Adverse effects are mostly dose related but can include insomnia so taking the dose in the morning can help with this, dizziness and this can be helped by slowly getting up from a lying position or taking the dose at night when drug levels are highest. Others include fatigue and headache and these can be helped by again taking the atomoxetine at night or reducing the dose. Emotional inability and suicidal ideation have also been reported in the clinical trials and these should be reported back to the prescribing team. Atomoxetine as a raw product is known to be a gastric irritant so there is also upper abdominal pain reported as well as nausea, vomiting and even anorexia. As drug levels are not affected by food taking the dose with food or after food may help reduce these adverse effects. As there can be small increases in heart rate and blood pressure in the beginning of therapy these might be monitored by the prescriber and if one experiences a racing heart rate then the dose might be adjusted. Dry mouth, constipation and urinary retention as well as dilating of the pupils of the eyes have also been reported.

Serious life threatening liver damage problems with elevated live function blood tests such as ALT and bilirubin have also been reported in small number of patients. The raised bilirubin causing jaundice will normalise once atomoxetine is ceased. The liver injury/damage may occur several months after initiation and persist for awhile after discontinuation. There is also a

warning about increased risk of suicidal ideation with atomoxetine and thus increased monitoring should be done in the initial stages of therapy.

Summary of trials in ASD populations

The general population trials published in 2004 were for acute treatment (9weeks) and long term (2 years) treatment for ADHD. There have not been the clinical trials in the younger age group or patients with comorbidities.

In a review by Fung et al in the journal, Pediatrics, the authors looked at irritable behaviour as measured by Aberrant Behavioral Checklist –Irritability (ABC-I) in various clinical trials and concluded for atomoxetine showed no significant difference from placebo for irritability but effect improvements in hyperactivity and impulsivity when measured on Aberrant Behavioural Checklist –Hyperactivity. (1). Irritable behaviour was defined as an excessive response to stimuli and also a consequence of emotional dysregulation. The atomoxetine study patients also had lower baseline scores for ABC-I when compared to other trial participants.

A larger study of nearly 100 children by Harfterkamp et al looked at the effect of atomoxetine on stereotyped behaviours and communication after small scale trials should some positive effect in ameliorating symptoms of ADHD in ASD patients. (2) When looking at the Children's Social Behaviour Questionnaire (CSBQ) subscale for fear of change there were better effects with atomoxetine than placebo but no beneficial effects of atomoxetine on social functioning after 8 weeks of treatment. When this study was continued as open label extension for a further 28 weeks, the adverse effects of atomoxetine subsided and there was continued improvement in ADHD symptoms in children and adolescents with ASD. With some patients with ASD improvements take more time even up to half a year longer than in typical ADHD before the full response to atomoxetine has been established. (3)

The original small studies for atomoxetine in ASD patients found some effect in ameliorating the effects of ADHD in children and adolescents especially in core symptoms of ASD and social functioning.(2)

Problems with taking atomoxetine

Atomoxetine capsules cannot be opened as the contents can be irritant to the eyes. There is NO commercial liquid preparation so if unable to swallow capsules, atomoxetine use should be reconsidered. Food does not affect the absorption so can be taken with or without food but as it can cause gastric upsets giving with or after food helps to minimise stomach ache, nausea and vomiting.

Tips

Atomoxetine therapeutic action may continue to improve for 8-12 weeks and onset of therapeutic action can be seen as early as first day of dosing but is not working within 6-8 weeks then it may not work at all. The actions of noradrenaline on acetylcholine can cause decreased appetite, increased heart rate and blood pressure, dry mouth as well as urinary retention. Most side effects are immediate and often decrease with time. Although original trials were twice daily dosing efficacy has been for single daily morning dose. Unlike other medications used for ADHD atomoxetine does not have the abuse potential or have the ability to be diverted.

Atomoxetine should also be used with caution with patient with known cardiac disease due to its ability to increase blood pressure and heart rate. Monitoring should occur for cardiac parameters as well as liver and other physical health measures such as weight and height.

References

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For further information on atomoxetine:

1. www.nps.org.au