Traffic light classification - Amber 1

Information sheet for Primary Care Prescribers

Indications
Attention Deficit Hyperactivity Disorder (ADHD) in children of 6 years and older and in adolescents as part of a comprehensive treatment program. – licensed¹

Any patient groups to be excluded from shared care
Patients > 18 years old – classified as Red in Nottinghamshire.
Children < 6 years old – unlicensed¹ and not recommended by NICE² – classified as Red in Nottinghamshire.

Therapeutic Summary
Atomoxetine is a treatment option recommended by NICE for the management of ADHD in children and young people². It may be considered for children with evidence of significant tic exacerbation that has been associated with methylphenidate. It may also be considered if methylphenidate had been ineffective or poorly tolerated, or if there were specific concerns of potential diversion and/or misuse of methylphenidate and when a non-stimulant drug is preferred. Unlike methylphenidate, response to atomoxetine occurs gradually over 6-8 weeks. Family need to be advised about this and supported during this time.

Atomoxetine is a noradrenaline reuptake inhibitor, although the precise mechanism by which it works on ADHD is unknown. It is thought to increase brain levels of noradrenaline and dopamine, predominantly in the cortex rather than in sub-cortical regions.

Following titration and dose stabilisation, prescribing and monitoring should be carried out under locally agreed shared care arrangements with primary care².

Medicines Initiation
Treatment with atomoxetine should only be initiated by a specialist (child and adolescent psychiatrist or paediatrician) with expertise in ADHD following a comprehensive assessment and diagnosis.² GPs may continue prescribing and monitoring drug treatment under shared care arrangements².

Products available
Atomoxetine (Strattera®) capsules – 10mg, 18mg, 25mg, 40mg, 60mg, 80mg or 100mg. Cost³:
10mg, 18mg, 25mg, 40mg, 60mg capsules x28 = £62.46, 80mg, 100mg capsules x28 = £83.28.
As the unit cost of a dose of atomoxetine (except 80mg and 100mg capsule) is the same regardless of strength, twice daily dosing could double the cost of treatment with this drug. Atomoxetine capsules are not intended to be opened. Atomoxetine is an ocular irritant¹.

Dosages and route of administration
Atomoxetine is given orally (with or without food), usually as a single daily dose in the morning, or in two divided doses (with the last dose no later than early evening) to minimize side-effects². The initial dose and subsequent dosing will be determined by the specialist and stated in written communication. The usual starting dose in children aged 6 years and older is determined by the patient’s actual body weight (see below). The dose is increased to a maintenance dose by the specialist.
Up to 70kg body weight: total starting dose of 0.5mg/kg/day, increased after 7 days to 1.2mg/kg/day\(^2\).

Over 70kg body weight: total starting dose of 40mg/day, increased after 7 days up to a maintenance dose of 80mg/day\(^2\). The usual target therapeutic dose is 1.2 mg/kg/day.

Increasing the dose of atomoxetine to 1.8mg/kg/day (max. 120mg/day) may occasionally be undertaken by a specialist in cases of poor response to drug treatment. Doses above 100mg/day are unlicensed and patients should be closely monitored for side-effects during the titration period\(^1,2,3\).

Duration of treatment
Following an adequate treatment response, drug treatment for ADHD should be continued for as long as it remains clinically effective. This should be reviewed every 6-12 months by the specialist.\(^2\)

In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood\(^2\). However, this scenario is not covered by the existing shared care protocol (RED classification) and arrangements will need to be made for patients approaching their 18\(^{th}\) birthday to be referred back to their specialist in plenty of time to ensure continuity of on-going care by a specialist.

Monitoring Requirements and Responsibilities
Pre-treatment assessment to be performed by specialist and will include: Behavioural rating scales (e.g. SDQ, Conners’) and descriptive reports from parents and teachers, medical history, physical examination (including height and weight) and evaluation of cardiovascular status (including heart rate, blood pressure) as a baseline.

Ongoing monitoring – monitoring will be performed monthly by the specialist for the first 3 months. Further physical monitoring will be performed by primary care (see below) and the results sent to the specialist for recording in the patients notes. Ongoing psychological response and assessment of continued need for atomoxetine will be performed by the specialist at 3 months and 6 months and then every 6-12 months.

If the child / young person fails to attend for physical monitoring, do not issue any further prescriptions, contact the patient/carer and inform the specialist.

<table>
<thead>
<tr>
<th>Ongoing monitoring(^2)</th>
<th>Frequency(^2)</th>
</tr>
</thead>
</table>
| Heart Rate and Blood Pressure | Three monthly.  
Also before and after each dose change.  
Compare with previous measurements.  
Blood pressure centile reference tables\(^6\) for children and young people (age/sex) are available within the Nottingham University Hospitals Children’s Hospital Hypertension Guidelines (Sep 2013).  
Most patients taking atomoxetine experience a modest increase in heart rate (mean <10bpm) and/or increase in blood pressure (mean <5mmHg).\(^1\)  
Approximately 8-12% of under 18’s experience more pronounced changes in heart rate (≥20bpm) or blood pressure (≥15-20mmHg) . Of these, 15-32% had sustained or progressive increases.\(^1\) |
| Weight | Following initiation, at three months and six months, |
then every 6 months. Plot on a growth chart (link: http://www.rcpch.ac.uk/growthcharts).

<table>
<thead>
<tr>
<th>Height</th>
<th>Six monthly. Plot on a growth chart.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug related side-effects*</td>
<td>At each visit</td>
</tr>
<tr>
<td>ECG, LFTs, FBC</td>
<td>Not recommended unless there is a clinical indication.</td>
</tr>
</tbody>
</table>

*Consider using standard symptom and side effect rating scales during treatment as an adjunct to clinical assessment.

**Explicit criteria for review and/or discontinuation of atomoxetine**

<table>
<thead>
<tr>
<th>Sustained resting tachycardia</th>
<th>Withhold or reduce dose and discuss with specialist team, with prompt cardiology input if necessary.</th>
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</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Withhold or reduce dose and discuss with specialist team, with prompt cardiology input if necessary.</td>
</tr>
<tr>
<td>Exertional chest pain, unexplained syncope or dyspnoea</td>
<td>Withhold or reduce dose and discuss with specialist team, with prompt cardiology input if necessary.</td>
</tr>
<tr>
<td>Systolic blood pressure &gt;95th percentile (or clinically significant increase)</td>
<td>Withhold or reduce dose and discuss with specialist team, with cardiology input if necessary.</td>
</tr>
<tr>
<td>Failure to attend for physical monitoring checks</td>
<td>Do not issue further prescriptions, discuss as soon as possible with specialist.</td>
</tr>
<tr>
<td>Erectile or ejaculatory dysfunction</td>
<td>Possible side-effect of atomoxetine discuss with specialist team.</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>Possible side-effect of atomoxetine discuss with specialist team.</td>
</tr>
<tr>
<td>Abdominal pain, unexplained nausea, malaise, or darkening of the urine</td>
<td>Withhold and discuss with specialist team. Consider rare possibility of liver injury from atomoxetine. Check LFTs.</td>
</tr>
<tr>
<td>Jaundice or laboratory evidence of liver injury</td>
<td>Discontinue and discuss with specialist team. Atomoxetine should not be restarted.</td>
</tr>
<tr>
<td>Urinary retention/hesitancy</td>
<td>Discuss with specialist team.</td>
</tr>
<tr>
<td>Agitation, irritability, aggressive behaviour, psychotic or manic symptoms, suicidal thinking, suicide attempt or self-harm</td>
<td>Discuss with specialist team and consider discontinuation.</td>
</tr>
<tr>
<td>Seizures in patients with no previous history</td>
<td>Withhold and discuss with specialist team.</td>
</tr>
<tr>
<td>Increase in seizure activity in patients with previous history of seizures</td>
<td>Discuss with specialist team immediately.</td>
</tr>
</tbody>
</table>

For a full list of Side Effects refer to the BNF/cBNF or Summary of Product Characteristics (SPC).

**IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE SPECIALIST TEAM.**

European guidelines on managing adverse effects of medication for ADHD were published in 2011. These provide additional guidance for clinicians.

**Relevant Contraindications**
Atomoxetine should not be used in patients with severe cardiovascular or cerebrovascular disorders whose condition would be expected to deteriorate if they experienced an increase in blood pressure or heart rate that could be clinically important (e.g. 15-20mmHg or 20bpm). This could include severe hypertension, heart failure, angina, myocardial infarction, cardiomyopathies, arrhythmias, cerebral aneurysm or stroke (see SPC).

Monoamine Oxidase Inhibitors (MAOIs) - Atomoxetine should not be used in combination with MAOIs or within a minimum of 2 weeks after discontinuing therapy with a MAOI. Treatment with a MAOI should not be initiated within 2 weeks after discontinuing atomoxetine.

Patients with narrow-angle glaucoma. In clinical trials the use of atomoxetine was associated with an increased incidence of mydriasis.

Patients with phaeochromocytoma or a history of phaeochromocytoma.

Relevant Precautions
Particular caution is needed in the following groups of patients:
- Patients with hypertension, tachycardia, cardiovascular or cerebrovascular disease, including those with congenital or acquired long QT or a family history of QT prolongation (but see contraindications above).
- Patients with a history of psychosis, depression and/or suicidal behavior.
- In patients with moderate and severe hepatic insufficiency the dose should be reduced to 50% and 25% of the usual dose respectively.
- Patients with a history of seizures.

Pregnancy and Breast-Feeding
There is limited experience of atomoxetine in pregnancy. It should be avoided in pregnancy unless potential benefit outweighs risk. If appropriate, female patients should be advised to use effective contraception during treatment with atomoxetine. In the event of a patient becoming pregnant whilst taking atomoxetine, or wishing to start a family, she should be advised to contact the specialist as soon as possible.

Atomoxetine should be avoided in breast-feeding. Discuss with specialist team.

Clinically Relevant Medicine Interactions and their Management
- Atomoxetine should not be used in combination with, or within 2 weeks of stopping an MAOI.
- Atomoxetine is metabolised by CYP2D6. Slower titration and lower final dosage of atomoxetine may be necessary in patients taking CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, terbinafine).
- Atomoxetine should be used cautiously with antihypertensive drugs as it may increase blood pressure.
- Potential for increased risk of QT interval prolongation when given with other QT prolonging drugs (e.g. neuroleptics, tricyclics, methadone, erythromycin) or in presence of electrolyte imbalance.
- Amiodarone / sotalol - increased risk of ventricular arrhythmias when atomoxetine given with amiodarone / sotalol.
- Potential risk of seizures with other drugs known to lower seizure threshold (e.g. antidepressants, neuroleptics, mefloquine, bupropion, or tramadol).
- Potential additive pharmacological effects with other noradrenergic drugs (e.g. tricyclics, venlafaxine).

For a full list of contraindications, precautions and drug interactions refer to the SPC.
Information Given to Patient / Carer

- The specialist will provide relevant, age-appropriate written information to people with ADHD and their families and carers about diagnosis, assessment, support groups, self-help, psychological treatment, drug treatment and possible side-effects.
- The patient / carer must be warned to report immediately any abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice, or suicidal thinking and self-harm to the GP.\(^2,3\)

Patient / Carer's Roles and Responsibilities

- The patient / carer will report any suspected adverse reactions to the GP for assessment.
- The patient / carer will report to their GP or specialist any new onset nausea, vomiting, abdominal discomfort, dark urine and jaundice as these could be adverse effects of atomoxetine.
- The patient / carer will report to their GP or specialist signs of clinical worsening, suicidal thoughts or self-harming behaviour, irritability, psychotic symptoms, agitation, or depression as these can be adverse effects of atomoxetine.
- The patient / carer will attend all follow-up appointments with GP and specialist. If they are unable to attend any appointments they should inform the relevant practitioner as soon as possible and arrange an alternative appointment.

Pharmacist Roles and Responsibilities

Pharmacists are well placed to stress the value of a balanced diet, good nutrition and regular exercise for all patients with ADHD. Pharmacists can offer support to help improve treatment adherence in people with ADHD. Pharmacists can explain that atomoxetine (unlike methylphenidate) has a much slower onset of action and may take some 6-8 weeks to become fully effective.

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References

1. Strattera 10mg, 18mg, 25mg, 40mg, 60mg, 80mg or 100mg hard capsules – Eli Lilly and Company Ltd. Summary of Product Characteristics [19/12/13] on Electronic Medicines Compendium: (accessed on 18/3/15) via [www.medicines.org.uk](http://www.medicines.org.uk/)