Atomoxetine for ADHD Children and Young People

Part of the shared care protocol for ADHD in Children and Young People
Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers

Indications

Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 to 17 who are under the care of a specialist (Consultant Psychiatrist, Community Pediatrician or Non-Medical Prescriber specializing in ADHD) as part of a comprehensive treatment program[1] – licensed.

Any patient groups to be excluded from this shared care:

Patients ≥ 18 years old – see separate Nottinghamshire APC shared care protocol and medication information sheets for adult ADHD
Children < 6 years old – unlicensed and not recommended by NICE

Therapeutic Summary

Atomoxetine is a treatment option recommended by NICE for the management of ADHD in children and young people[2]. 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 care[2].

Medicines Initiation

Treatment with atomoxetine should only be initiated by a specialist with expertise in ADHD following a comprehensive assessment and diagnosis[2]. It may be considered for children aged 5 years and over and young people if:

- They cannot tolerate methylphenidate or lisdexamfetamine
- Neurodevelopmental disorders
- Mental health conditions
- Physical health conditions

Use in combination with methylphenidate or lisdexamfetamine is felt to be clinically appropriate.

GPs may continue prescribing and monitoring medication treatment under shared care arrangements[2].

Products available

Atomoxetine capsules – 10mg, 18mg, 25mg, 40mg, 60mg, 80mg or 100mg. 10mg, 18mg, 25mg, 40mg, 60mg capsules x28 = £53.09, 80mg, 100mg capsules x28 = £70.79[3].

Atomoxetine (Strattera®) liquid – 4mg/mL. Cost x 300mL bottle = £85.00. This is restricted to patients that are unable to swallow capsules.

As the unit cost of a dose of atomoxetine (except 80mg and 100mg capsule) is approximately the same regardless of strength, twice daily dosing could double the cost of treatment with this medication.

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-effects[2]. 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 medication treatment. Doses above 100mg/day are unlicensed and patients should be closely monitored for side-effects during the titration period[1,2,3].

Dosage may be altered by specialists to reflect the child's current physical condition, symptoms or social demands. The patient should require no extra monitoring than already described in this guidance if dosage is adjusted by the specialist in this way.

As a child grows, the dose of atomoxetine will need to be amended to ensure the treatment remains at steady state. A patient's weight and height should be monitored as described under "Ongoing monitoring", and dosage may be increased if required as per the section above; "dosage and route of administration".

Increases in medication dose due to growth of the patient should be viewed as a patient's treatment being "stable".

Where a patient has been switched between medications (i.e. methylphenidate to atomoxetine or vice-versa) further monitoring may be required, as per specialist instruction.

Duration of treatment
Following an adequate treatment response, medication treatment for ADHD should be continued for as long as it remains clinically effective. This should be reviewed at least annually 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]. It is the specialist's responsibility to transfer care to the appropriate adult service if ADHD treatment is deemed appropriate to continue into adulthood. See the Nottinghamshire Area Prescribing Committee shared care protocol and medication information sheets for adult ADHD at: https://www.nottsapc.nhs.uk/shared-care/.

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.

LFTs may occasionally be needed to be checked prior to starting and only in children with a known history of liver disease.

Ongoing monitoring – monitoring will be performed by the specialist within 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 at least annually.

If the child / young person fails to attend for physical monitoring, despite attempts to re-appoint, do not issue any further prescriptions, contact the patient/carer and inform the specialist. The patient should be informed of this policy when treatment begins.

Ongoing monitoring[2]	**Frequency[2]**
Heart Rate and Blood Pressure	Six monthly. Also before and after each dose change (note that increases in dose due to growth should be viewed as a patient being "stable" on their treatment, and should require no extra monitoring). Compare with previous measurements. Information on blood pressure and heart rate monitoring in children (including centile reference tables) is available on the Nottinghamshire Area Prescribing Committee website.[6] 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 3 months in children 10 years and under. • Every 6 months in children over 10 years and young people Plot on a growth chart (link: http://www.rcpch.ac.uk/growthcharts). If weight loss or reduced weight gain this should be discussed with the specialist.
Height	Six monthly. Plot on a growth chart. If growth is affected significantly this should be discussed with the specialist
Medication related side-effects*	At each visit
ECG, LFTs, FBC	Not recommended unless there is a clinical indication.

*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[2]

Sustained resting tachycardia	Withhold or reduce dose and discuss with specialist team, with prompt cardiology input if necessary.
Arrhythmia	Withhold or reduce dose and discuss with specialist team, with prompt cardiology input if necessary.
Exertional chest pain, unexplained syncope or dyspnoea	Withhold or reduce dose and discuss with specialist team, with prompt cardiology input if necessary.
Systolic blood pressure >95th percentile (or clinically significant increase) Take three measurements (with appropriate cuff) within 10 minutes, patient at rest	Withhold or reduce dose and discuss with specialist team, with cardiology input if necessary.
Failure to attend for physical monitoring checks	Do not issue further prescriptions, discuss as soon as possible with specialist.
Erectile or ejaculatory dysfunction	Possible side-effect of atomoxetine discuss with specialist team.
Dysmenorrhoea	Possible side-effect of atomoxetine discuss with specialist team.
Abdominal pain, unexplained nausea, malaise, or darkening of the urine	Withhold and discuss with specialist team. Consider rare possibility of liver injury from atomoxetine. Check LFTs.
Jaundice or laboratory evidence of liver injury	Discontinue and discuss with specialist team. Atomoxetine should not be restarted[1].
Urinary retention/hesitancy	Discuss with specialist team.
Agitation, irritability, aggressive behaviour, psychotic or manic symptoms, suicidal thinking, suicide attempt or self-harm	Discuss with specialist team and consider discontinuation.
Seizures in patients with no previous history	Withhold and discuss with specialist team.
Increase in seizure activity in patients with previous history of seizures	Discuss with specialist team immediately.

For a full list of Side Effects refer to the BNF/BNFC or Summary of Product Characteristics (SPC)[1].

Atomoxetine capsules are not intended to be opened. Atomoxetine is an ocular irritant[1].

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[5].

Relevant Contraindications[1]

- Hypersensitivity to the active substance or to any of the excipients
- 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[1,3].

If appropriate, female patients should be advised to use effective contraception during treatment with atomoxetine. In the event of a female 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; it is not known whether atomoxetine is excreted in human milk[1].

Clinically Relevant Medicine Interactions and their Management[1,3]
- Monoamine Oxidase Inhibitors (MAOIs) including isocarboxazid, moclobemide, phenelzine and tranylcypromine – atomoxetine should not be used in combination with MAOIs or within 2 weeks of stopping a MAOI due to risk of hypertensive crisis.
- Atomoxetine is metabolised by the CYP2D6 pathway. 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 medicines as it may increase blood pressure and therefore decrease the effectiveness of antihypertensive drugs.
- Potential for increased risk of QT interval prolongation when given with other QT prolonging medicines (e.g. neuroleptics, tricyclics, methadone, erythromycin) or in presence of electrolyte imbalance.
- Potential risk of seizures with other medicines known to lower seizure threshold (e.g. TCAs, neuroleptics, mefloquine, bupropion and tramadol).
- Potential additive pharmacological effects with other noradrenergic medicines (e.g. TCAs, venlafaxine, mirtazapine and decongestants such as pseudoephedrine).

For a full list of contraindications, precautions and medication interactions refer to the SPC[1].

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, medication treatment and possible side-effects.
- The patient must be warned to report immediately any abdominal pain, unexplained nausea, malaise, darkening of the urine, jaundice, or suicidal thinking and self-harm to the GP[2,3].
- An information leaflet for parents and carers is available from Medicines for Children.

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.

References

1. Strattera 10mg, 18mg, 25mg, 40mg, 60mg, 80mg or 100mg hard capsules – Eli Lilly and Company Ltd. Summary of Product Characteristics [07/05/15] on Electronic Medicines Compendium: (accessed on 02.12.2019) via www.medicines.org.uk/

2. Attention deficit hyperactivity disorder: Diagnosis and management. NICE Clinical Guideline 87 (March 2018). Available: http://www.nice.co.uk/guidance/ng87

3. BNFc Online, Available from https://www.medicinescomplete.com, accessed [02.12.19]

4. The Electronic Drug Tariff. Available from http://www.ppa.org.uk/ppa/edt_intro.htm [accessed 02.12.19].

5. Graham J et al. European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry (2011), 20:17-37. On-line at: http://www.springerlink.com/content/y667034856017253/fulltext.pdf

6. Nottinghamshire Area Prescribing Committee. September 2020. Blood pressure and heart rate monitoring in children. Information Sheet for Primary Care Prescribers. Available from https://www.nottsapc.nhs.uk/media/1627/bp_and_hr_monitoring_for_children.pdf.

Version Control - **Children and Young people ADHD - Atomoxetine Information Sheet**			
Version	Author(s)	Date	Changes
1.1	Hannah Godden, Mental Health Interface and Efficiencies Pharmacist, Nottingham and Nottinghamshire CCGs/ Nottinghamshire Healthcare NHS Foundation Trust	April 2021 (interim update)	-Added standard header & version control -Added link to Notts APC guideline on blood pressure and heart rate monitoring in children -Removed link to NUH guideline

			on blood pressure monitoring in children -Updated information about transition of care and Notts APC adult ADHD shared care protocol -Updated wording of pregnancy&breastfeeding and interactions sections in line with adult information sheet
1.0	Professor Chris Hollis, Dr Barbara Houghton, Dr Val Teung, John Lawton (Nottinghamshire Healthcare NHS Foundation Trust) Dr Jane Williams, Dr Rosemary Gradwell, Dr Katherine Martin, Dr Amy Taylor (Community Paediatrics, Nottingham University Hospitals) Dr Esther Corker, Dr Mike Farrall (Community Paediatrics, Sherwood Forest Hospitals) Nick Sherwood, Mental Health Interface and Efficiencies Pharmacist, Nottinghamshire CCGs/ Nottinghamshire Healthcare NHS Foundation Trust	December 2019	