Therapeutics Advisory Group

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Norfolk and Waveney Integrated Care System

NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT FRAMEWORK

Shared care guidelines for Atomoxetine for Attention Deficit Hyperactivity Disorder (ADHD) in Children & Young People aged at least 6 years old

Monitoring level 3 - Prescribe the drug and perform significant monitoring including measurements such as height, weight, blood pressure and ECG.

Generic and Proprietary/Brand Name

- Atomoxetine capsules
- Atomoxetine 4mg/ml oral solution sugar free - Strattera®

Indications for shared care

Atomoxetine is indicated for the treatment of ADHD in children and adolescents 6 years of age and older (according to DSM-5 or ICD-11 diagnosis).

Although NICE guidance (NG87)[1] recommends that children may treated from age 5 years, the licensed age range stands regarding the scope of this shared care prescribing agreement. This is a TAG recommendation since local GPs may not currently refer such young children to the specialist service, and medications would be off-label.

Specialist Prescribing and Monitoring Responsibilities	GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities
Prescribing responsibilities: Initiation, dose titration and stabilisation on medication for at least two consecutive consultations with no change in dose. **Specialist monitoring**: Monitoring at baseline, during initiation & following dose adjustments is the responsibility of the specialist**:** • **Height** and **weight** should be monitored and plotted on a growth chart. • Monitoring of **heart rate** and **blood pressure**; to be compared with the normal range for age before and after each dose change. Additional monitoring: • Monitor young people with ADHD for sexual dysfunction (that is, erectile and ejaculatory dysfunction) as potential adverse effects of Atomoxetine[1]. • Monitor for appearance or worsening of anxiety, depression or tics[2]. • Monitor for psychiatric symptoms / disorders. • Monitor levels of agitation, irritability and/or the occurrence of self-harming behavior /suicidal thoughts.	**Prescribing responsibilities**: To accept shared care when patient is on a 'stable' dose and evidence of benefit is stated. To prescribe treatment from the date specified by specialist. **Monitoring responsibilities**[1]: • Measure **height** at least **every 6 months** in children and young people taking medication for ADHD. • Measure **weight** at least every **3 months** in children **aged 10 years and <u>under</u>** • For children **<u>over</u> 10 years** and young people measure **weight** at **3 and 6 months after starting treatment**, and **then at least 6 monthly thereafter**. • If concerns arise weight should be measured more often. • Monitor **heart rate** and **blood pressure** and compare with the normal range for age **every 6 months**. • Monitor for psychiatric symptoms / disorders.

• Monitor for the rare possibility of hepatic disorders; ensure patients and carers are aware of the risk and how to recognise symptoms[2]. Annual review: A review with the specialist is required at least once a year to discuss whether medication should be continued. As the young person can 'grow out' of ADHD (secondary to neuro-developmental maturation or changes in circumstances).	

Patient Information

Families / carers will be provided with relevant patient information booklets by the specialist service.

For additional medicines information, including patient information leaflets, please see: http://www.choiceandmedication.org/nsft/.

Specialist Contact Details

- Norwich Community Health and Care NHS Trust, Neurodevelopmental Service, Tel 01553 668712
- The James Paget University Hospital, Newberry Clinic, Tel 01493 442322
- Children's Community Medical Team, West Suffolk NHS Foundation Trust, Tel 01284 741700
- Autism Diagnostic Service Suffolk, Tel 01449 745389 (aged over 11 years)
- Child and Adolescent Mental Health Service (CAMHS);
    - Central and West Norfolk - Tel 0300 790 0371
    - East Norfolk, Great Yarmouth and Waveney – Telephone 0300 123 1882

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.
- **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Atomoxetine is a sympathomimetic drug indicated for the treatment of ADHD. Atomoxetine is a noradrenaline reuptake inhibitor with a different side effect profile to stimulant drugs. As per NICE guidance (NG87)[1] atomoxetine is recommended as a 3rd / 4th line option after stimulant medication has not been tolerated or is ineffective. NICE[1] states offer atomoxetine to children & young people if:

- They cannot tolerate methylphenidate or lisdexamfetamine or
- Their symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.

Licensed use and agreed local off-label use

Atomoxetine is indicated for the treatment of ADHD in children aged 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme[3].

Treatment must be initiated by a specialist in the treatment of ADHD, such as a consultant paediatrician or a child/adolescent psychiatrist. Diagnosis should be made according to current DSM criteria or the guidelines in ICD[3].

Criteria for Patient Selection

The patient's ADHD symptoms of hyperactivity/ impulsivity and/or inattention:

- meet the diagnostic criteria in DSM-5 or ICD-11 **and**
- cause at least moderate psychological, social and/or educational or occupational impairment based on interview and/or direct observation in multiple settings **and**
- are pervasive, occurring in 2 or more important settings including social, familial, educational and/or occupational settings.

Children should only be offered medication if all of following criteria are met:

- a baseline assessment has been carried out.
- they and their family/ and carers have discussed information about ADHD.
- patient has completed psychoeducation and environmental modifications have been implemented and reviewed.
- ADHD symptoms are still causing a **persistent significant impairment** in at least one domain.

Atomoxetine may be specifically considered for the following indications when treating ADHD:

- ADHD with significant co-morbidity of anxiety and/or depression.
- Tourette's Syndrome.

- Where symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses[1].
- Significant side effects with stimulant medication e.g., tics caused by stimulants which cannot be tolerated and where the dose cannot be reduced.
- Concern from young person, parent or carer about stimulant medication.
- Positive choice for atomoxetine by young person, parent or carer.
- ADHD where there is substance misuse or likelihood of this. Concerns about substance misuse within the young person's wider milieu.
- Teenagers who require significant control of their ADHD symptoms for more than 12 hours a day (stimulant medication treatment is usually tolerated better if there is a break of 8-12 hours between doses).

Form and strength of preparation

1) Hard capsules: 10mg, 18mg, 25mg, 40mg, 60mg, 80mg and 100mg.

2) Oral solution 4mg/ml sugar free.

Side Effects (Please refer to the BNFC and the individual products SPC)

Atomoxetine can affect heart rate and blood pressure. Combined data from controlled and uncontrolled ADHD clinical trials show that approximately 8-12% of children and adolescents experience more pronounced changes in heart rate (20 beats per minute or greater) and blood pressure (15-20 mmHg or greater).

Suicide-related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine. In double-blind clinical trials, suicide-related behaviours were uncommon, but more frequently observed among children and adolescents treated with atomoxetine compared to those treated with placebo, where there were no events. Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide related behaviour.

The emergence of psychotic symptoms has also been reported sporadically.

Although uncommon, allergic reactions, including anaphylactic reactions, rash, angioneurotic oedema, and urticaria, have been reported in patients taking atomoxetine.

The BNFC[2] lists the following side effects for atomoxetine:
Common or very common
Anxiety; appetite decreased; asthenia; chest pain; constipation; depression; dizziness; drowsiness; gastrointestinal discomfort; headaches; insomnia; mood altered; mydriasis; nausea; skin reactions; tic; vomiting; weight decreased

Uncommon
Behaviour abnormal; dyspnoea; hallucination; hyperhidrosis; hypersensitivity; palpitations; psychosis; QT interval prolongation; seizure; sensation abnormal; sinus tachycardia; suicidal behaviour; syncope; tremor; vision blurred

Rare or very rare
Genital pain; **hepatic disorders**; priapism; Raynaud's phenomenon; urinary disorders

Frequency not known.
Sudden cardiac death

Drug Interactions (Please refer to the BNFC and the individual products SPC)

Effects of other drugs on atomoxetine:

Monoamine oxidase inhibitors (MAOIs) and atomoxetine should not be used together; in extensive metabolisers the co-administration of CYP2D6 inhibitors (e.g., fluoxetine, paroxetine) will lead to increased levels (and side effects), equivalent to that seen in poor metabolisers; caution should be taken when co-administering drugs with potential pressor effects on the cardiovascular system e.g., beta2-agonists. However, studies show that combined use with methylphenidate does not lead to increased cardiovascular side effects.

Effect of atomoxetine on other drugs:

There appears to be no clinically significant inhibition or induction of cytochrome P450 enzymes.

Cautions and Contraindications (For the most up to date information please refer to the BNFC and the individual products SPC)

Cautions[2]:

QT-interval prolongation; aggressive behaviour; cardiovascular disease; cerebrovascular disease; emotional lability; history of seizures; hostility; hypertension; mania; psychosis; structural cardiac abnormalities; susceptibility to angle-closure glaucoma; tachycardia.

- Driving/machinery operation: relevant studies not done, tiredness/somnolence can be an (initial) side effect. Patients should use caution until they have established for themselves that their performance is not negatively affected.
- Pregnancy and lactation.
- There have been rare reports of (reversible) liver function abnormalities. Clinicians should make patients aware of this and the potential signs and symptoms such as abdominal pain, unexplained nausea, malaise, darkening of the urine and jaundice. Prompt medical attention should be sought.
- Hepatic impairment: initial and target doses should be reduced.
  - Moderate hepatic insufficiency reduce starting and target doses to 50% of usual (reduce dose by half)
  - Severe hepatic insufficiency reduce starting and target doses to 25% of usual (reduce dose by three quarters)
- Renal insufficiency: No adjustment is necessary but be aware that atomoxetine may exacerbate hypertension in patients with end stage renal disease.
- Known CYP2D6 poor metaboliser genotype: Due to several-fold increase in atomoxetine exposure, consider a lower starting dose and slower up-titration.

Contraindications[2]:

Phaeochromocytoma; severe cardiovascular disease; severe cerebrovascular disease

Initiation of therapy

All medication for ADHD should only be initiated by a specialist (who is a registered healthcare professional) with training and expertise in diagnosing and managing ADHD. Registered healthcare professionals initiating medication for ADHD should:

- be familiar with the pharmacokinetic profiles of all preparations available for ADHD.
- ensure that treatment is tailored effectively to the individual needs of the child or young person.
- take account of variations in bioavailability or pharmacokinetic profiles of different preparations to avoid reduced effect or excessive adverse effects.

Initial dose and method of administration and supply

The specialist will be responsible for initiation, dose titration and stabilisation on medication.

Atomoxetine can be offered to children and young people for the treatment of ADHD if:

- they cannot tolerate methylphenidate or lisdexamfetamine **or**
- their symptoms have not responded to separate 6-week trials of methylphenidate and lisdexamfetamine, having considered alternative preparations and adequate doses.

If there is a choice of more than one appropriate formulation of a drug, the product that is the most cost-effective should be prescribed.

Dose by mouth[2]:

Child 6–17 years (body-weight up to 70 kg)

Initially 500 micrograms/kg daily for 7 days, dose is increased according to response; maintenance 1.2 mg/kg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 1.8 mg/kg per day; maximum 120 mg per day*.

Child 6–17 years (body-weight 70 kg and above)

Initially 40 mg daily for 7 days, dose is increased according to response; maintenance 80 mg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 120 mg per day*.

* Doses above 100 mg daily not licensed.[2]

Maintenance Dose and Administration

See information above.

Capsules are not intended to be opened. Atomoxetine is an ocular irritant.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

To establish continued need for medication a healthcare professional with training and expertise in managing ADHD should review the ADHD medication at least **once a year**. They should discuss with the person with ADHD (and their families and carers as appropriate) whether medication should be continued. The review should include a comprehensive assessment of the:

- preference of the child or young person with ADHD (and their family or carers as appropriate)
- benefits, including how well the current treatment is working throughout the day.
- adverse effects
- clinical need and whether medication has been optimised
- impact on education and employment
- effects of missed doses, planned dose reductions and periods of no treatment.
- effect of medication on existing or new mental health, physical health or neurodevelopmental conditions

- need for support and type of support (for example, psychological, educational, social) if medication has been optimised but ADHD symptoms continue to cause a significant impairment.

Patients with ADHD should be encouraged to discuss any preferences to stop or change medication and to be involved in any decisions about stopping treatments. Trials of treatment-free periods, or dose reductions should be considered where appropriate and be managed by the specialist. If the decision is made to continue medication, the reasons for this should be documented. Drug treatment should only be continued for as long as it is clinically effective.
Children & young people should be monitored for effectiveness of treatment and side-effects. If the child develops new, or has worsening of existing seizures, review drug treatment and stop any drug that might be contributing to the seizures; treatment can be cautiously reintroduced if it is unlikely to be the cause. If there is worsening of behaviour, consider adjusting drug treatment and reviewing the diagnosis.
When conducting treatment reviews the specialist will send a written summary of the consultation to the patient's GP.

The general tendency is for reduction in need for continuation of pharmacotherapy towards the end of puberty. In some cases, it might be appropriate to continue treatment into adulthood.

Initial monitoring / baseline assessment – by Specialist

Monitoring at baseline and during initiation is the responsibility of the specialist.

Baseline assessment:[1]

- Review to confirm the patient meets the criteria for ADHD and requires pharmacological treatment.
- Review of patient's mental health and social circumstances, including:
  - presence of coexisting mental health and neurodevelopmental conditions
  - current educational or employment circumstances
  - care needs
- Review of physical health, including;
  - medical history, taking into account conditions that may be contraindications for specific medicines.
  - current medication
  - height and weight (measured and recorded against the normal range for age, height and sex)
  - baseline pulse and blood pressure (measured with an appropriately sized cuff and compared with the normal range for age)
  - a cardiovascular assessment.

Monitoring during dose titration:[1]

During the titration phase, ADHD symptoms, impairment and adverse effects should be recorded at baseline and **at each dose change** on standard scales by parents and teachers, and progress reviewed regularly (for example, by weekly telephone contact) with the specialist.

Height and **weight** should be monitored and plotted on a growth chart.

Monitor **heart rate** and **blood pressure** and compare with the normal range for age before and after each dose change. Reduce dose and refer to a paediatric hypertension specialist if a patient taking ADHD medication has;

- that have sustained resting tachycardia (more than 120 beats per minute),
- arrhythmia
- or systolic blood pressure greater than the 95th percentile (or a clinically significant increase) measured on 2 occasions.

Additional monitoring:

- Monitor young people with ADHD for sexual dysfunction (that is, erectile and ejaculatory dysfunction) as potential adverse effects of Atomoxetine[1].
- Monitor for appearance or worsening of anxiety, depression or tics[2].
- Monitor for psychiatric symptoms / disorders.
- Monitor levels of agitation, irritability and/or the occurrence of self-harming behavior /suicidal thoughts.
- Monitor for the rare possibility of hepatic disorders; ensure patients and carers are aware of the risk and how to recognise symptoms[2].

Annual review:[1]

A review with the specialist is required at least once a year to discuss whether medication should be continued. As the young person can 'grow out' of ADHD (secondary to neuro-developmental maturation or changes in circumstances). This review should include a comprehensive assessment of:

- preference of the child or young person with ADHD (and their family or carers as appropriate).
- benefits, including how well the current treatment is working throughout the day.
- adverse effects
- clinical need and whether medication has been optimised.
- impact on education and employment.
- effects of missed doses, planned dose reductions and periods of no treatment.
- effect of medication on existing or new mental health, physical health or neurodevelopmental conditions.
- need for support and type of support (for example, psychological, educational, social) if medication has been optimised but ADHD symptoms continue to cause a significant impairment.
- **Height, weight, blood pressure** and **pulse rate** to be checked at annual review. **Results of annual review to be communicated to the GP**.

Specialist monitoring responsibilities

See above - Initial monitoring / baseline assessment.

GP / Community Team or other Primary Care monitoring responsibilities

Primary care monitoring:[1]

- Measure **height** at least **every 6 months** in children and young people taking medication for ADHD.
- Measure **weight** at least every **3 months** in children **aged 10 years and under**
- For children **over 10 years** and young people measure **weight** at **3 and 6 months after starting treatment**, and **then at least 6 monthly thereafter**.

- If concerns arise weight should be measured more often.
- Monitor **heart rate** and **blood pressure** and compare with the normal range for age **every 6 months**.
- Monitor for psychiatric symptoms / disorders.
- Alertness to possible side effects of medication emerging.
- Review of all results of monitoring parameters, including those provided by the specialist, to identify any trends which indicate the possible emergence of adverse effects of the treatment. e.g. MHRA advice about increased heart rate and BP and rare chance of liver problems.
- Assessment of adherence, and for any indication of atomoxetine abuse, misuse, or diversion.

Consultant / Specialist prescribing responsibilities

The specialist is responsible for initiation, dose titration and stabilisation on medication for at least two consecutive consultations with **no change in dose**.

Transfer of monitoring and prescribing to primary care is normally after at least 12 weeks, and when the patient's dose has been optimised, and with satisfactory investigation results for at least 4 weeks.

The specialist will provide relevant age-appropriate information to the patient and their family/ carer about the risks and benefits of pharmacological treatment.
The specialist will ensure that the patient has an adequate supply of medication.

GP prescribing responsibilities

To accept shared care when patient is on a 'stable' dose and evidence of benefit is stated.
To prescribe treatment from the date specified by specialist.

Indications for referral back to Specialist

- Common side effects for class of medication, not responsive to (temporary) dose reduction.
- Uncommon, severe or unexpected side effects; this includes newly arising or worsening pre-existing psychiatric co-morbidities.
- Lack of efficacy.
- If there are concerns or queries.

Further information and supporting documents

1. National Institute for Health and Care Excellence (NICE) Guideline NG87. Attention deficit hyperactivity disorder: diagnosis and management. [Updated13 September 2019]. Available from: Attention deficit hyperactivity disorder: diagnosis and management (nice.org.uk)
2. British National Formulary for Children (BNFC). Attention deficit hyperactivity disorder, treatment summary. [Updated 28/02/24]. Available from: Attention deficit hyperactivity disorder | Treatment summaries | BNFC | NICE
3. Electronic medicines compendium. Atomoxetine 10mg hard capsules. [Updated December 2020]. Available from: https://www.medicines.org.uk/emc/product/10507/smpc

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Appendix 1: Blood Pressure Levels for Boys & Girls by Age and Height Percentile

BP centiles.pdf

Document history:

Version	Date	Author / Editor	Status	Comment
9.0	May 2024	Medicines Optimisation Team	Draft	Document restarted on new template. Addition of new product - Atomoxetine 4mg/ml oral solution sugar free - Strattera®. Specialist contact details updated; references updated. Shared care previously said '*Can open capsule and sprinkle contents onto spoonful of sauce/yogurt (Caution – risk of irritation to eyes if opened).* Now reads '*Capsules are not intended to be opened. Atomoxetine is an ocular irritant*.' Title changed to 'Shared care guidelines for Atomoxetine for Attention Deficit Hyperactivity Disorder (ADHD) in Children & Young People aged at least 6 years old'. ICD-10 updated to ICD-11 in text.
9.1	June 2024	Medicines Optimisation Team	Final	Appendix 1 Blood pressure table replaced with PDF - Blood Pressure Centiles for Boys & Girls by Age and Height Percentile. Supported by TAG and MOPB – July 2024