South West Yorkshire Area Prescribing Committee

Atomoxetine Shared Care Guideline for Attention Deficit Hyperactivity Disorder (ADHD) in school-aged children, adolescents and adults.

Introduction	
General Statements	• This guideline relates to children, adolescents and adults with ADHD with moderate to severe levels of impairment. • This guideline sets out details for the shared care of patients taking atomoxetine, and follows the recommendations of NICE clinical guideline and NICE Technology Appraisal. • Patients will receive prescriptions for supplies of medication from secondary care until shared care is agreed with the primary care doctor. • Prior to seeking shared care with the patient's GP: 1. The patient's clinical condition will be stable or predictable. 2. The patient will have been stabilised on the drug with time allowed for common adverse events and side-effects to have occurred. • If a patient changes GP, then the new GP and the Secondary Care Prescriber will need to discuss setting up shared care for the patient. • The full summary of product characteristics (SPC – formerly datasheet) for the appropriate product should be read before prescribing – available at www.medicines.org.uk.
Indication	• Atomoxetine is indicated for the treatment of ADHD in children of 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme. Treatment must be initiated by a Specialist in the treatment of ADHD, such as a paediatrician or psychiatrist. Diagnosis should be made according to current DSM criteria or the guidelines in ICD. NICE CG72 recommends pharmacological intervention as the first-line treatment for adults with ADHD symptoms causing moderate to severe impairment.
Background	NICE clinical guideline states Diagnosis of ADHD • Diagnosis should only be made by a specialist psychiatrist, paediatrician or other healthcare professional with training and expertise in the diagnosis of ADHD. • Diagnosis should be based on: – a full clinical and psychosocial assessment. Discuss behaviour and symptoms in the different domains and settings of the person's everyday life – a full developmental and psychiatric history, and – observer reports and an assessment of mental state. • Diagnosis should be made when symptoms of hyperactivity/impulsivity and/or inattention: – meet the criteria in DSM-5 or ICD-10 (hyperkinetic disorder), and – are associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and/or observation in multiple settings, and – are pervasive, occurring in at least two settings. • As part of the diagnostic process, include an assessment of needs, coexisting conditions, social, familial and educational or occupational circumstances and

	physical health. For children and adolescents also include an assessment of the parents' or carers' mental health. Drug treatment in children and adolescents • Drug treatment should: – only be started by a healthcare professional with expertise in ADHD – be based on comprehensive assessment – always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. • Drug treatment is not indicated as the first-line treatment for all school-age children and adolescents with ADHD. It should be reserved for those with severe symptoms and impairment or for those with moderate levels of impairment who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group psychological treatment • GPs may continue prescribing and monitoring drug treatment under shared care arrangements • If improvement of symptoms is not seen after appropriate dose adjustment, atomoxetine will be discontinued. Drug treatment in adults • NICE recommends pharmacological intervention as the first-line treatment for adults with ADHD symptoms causing moderate to severe impairment. • GPs may continue prescribing and monitoring drug treatment under shared care arrangements. • If improvement of symptoms is not seen after appropriate dose adjustment, atomoxetine will be discontinued.
Pharmacological Summary	• Atomoxetine is a highly selective noradrenaline reuptake inhibitor. It blocks the presynaptic noradrenaline transporter and has 2 main effects in the brain – increasing the availability of noradrenaline in the synapse and increasing synaptic dopamine in the prefrontal cortex. • Atomoxetine is well-absorbed from the gastrointestinal tract after oral administration, reaching peak plasma concentrations 1 to 2 hours after dosing.

Individuals Responsibilities	
Specialist's Responsibilities	1. Confirm the diagnosis of ADHD following full assessment, drawing upon information from all sources and first-hand observation of the patient. 2. Before starting drug treatment, children, adolescents and adults with ADHD should have a full pre-treatment assessment, which should include: – a full mental health and social assessment – a full history and physical examination, including: o assessment of history of exercise syncope, undue breathlessness and other cardiovascular symptoms o heart rate and blood pressure (plotted on a centile chart for children and adolescents) o height and weight (plotted on a growth chart for children and adolescents) o family history of cardiac disease and examination of the cardiovascular system – an electrocardiogram (ECG) if there is past medical or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination – risk assessment for substance misuse and drug diversion. 3. Initiation of atomoxetine therapy and supply of the medicine for one further month after the dose has been stabilised before considering shared care. 4. Ensure that the patient has an adequate supply of medication until GP prescribing can be agreed and arranged. 5. Ensure patient/parent/carer are advised of the risk of hepatic disorders and told how to recognise symptoms, and that prompt medical attention should be sought

	in the case of abdominal pain, unexplained nausea, malaise, darkening of urine, or jaundice. 6. Ensure that patient/parent/carer are advised about the risk of suicidal ideation and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation or depression. 7. Patients with additional risk factors for cerebrovascular conditions (such as a history of cardiovascular disease and concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with atomoxetine. 8. Review the patient at regular intervals 4-weekly initially and then as necessary, but all patients should be seen once a year by the Specialist. 9. Review the patient promptly if requested to do so by the GP. 10. Review the need for treatment at school leaving age and if necessary arrange transition to adult services. 11. Monitor heart rate and blood pressure before and after any dose change, and monitor height and weight before treatment and then 3 months and 6 months into treatment (see below). It is recommended that these measurements are recorded on a centile chart or other appropriate monitoring chart to detect clinically-informed increases. 12. Adjusting treatment as appropriate e.g. varying dosage or timing, and informing the GP of any changes in writing. 13. Continuing supply of atomoxetine for children under 6 years old. 14. Inform and decide with GP any action if patient misses an appointment. 15. Stopping treatment when appropriate. Baseline tests: Height, weight, blood pressure and heart rate (height does not need to be measured in adults). Patient Information to be received by the GP from the Specialist: • Details of patient follow-up, including Care Plan. • The Specialist's review letter - sent after initial assessment and following each further appointment and including any changes to the patient's medication regimen. • When dose titration has been completed and the treatment is stable, the GP should be asked by the Specialist to continue prescribing and monitoring under a shared care arrangement. A copy of this Shared Care Guideline should then be sent to the GP.
General Practitioner's Responsibilities	1. The GP must reply in writing to the request for shared care within two weeks if unwilling to participate in shared care. 2. Arrange to see the patient on a regular basis to monitor their health and well-being. This includes undertaking any necessary physical health monitoring to ensure that monitoring requirements are maintained beyond Specialist review appointments (see below). 3. Report and discuss with Specialist any adverse effects of medication, possible drug interactions or deteriorating behaviour. 4. Upon acceptance of shared care, provide the patient with prescriptions of atomoxetine. 5. To only continue prescriptions if monitoring compliance and results are satisfactory. 6. To ensure no drug interactions with concomitant medicines. Maintenance physical health monitoring: Height and weight measured every 6 months (height does not need to be measured in adults). Heart rate and blood pressure measured every 3 months. Atomoxetine can cause tachycardia and elevated blood pressure. If there is a **persistent** increase above baseline there should be a discussion with secondary care on whether medication should be reduced or referral made to paediatrics for an opinion to ensure that there are no other medical reasons for **the persistent** elevation.

	Further information on monitoring blood pressure in children can be found at http://www.gosh.nhs.uk/health-professionals/clinical-guidelines/blood-pressure-monitoring Patient Information to be received by the Specialist from the GP: • Details of any adverse effects experienced by the patient. • Any relevant medical information, including any test results. • Any changes to the patient's medication regimen. • Notification of patient's failure to attend regularly for monitoring.
Joint Responsibilities of GP and Specialist	It is the joint responsibility of the GP and Specialist to ensure the patient/parent/carer are aware of their responsibilities: 1. To attend appointments. 2. To have the recommended tests. 3. To inform the GP if health problems arise. 4. To be aware of side effects listed in the patient information leaflet supplied with the medication and report any relevant symptoms.
When and How to Discontinue Treatment (Only on the advice of the Specialist, except in the case of significant adverse effects)	In cases of significant adverse effects, atomoxetine may be stopped abruptly; otherwise the drug may be tapered off over a suitable time period. However, on withdrawal of the medication, careful supervision is necessary as depression as well as renewed overactivity can be unmasked.
Information given to the patient	A pharmaceutical company patient information leaflet (PIL) will be provided with each supply. NICE website address for further information is www.nice.org.uk. www.choiceandmedication.org/swyp
Contact Details	These will be included in Specialist's letter

Product Information	
The information in this Shared Care Guideline should be used in conjunction with the latest edition of the BNF and Summary of Product Characteristics	
Dosage and Administration	Atomoxetine can be taken as a once-daily dose in the morning or as a twice-daily dose in the morning and early evening if tolerability or efficacy are an issue. Dosing is based on weight and should be titrated to a treatment dose. • Up to 70kg body weight - Start at a dose of approximately 500 micrograms/kg daily for a minimum of 7 days and then titrate dose upwards based on clinical response and tolerability to usual maintenance dose of 1.2mg/kg per day, which may be increased to 1.8mg/kg daily (max 120mg daily) under the direction of a Specialist. • 70kg body weight or greater - Start at a dose of 40mg daily for a minimum of 7 days and then titrate upwards to usual maintenance dose of 80mg daily, which may be increased to 120mg daily under the direction of a Specialist. Special populations For patients with moderate hepatic insufficiency (Child-Pugh class B), initial and target doses should be reduced to 50% of the usual dose. For patients with severe hepatic insufficiency (Child-Pugh class C), initial and target doses should be reduced to 25% of the usual dose.
Adverse Effects and their Suggested Management	Very common (≥ 1 in 10): Appetite decreased – This is most common at the start of treatment. It usually settles after a couple of weeks. Headache – Patients should be advised to try a mild analgesic such as paracetamol. Nausea and vomiting – This is most common at the start of treatment. Patients should be advised to try taking the dose with or after food. Common (≥ 1 in 100 to < 1 in 10): Abdominal pain – This is most common at the start of treatment. It usually settles after a couple of weeks. The dose can be taken with or after food.

<table>
<tr><td></td><td>Anorexia and weight loss – Weight gain and growth should be monitored. If there is notable weight loss or lack of weight gain consider stopping atomoxetine.
Constipation – Patients should be advised to maintain a good fluid intake, a fibrous diet, and exercise regularly. If not responsive to such interventions, patients may require a mild laxative.
Dizziness – Patients should be advised to avoid standing up quickly. If they feel dizzy, they should try to lie down. Patients should be advised not to drive (if applicable).
Drowsiness – Patients should be advised not to drive (if applicable).
Dyspepsia – Patients should be advised to try sleeping propped up on pillows.
Insomnia – This is most common at the start of treatment. It usually settles after a couple of weeks. It is continues, it may be appropriate to reduce the dose or change the dosage regimen.
Rashes and pruritus – If the rash is severe and itchy or does not remit, it may be necessary to discontinue atomoxetine.

<u>Uncommon (≥ 1 in 1000 to < 1 in 100):</u>
Allergic reactions, blurred vision, irritability and mood swings, migraine, palpitations and tachycardia, QT interval prolongation, sexual dysfunction, suicidal ideation, syncope, tics.

<u>Rare (≥ 1 in 10,000 to < 1 in 1000):</u>
Hepatic disorders, priapism, treatment-emergent psychotic or manic symptoms, Raynaud's phenomenon, seizures.</td></tr>
<tr><td>Precautions and Contra-indications</td><td>Precautions:
• Atomoxetine should be used with caution in patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease.
• Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.
• Patients should be monitored for the appearance or worsening of suicide-related behaviour, hostility and emotional lability.
• Seizures are a potential risk and atomoxetine should therefore be introduced with caution in patients with a history of seizures. Discontinuation should be considered in any patient developing seizures or if there is an increase in seizure frequency.
• Reports of QT interval prolongation have been received in association with atomoxetine. Atomoxetine should be used with caution in those with congenital or acquired Long QT Syndrome or a family history of QT prolongation. This risk may be increased if atomoxetine is used concomitantly with other drugs that produce QT prolongation, electrolyte disturbances, and CYP2D6 inhibition.
• The concomitant use of high-risk QTc-prolonging agents with atomoxetine should be avoided as it may enhance the QTc-prolonging effect. Any use of such combinations should only be undertaken with caution and should be avoided when possible. The use of such a combination should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm. Some of the more commonly encountered high-risk QTc-prolonging drugs are listed below - this list is not exhaustive but is designed to give examples of the more commonly used drug classes:
<table>
<tr><th>Antiarrhythmics</th><th>Antimicrobials</th></tr>
<tr><td>Amiodarone
Dronedarone
Flecainide
Sotalol</td><td>Clarithromycin
Erythromycin
Fluconazole
Moxifloxacin</td></tr>
<tr><th>Antidepressants</th><th>Antipsychotics</th></tr>
<tr><td>Citalopram
Escitalopram</td><td>Chlorpromazine
Haloperidol
Pimozide
Sulpiride</td></tr>
<tr><th>Antiemetics</th><th>Others</th></tr>
</table>
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	<table><tr><td>Domperidone Droperidol Ondansetron</td><td>Chloroquine Methadone</td></tr></table> Pregnancy – there is no clinical data in exposed pregnancies available. Atomoxetine should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus. Breast-feeding - Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Because of the lack of data, atomoxetine should be avoided during breast-feeding Contra-indications: • Narrow-angle glaucoma. • Phaeochromocytoma or a history of phaeochromocytoma. • Severe cardiovascular or cerebrovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate that could be clinically important (for example, 15-20 mmHg in blood pressure or 20 beats per minute in heart rate). • Hypersensitivity to atomoxetine or to any of the excipients. • During or within 14 days following the administration of a MAOI.
Clinically-relevant Drug Interactions and their Suggested Management	• MAOIs may enhance the central neurotoxic effect of atomoxetine. Atomoxetine should not be used within 14 days of a MAOI. • $Beta_2$-agonists: Atomoxetine may enhance the cardiovascular effects of $beta_2$-agonists (e.g. tachycardia, hypertension). Monitor for increased cardiovascular effects. • Sympathomimetics: Atomoxetine may enhance the hypertensive and tachycardic effects of sympathomimetics. Monitor for tachycardia and hypertensive effects with initiation / dose increase of atomoxetine and concomitant sympathomimetic therapy. • QT prolonging drugs: see 'Precautions' for details. • CYP2D6 inhibitors can increase plasma concentrations of atomoxetine by 3- to 5-fold. Consider initiating atomoxetine at a reduced dose (patients < 70kg: 0.5mg/kg/day; patients ≥ 70kg: 40mg/day) and only increasing dose to usual treatment doses if symptoms fail to improve after 4 weeks. Patients already established on atomoxetine therapy may require dosage reductions and should be monitored for adverse effects with initiation / dose increase of a CYP2D6 inhibitor. Significant inhibitors of CYP2D6 include: Antidepressants: duloxetine, fluoxetine, paroxetine, sertraline, tricyclic antidepressants. Antipsychotics: chlorpromazine, clozapine, haloperidol, levomepromazine. Others: bupropion, methadone, ritonavir, terbinafine, tipranavir.

References	
References	• SPC/PIL for Strattera®. • NICE Technology Appraisal No 98. – Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents. • NICE clinical guideline No 72 –Attention deficit hyperactivity disorder - Diagnosis and management of ADHD in children, young people and adults.