Cardiff & Vale (C&V) UHB Corporate Medicines Management Group (c MMG)

SHARED CARE

Drug: ATOMOXETINE **Protocol number: CV 46**

Indication: ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD), HYPERKINETIC DISORDER (HKD) IN CHILDREN 6 YEARS AND OLDER, ADOLESCENTS AND ADULTS

General Guidance

This protocol sets out details for the shared care of patients taking **atomoxetine** and should be read in conjunction with the General Guidelines for Shared Care and the current NICE Clinical Guideline (No 72 Sep 2008).

Sharing of care requires communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **The doctor who prescribes the medication legally assumes responsibility for the drug and the consequences of its use.** The prescriber has a duty to keep themselves informed about the medicines they prescribe, their appropriateness, effectiveness and cost. They should also keep up to date with the relevant guidance on the use of the medicines and on the management of the patient's condition

Background

Atomoxetine is recommended as one of the options for use as outlined in NICE Guidance where drug treatment is deemed appropriate as part of a "comprehensive treatment programme" for children and adults with a diagnosis of Attention Deficit/ Hyperactivity Disorder (ADHD)

The decision regarding whether to use atomoxetine or an alternative drug should be based on the following:

- Presence of co-morbidities (e.g. tic disorders, Tourette's syndrome, epilepsy)
- Different adverse effects profiles of the drugs
- Specific compliance issues e.g. need to administer a mid-day dose at school or work.
- Potential for drug diversion/misuse
- Preferences of child/adolescent/ adult and/or parent/guardian based on clinical features of the patient.

Treatment with atomoxetine should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD and should be based on a comprehensive assessment and diagnosis.

NICE recommends:

In Pre-school children - drug treatment is not recommended

In patients with moderate ADHD and moderate impairment – drug treatment should be reserved for those with moderate impairment where non-drug interventions have been refused or where there are persisting significant impairment following parent-training/education programme or group psychological treatment

In patients with severe ADHD (hyperkinetic disorder) and severe impairment – offer drug treatment first-line (also offer parents a group based training programme)

NICE CG 72 recommends

- Methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present.
- Atomoxetine if methylphenidate has been tried and had been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate.

Atomoxetine is now licensed for use in adults with ADHD and is not restricted to adults where treatment with atomoxetine began in childhood In adults, the presence of symptoms of ADHD that were pre-existing in childhood should be confirmed. Third-party corroboration is desirable and atomoxetine should not be initiated when the verification of childhood ADHD symptoms is uncertain. Diagnosis cannot be made solely on the presence of one or more symptoms of ADHD. Based on clinical judgment, patients should have ADHD of at least moderate severity as indicated by at least moderate functional impairment in 2 or more settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

Responsibilities

A. Consultant responsibilities

1. When treatment is **initiated** send Shared Care request form with Shared Care Protocol to GP
2. Initiate therapy following full discussion with the patient/carer of different treatment options, benefits and risks
3. Comprehensive baseline assessment, initial prescribing and baseline and continued monitoring (see page 3,4)
4. To warn parents and/or carers about the potential for suicidal thinking and self-harming behaviour and to report immediately to GP or specialist
5. To warn parents and /or carers about the potential for liver damage in rare cases and to contact their GP immediately if any of the following occur: abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice).
6. Liaise with GP, School, and any other agency involved with the patient, provide a comprehensive treatment programme for the patient, determine the

frequency of specialist review following stabilisation and be aware of ongoing issues relating to prescribing when reaching young adulthood.
7. Titrate atomoxetine dose, adjusting dose as appropriate and undertake monitoring of clinical response and side effects.
8. When a positive GP response to SC has been received and patient has been stabilized send a letter to GP "handing over" the Shared Care of the patient to the GP.
9. Respond to any request from GP to review the patient due to adverse effects of therapy.
10. Report adverse effects of therapy to the Medicines and Health Care products Regulatory Agency (MHRA).
11. Advise the GP on continuing or stopping atomoxetine therapy following medical review of the patient and associated drug therapy
12. Notify GP if patient is failing to attend for appropriate monitoring and advise GP on appropriate action.
13. Review patient at 18 years of age and refer to appropriate adult services if patient is to continue on atomoxetine. Advise GP of decision.

B. General practitioner responsibilities

1. Within one week of receipt return the completed Shared Care request form to indicate whether or not willing to undertake Shared Care.
2. Prescribe atomoxetine as part of the shared care agreement once patient is stabilised.
3. Monitor the general health of the patient.*
3. Report adverse effects of therapy to the consultant and the Medicines and Health Care products Regulatory Agency (MHRA).
4. Act on advice provided by the Consultant if patient does not attend for appropriate monitoring.

*monitoring will be undertaken by the Secondary Care Health Professional until the patient is stable on treatment and at least every 6 months thereafter. If the GP becomes aware in the interim that the patient is experiencing an adverse effect or unexplained symptom such as weight loss and does not have an imminent appointment with the Consultant, they should request that the appointment be expedited.

Dosage Regimen

Using atomoxetine in patients with ADHD:

- NICE CG 72 states that atomoxetine should be used if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate

- Atomoxetine can be administered as a single daily dose in the morning, with or without food. Patients who do not achieve a satisfactory clinical response (tolerability or efficacy) when taking atomoxetine as a single daily dose might benefit from taking it as twice daily evenly divided doses in the morning and late afternoon or early evening.

- Atomoxetine oral solution can be used for patients unable to swallow capsules either because they are immature or have sensory needs or severe learning difficulties. Patients on doses above 25mg should be encouraged to take tablets where possible.
- For children up to 70kg body weight atomoxetine should be initiated at a total daily dose of approximately 0.5mg/kg. The dose should be titrated after a minimum of 7 days up to a maintenance dose of 1.2mg/kg/day according to clinical response and tolerability and depending on the patient's weight and available atomoxetine dosage strengths.

  For children over 70kg body weight and adults the total initial daily dose is 40mg, titrated after a minimum of 7 days to a recommended maintenance dose of 80mg for children and 80 to 100mg for adults. In children no additional benefit has been demonstrated for doses higher than 80mg. The maximum recommended total daily dose for children over 70kg body weight and adults is 100mg.

Following an adequate treatment response, drug treatment for ADHD should be continued for as long as it remains clinically effective. This should be reviewed at least every six months. The review should include a comprehensive assessment of clinical need, benefits and side effects, taking into account the views of the child or young person, as well as those of parents, carers and teachers, and how these views may differ. The effect of missed doses, planned dose reductions and brief periods of no treatment should be taken into account and the preferred pattern of use should also be reviewed. Co-existing conditions should be reviewed, and the child or young person treated or referred if necessary. The need for psychological and social support for the patient and for the parents or other carers should be assessed.

Monitoring in Secondary Care

*monitoring will normally be undertaken by the Secondary Care Health Professional however if a GP becomes aware that a patient is experiencing an adverse effect such as weight loss and does not have an imminent appointment with the Consultant Paediatrician or CAMHS, they should request that the appointment be expedited.

The patient's emotional, social and educational progress should be monitored and if there are significant problems a referral to specialist CAMHS should be considered if not already in place.

<u>Before treatment</u>

Patients with ADHD should have a full pre-treatment assessment, which should include:

- full mental health and social assessment
- full history and physical examination, including:
  - assessment of history of exercise syncope, undue breathlessness and other cardiovascular symptoms
  - heart rate and blood pressure (plotted on a centile chart)

  - height and weight (plotted on a growth chart) (children and young people). Adults would not need monitoring of weight, unless clinical concern over weight loss
  - 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 (where the drug is passed on to others for non-prescription use).

- Enquiry about history of seizures or tics

Majority of young adults presenting with ADHD have a diagnosis made in childhood or adolescence and previous treatment documented in medical records. In the absence of documented diagnosis specialist assessment by a practitioner with special interest in ADHD is recommended prior to treatment

<u>During treatment</u>:

NICE states that for people taking atomoxetine routine blood tests and ECGs are not recommended unless there is a clinical indication.

FBC or other blood tests only if clinically indicated (Stop treatment if WCC <4.0 x 10^9/L

Blood pressure, and heart rate should be monitored before and after each dose change and every 6 months. Sustained resting tachycardia, arrhythmia or systolic BP greater than 95th centile (or a clinically significant increase) measured on 2 occasions should prompt dose reduction and referral for assessment.

Height should be monitored 3 monthly during titration phase and thereafter at 6 monthly intervals in children and young people.

Weight should be measured at 3 and 6 months after the start of treatment, then 6 monthly thereafter in children and young people.

In children, these values should be plotted on a growth centile chart such as the Child Growth Foundation Chart (CGFC). This should be reviewed by the Specialist responsible for treatment.

In a child, if the height/weight centile falls by space equivalent to the gap between two centile lines on the CGFC, ensure patient is seen by a Consultant Paediatrician or CAMHS-**please refer to the first paragraph in the 'monitoring in secondary care' section on page 4**

<u>Adults</u>

Blood pressure monitored annually. There is no need to monitor weight unless there is clinical concern of weight loss.

Adverse effects

Patients treated with atomoxetine should be closely observed for agitation, irritability, suicidal thinking and self-harming behaviour, and unusual changes in behaviour, particularly during the initial months of treatment, or after a change in dose.

Headache, abdominal pain and decreased appetite are the most common adverse events but seldom lead to discontinuation. They are usually transient. Minor side effects may be reduced by dividing the daily dose into two doses at 12 hour intervals.

Some patients lose weight early in treatment as a result of decreased appetite, but during long-term treatment a mean increase in weight is seen and growth rates (weight and height) after 2 years of treatment are near normal.

Nausea or vomiting can occur in about 10% of patients particularly during the first month but these are usually mild-moderate in severity and transient.

Although uncommon, allergic reactions have been reported such as rash, angioneurotic oedema and urticaria.

Most patients experience a modest increase in pulse and/or BP (see Special Warnings and Precautions).

Interactions

Atomoxetine should not be used in conjunction with MAOI's.

The following drugs should be used with caution if co-administered with atomoxetine:-CYP2D6 inhibitors (fluoxetine, paroxetine), Salbutamol or other beta agonists (high dose nebulised or systemic e.g. oral or IV), pressor agents, Drug that affect noradrenaline (e.g. venlafaxine, pseudoephedrine, phenylephrine, imipramine or mirtazapine).

There is the potential for an increased risk of QT interval prolongation when atomoxetine is administered with other QT prolonging drugs (such as neuroleptics, class IA and III anti-arrhythmics, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium, or cisapride), drugs that cause electrolyte imbalance (such as thiazide diuretics), and drugs that inhibit CYP2D6.

Seizures are a potential risk with atomoxetine. Caution is advised with concomitant use of medicinal drugs which are known to lower the seizure threshold (such as antidepressants, neuroleptics, mefloquine, bupropion, or tramadol).

Contraindications:

Hypersensitivity to atomoxetine or to any of the excipients.
Atomoxetine should not be used in combination with monoamine oxidase inhibitors (MAOIs). Atomoxetine should not be used 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.
Atomoxetine should not be used in patients with narrow angle glaucoma, as in clinical trials it was associated with an increased incidence of mydriasis.
Atomoxetine should not be used in pregnancy unless potential benefit justifies the risk to the foetus (no clinical data on exposed pregnancies are available).

Special warnings and precautions:

Atomoxetine should be used with caution in patients with hypertension, tachycardia, cardiovascular or cerebrovascular disease. Most patients experience a modest increase in pulse and/or BP. For most patients these changes are not clinically significant. Orthostatic hypotension has also been reported and it should be used with caution in any conditions which may predispose to this.

Atomoxetine should be used with caution in patients with congenital or acquired long QT or a family history of QT prolongation.

Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Very rarely, liver toxicity, manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported.

Suicide-related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine. In double-blind clinical trials, suicide-related behaviours occurred at a frequency of 0.44% in atomoxetine-treated patients (6 out of 1,357 patients treated, one case of suicide attempt and five of suicidal ideation). There were no events in the placebo group (n = 851). The age range of children experiencing these events was 7 to 12 years. It should be noted that the number of adolescent patients included in the clinical trials was low.
Hostility (predominantly aggression, oppositional behaviour, and anger) and emotional lability were more frequently observed in clinical trials among children and adolescents treated with atomoxetine compared to those treated with placebo.
Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide-related behaviour, hostility, and emotional lability. As with other psychotropic medication, the possibility of rare, serious psychiatric adverse effects cannot be excluded.

Seizures are a potential risk with atomoxetine and it should be introduced with caution in patients with a history of seizure. Discontinuation of atomoxetine should be considered in any patient developing a seizure or if there is an increase in seizure frequency where no other cause is identified.

Date of update May 2106 **Date of next review May 2019**