Methylphenidate, Atomoxetine and Lisdexamfetamine (Elvanse®)▼

(TLS Amber with shared care)

Shared Care Guidelines: For the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults with no other serious mental health co-morbidities.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of methylphenidate, atomoxetine and lisdexamfetamine for ADHD in adults can be shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If the GP is not confident to undertake these roles, then he or she is 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.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with ADHD are under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for methylphenidate, atomoxetine and lisdexamfetamine and the consequences of its use.

RESPONSIBILITIES and ROLES

	Specialist responsibilities
1	To confirm diagnosis following full assessment.
2	To undertake • a complete history including medication history • a review of physical health including weight measurement • an assessment of baseline cardiovascular status, including blood pressure and heart rate before prescribing and seek specialist cardiac advice if appropriate. Liaise with the GP to organise an ECG if the treatment may affect the QT interval.
3	After transition to adult services, adult healthcare professionals should carry out a comprehensive assessment of the person with ADHD that includes personal, educational, occupational and social functioning, and assessment of any coexisting conditions, especially drug misuse, personality disorders, emotional problems and learning difficulties.
4	Carry out a general social and risk assessment for substance misuse.
5	Review concurrent medications for potential interaction prior to initiation of a treatment for ADHD. To prescribe the medication until the dosage is stabilised. Usually this would take up to 3 months.
6	To provide the patient with information about the medication.
7	To look out for signs of diversion (transfer of the medicine from the individual for whom it was prescribed to one for whom it is not prescribed), misuse and abuse of methylphenidate or lisdexamfetamine.
8	To review the patient and monitor the following on an annual basis and communicate these results to the GP: • Weight • Blood pressure and pulse (also following dose adjustments) • To refer patients who develop symptoms such as medication related palpitations, exertional chest pain, unexplained syncope, dyspnoea, or other symptoms suggestive of heart disease for prompt cardiac evaluation. • The development of new or worsening of pre-existing, psychiatric symptoms (also following dose adjustments and at every visit)
9	To notify GP of patient's failure to attend appointments and give advice on stopping the medication.
10	All test results should be notified to the patient's GP.
11	To inform the patient of the possible effect on driving (for example, ADHD symptoms may impair a person's driving and ADHD medication may improve this; people with ADHD must declare their diagnosis to the DVLA if their ADHD symptoms or medication affect their ability to drive safely).
12	Report any adverse effects to the MHRA via the yellow card scheme.

General Practitioner responsibilities	
1	Initial referral to secondary care with a full history of any diagnosis or history where caution is needed or methylphenidate, atomoxetine or lisdexamfetamine are contraindicated.
2	To inform specialist if unwilling to enter into shared care arrangements.
3	Complete relevant physical and cardiovascular assessments, if requested by the specialist.
4	To provide repeat prescriptions after stabilisation of dose. Prescriptions for methylphenidate and lisdexamfetamine should be restricted to a maximum of 30 day's supply and are only valid for 28 days from the date of signature as they are schedule 2 controlled drugs. This is because methylphenidate and lisdexamfetamine are controlled drugs subject to safe custody and specific regulations for prescribing.
5	To contact the specialist if deterioration in behaviour.
6	To refer patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea, or other symptoms suggestive of heart disease for prompt specialist cardiac evaluation.
7	To look out for signs of diversion (transfer of the medicine from the individual for whom it was prescribed to one for whom it is not prescribed), misuse and abuse of methylphenidate or lisdexamfetamine.
8	To act upon results communicated by the specialist
9	Report any adverse effects to the MHRA via the yellow card scheme

Patient's role	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Share any concerns in relation to treatment with medicine.
3	Report any adverse effects to the specialist or GP whilst taking the medicine.
4	Return any unused or no longer needed medication promptly to the supplying pharmacy for destruction

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone number/ e-mail
Dr Dietmar Hank, Consultant Psychiatrist, AWP Adult ADHD clinic, Petherton Resource Centre, Hengrove, Bristol, BS914 9BP	01275 796262 Awp.specialisedADHDservices@nhs.net
Tania Thomas, RMN, Independent Nurse Prescriber, AWP Adult ADHD service, address as above.	01275 796262 Awp.specialisedADHDservices@nhs.net

Summary of medication used and licensed indications[1] for the full summary of product characteristics visit www.medicines.org.uk

First Choice option: Methylphenidate

Methylphenidate (available as immediate or extended release forms). -

Methylphenidate is a central nervous stimulant thought to regulate dopamine and noradrenaline neurotransmission. Methylphenidate is a Schedule 2 controlled drug. It is available in immediate-release tablets (e.g. Ritalin®, Equasym®, Medikinet®) that are usually given in two or three daily doses. Methylphenidate is also available in modified-release formulations that enable once-daily dosing (e.g. Xaggitin®, Xenidate®, Delmosart®, Matoride®, Concerta XL®, Equasym XL®, Medikinet XL®, other brands are available). Modified-release brands provide different release profiles of methylphenidate and switching between brands should be only considered with specialist advice. If a Concerta release profile is required, the branded generic XAGGITIN should be used for NEW patients. Concerta XL should only be used for existing patients or if Xaggitin is found to not be effective.

First choice option: Lisdexamfetamine

Lisdexamfetamine (Elvanse)▼[2] is a long acting prodrug of dexamfetamine, a CNS stimulant. The clinical effect of the drug is 12-13hrs, with significant advantages in safety and clinical effect compared to shorter acting compounds. Lisdexamfetamine allows for once daily dosing and has a lower abuse potential than dexamfetamine. It is a schedule 2 controlled drug. Lisdexamfetamine has a black triangle (▼) status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA.

Offer atomoxetine to adults if:

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

Atomoxetine – Treatment of attention deficit hyperactivity disorder (under specialist supervision)
Atomoxetine is a non-stimulant, non-amphetamine inhibitor of noradrenaline reuptake, although the precise mechanism by which it works on ADHD is unknown. It is not a controlled drug. It is occasionally used when CNS stimulants have not been effective or poorly tolerated or concerns are raised over the abuse potential of the CNS stimulants. Atomoxetine usually takes between 4-12 weeks to be fully effective.

Treatment Aims (Therapeutic plan)
Attention deficit hyperactivity disorder is usually diagnosed according to criteria specified in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V).

ADHD is a chronic condition, which may require long-term treatment. All adults with ADHD will benefit from behavioural, educational and psychological input. For some this is all that is required, but for others pharmacological measures will also be needed. These are initiated by a specialist and shared care can be used to minimise the disruption caused by multiple and ongoing outpatient appointments.

In March 2018, NICE updated clinical guidance titled "Attention deficit hyperactivity disorder: diagnosis and management." [1].

Please consult the NICE quick reference guide for more information:
https://www.nice.org.uk/guidance/NG87

Treatment Schedule (including dosage and administration)

Please note that adult ADHD medications are unlikely to increase in dosage once the medication dose is stabilised. Patients with a history of drug dependence or alcoholism may increase their dose on their own initiative. Always ensure dose changes have been authorised by the specialist.

Methylphenidate
Not all preparations of methylphenidate have a UK marketing authorisation for treating symptoms of ADHD in adults, although the specialist will preferentially use a licensed preparation in adults. Methylphenidate is not currently licensed for initiation in adult patients but NICE NG87 supports its use as a first line option in adults.
The usual initial dose of the immediate release preparation is 5mg twice daily increased in weekly increments. Occasionally slower starting regimen may be used depending upon the individual patient. The dose should then be titrated to response and is usually divided two or three times a day. The maximum recommended dose for methylphenidate is 100mg daily and this is rarely exceeded in clinical practice. Modified release preparations usually start at the lowest available dose (18mg for Xaggitin® or Concerta® or 10mg for Equasym® Xl and Medikinet® XL) and are then increased gradually in weekly increments. The maximum licensed daily dose for e.g. Xaggitin® or Concerta® XL is 54mg daily while for Equasym® and Medikinet® is 60mg per day. N.B: use Xaggitin 1st line rather than Concerta XL for NEW patients.

Lisdexamfetamine (Elvanse®)[2]
Lisdexamfetamine is licensed for use in adults with symptoms of ADHD that pre-existed in childhood.
Although lisdexamfetamine is not currently licensed for initiation in adult patients, NICE NG87 supports its use as a first line option in adults.
Lisdexamfetamine is usually initiated at 30mg daily and increased by 10-20mg weekly depending on response and tolerability. Occasionally a lower starting dose of 20mg per day is used if clinically indicated. The maximum daily dose is 70mg / day. Although the manufacturer recommends dose increases on a weekly basis, dose adjustment may well be done on a monthly basis in practice.

Atomoxetine
Atomoxetine is licensed for use in adults with symptoms of ADHD that pre-existed in childhood.
Atomoxetine should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The

recommended maintenance daily dose is 80mg to 100mg. The maximum recommended total daily dose is 100 mg. Atomoxetine can be administered as a single dose in the morning. Doses can be taken with or after food. For patients that have difficulties tolerating atomoxetine, the dose can be split into a twice daily regimen.
Atomoxetine's mechanism of action makes it less likely to have abuse potential or to cause motor ticks. Peak plasma levels are reached 1 -2 hours after ingestion. The effects of atomoxetine last longer than would be expected from its pharmacokinetics, and once a day administration is effective.

Contra-indications and precautions for use (not exhaustive, for full details see SmPC)

Methylphenidate

- Anxiety or agitation; severe depression, suicidal ideation; tics or a family history of Tourette's syndrome; drug or alcohol dependence ; psychosis; hyperthyroidism; cardiovascular disease; breast feeding.

- Diagnosis or history of severe depression, anorexia nervosa or anorexic disorders, suicidal tendencies, psychotic symptoms, mania, schizophrenia, severe mood disorders, or psychopathic or borderline personality disorder.

- Diagnosis or history of severe and episodic (type1) bipolar (affective) disorder that is not well-controlled.

- Pre-existing cerebrovascular disorders – e.g cerebral aneurysm and vascular abnormalities, including vasculitis or stroke. Unless specialist cardiac advice has been obtained: in pre-existing cardiovascular disorders, including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant.

- Congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias, and dysfunction of cardiac ion channels.

- Misuse and cardiovascular events: Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

- Seizures: Methylphenidate may lower the convulsive threshold and should be used with caution in patients with epilepsy.

- Concomitant use of monoamine oxidase inhibitors (MAOIs) or within 14 days after treatment (due to risk of hypertensive crisis).

Lisdexamfetamine
As for methylphenidate above and hyperthyroidism or thyrotoxicosis, moderate to severe hypertension, glaucoma.

Atomoxetine

- Cardiovascular disease including hypertension and tachycardia; monitor growth in children; QT interval prolongation (avoid concomitant administration of drugs that prolong QT interval); history of seizures; susceptibility to angle-closure glaucoma; hepatic impairment or hepatic disorders; pregnancy; breast-feeding. Seizures are a potential risk with atomoxetine and therefore it should be used with caution in patients with a history of seizure. Discontinuation of atomoxetine should be considered in any patient developing seizure or if there is an increase in seizure frequency.

- Reports of QT interval prolongation have been received in association with atomoxetine. Therefore, it should be used with caution in those with congenital or acquired long QT or a family history of QT prolongation. This risk may be increased if atomoxetine is used concomitantly with other drugs that produce QT prolongation, drugs that can cause electrolyte disturbances and those that inhibit cytochrome P450 2D6 (may increase atomoxetine plasma levels).

- Due to concerns about an increased risk of suicidal thoughts and behaviour, patients should be monitored for signs of depression, suicidal thoughts or suicidal behaviour and referred for appropriate treatment if necessary. Patients and their carers should be informed about the risk and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression.

- There is a risk of rare, but sometimes severe, hepatic disorders. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Patients and carers should be advised of the risk and be told how to recognise symptoms; prompt medical attention should be sought in case of abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice.

- Concomitant use of monoamine oxidase inhibitors (MAOIs) or within 14 days after treatment (due to risk of hypertensive crisis).

Side-effects

This list is not exhaustive, for full details consult the latest SmPC

Methylphenidate

Very common (≥1/10): Headache (usually transient. If it persists, consider stopping treatment and seek advice), insomnia (may be transient, refer back to specialist if it persists), nervousness

Common (≥1/100 to ≥1/10): Nasopharyngitis, tic, aggression, anxiety, affect lability, mood swings, depressed mood, dizziness, cough, pharyngo-laryngeal pain, abdominal pain, vomiting, nausea, diarrhoea, stomach discomfort (seek advice if this persists), irritability, pyrexia, decreased weight and appetite (usually transient, try taking medication after meals to improve appetite). Growth retardation during prolonged use and changes in blood pressure and heart rate (usually an increase). If the pulse is >100, contact the specialist team. Erectile dysfunction (contact specialist team for advice).

Lisdexamfetamine

- Very common (≥ 1/10): Decreased appetite (usually transient, weight loss is rare in adults), insomnia (usually transient. If it persists, consider stopping treatment and seek advice), headache (usually transient. If it persists, consider stopping treatment and seek advice), dry mouth.
- Common (≥1/100 to ≥1/10): Agitation, anxiety, tics, aggression, tremor, dizziness, somnolence, tachycardia, hypertension, palpitations, diarrhoea, constipation, nausea, vomiting, irritability, libido reduced, erectile dysfunction, fatigue, dyspnoea.
- Very Rare (< 1/10,000): Neuroleptic Malignant syndrome - Stop drug and refer. This can be characterised by: hyperthermia, fluctuating conscious level, muscular rigidity, autonomic dysfunction with pallor, tachycardia, labile blood pressure and urinary incontinence, Leucopaenia, thrombocytopenia and anaemia - Refer to specialist team drug may need to be stopped.

Effects on ability to drive and use machines:

Methylphenidate and lisdexamfetamine can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

  o The medicine has been prescribed to treat a medical or dental problem and

  o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

  o It was not affecting your ability to drive safely.

Atomoxetine

Increase in pulse and BP: Patients may experience a modest increase in pulse (mean <10 bpm) and/or increase in blood pressure (mean <5 mmHg). In most cases these are not clinically important. Due to potential for additive pharmacological effects, caution is advised in patients with hypertension, tachycardia, cardiovascular or cerebrovascular disease.

Very common (≥ 1/10): decreased appetite, headache, somnolence, abdominal pain, vomiting, nausea, blood pressure and heart rate increased. GI disturbance is usually transient.

Common (≥1/100 to ≥1/10): Anorexia, irritability, mood swings, insomnia, agitation, anxiety and depression, tics, dizziness, mydriasis, constipation, dyspepsia, rash, fatigue, lethargy, weight decreased, decreased libido, erectile or ejaculatory disorder, dysmenorrhoea or menstrual irregularities, hot flushes, rash.

Suicidal ideation is a rare side-effect which has been reported.

Effects on ability to drive and use machines:

Data on the effects on the ability to drive and use machines are limited. Atomoxetine has a minor influence on the ability to drive and use machines. Atomoxetine has been associated with increased rates of fatigue, somnolence, and dizziness relative to placebo. Patients should be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

Pregnancy and Lactation

Females of child-bearing potential (females post-menarche) should use effective contraception. Please take expert advice if dealing with patient groups likely to be affected by pregnancy and lactation.

Interactions

Please consult the relevant SPC or the BNF for relevant information concerning drug interactions.

Issues to note are:-

Atomoxetine

Undergoes biotransformation primarily through the cytochrome P450 2D6. Caution in CYP2D6 inhibitors such as fluoxetine, paroxetine, quinidine and terbinafine.

Methylphenidate and lisdexamfetamine

Contraindicated in patients treated with an MAOI, caution when administering with dopaminergic drugs (such as antipsychotics).

CNS effects of methylphenidate & lisdexamfetamine possibly enhanced by alcohol.

Anti-hypertensives: Lisdexamfetamine may reduce the effect of antihypertensives.

Others: Not to be given with other sympathomimetics e.g pseudoephedrine & decongestants.

Monitoring for Methylphenidate and lisdexamfetamine

Parameter	Frequency of monitoring	Action	By whom
Full blood count	As clinically indicated	Low threshold for investigation rather than schedule for routine testing e.g. if recurrent infections or purpuric rash occur	Specialist/GP as agreed
Blood pressure and pulse	At initiation, every 6 months or following a dose change	Monitor whilst taking medication & if necessary do an ECG. If the pulse is >100, contact the specialist team.	Specialist/GP as agreed
Weight	At initiation, every 6 months or following a dose change.	If adversely affected consideration should be given to dose reduction or interrupting therapy in those on long-term treatment.	Specialist/GP as agreed
Monitor for insomnia, mood and appetite changes and the development of tics	Ongoing basis and at follow up	If adversely affected consideration should be given to dose reduction or interrupting therapy in those on long-term treatment.	Specialist/GP as agreed

Monitoring for atomoxetine

Parameter	Frequency of monitoring	Action	By whom
Appearance of suicidal behaviour, self-harm or hostility	Ongoing basis and at follow up	Patients/parents should be advised of this risk and made aware of possible signs/symptoms to report back to the specialist immediately if noticed	Specialist
Blood pressure and pulse	At initiation, 6 monthly or following a dose change	Monitor whilst taking medication	Specialist/GP as agreed
Weight	At initation, 6 monthly or following a dose change	If adversely affected consideration should be given to dose reduction or interrupting therapy in those on long-term treatment.	Specialist/GP as agreed
LFTs	As clinically indicated - If physical examination reveals jaundice or other signs of liver abnormalities	Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted	Specialist/GP as agreed

If a person taking ADHD medication has 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, reduce their dose and refer them to a specialist (NICE NG87). Local specialists however recommend that a threshold of 100 beats per minute is used to contact the specialist for advice.

Duration of treatment:
Patients can choose to try stopping the medication every 1-5 years, with the guidance of the specialist clinic if desired. There is no criterion with specific predictivity on this point, except that patients will generally report definitively either way, if they feel they still need the medication once they are off it for longer than a few days.

Costs of extended-release methylphenidate preparations
At October 2017 electronic drug tariff prices, the cost of 30 day's treatment is as follows:

Brand of XL product	Strength	Pack Size	Price
Concerta XL (Existing pts)	54mg	30	£73.62
Xaggitin XL (1st line for NEW pts)	54mg	30	£36.80
Xenidate XL	54mg	30	£36.79
Delmosart	54mg	30	£36.81
Matoride XL	54mg	30	£60.48
Concerta XL (Existing pts)	36mg	30	£42.45
Matoride XL	36mg	30	£33.96
Xenidate XL	36mg	30	£21.21
Xaggitin XL (1st line for NEW pts)	36mg	30	£21.22
Delmosart	36mg	30	£21.23
Concerta XL (Existing pts)	27mg	30	£36.81
Xenidate XL	27mg	30	£18.39
Xaggitin XL (1st line for NEW pts)	27mg	30	£18.40
Delmosart	27mg	30	£18.41
Concerta XL (Existing pts)	18mg	30	£31.19
Xenidate XL	18mg	30	£15.57
Delmosart	18mg	30	£15.59
Xaggitin XL (1st line for NEW pts)	18mg	30	£15.58
Matoride XL	18mg	30	£24.95

NOTE: Prescriptions written generically for methylphenidate XL would be charged as per the originator brand, Concerta XL. So prescriptions should be written by BRAND NAME to achieve prices noted above.

Document review	Date	Whom
First edition	May 2018	Approved by the Bath Area Partnership Therapeutics Committee May 2018
Minor update	July 2019	Removed brand name 'Strattera®' now atomoxetine available as generic.

References

1) National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: diagnosis and management. NG87; March 2018; available at: https://www.nice.org.uk/guidance/NG87