SHARED CARE PROTOCOL FOR: METHYLPHENIDATE, ATOMOXETINE, LISDEXAMFETAMINE and DEXAMFETAMINE FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS

This protocol is under review.

- **For continued prescribing in patients transferred to adult services.**
- **For newly diagnosed adults**

This protocol provides prescribing and monitoring guidance for ADHD treatment in adults. For guidance in <18 year olds refer to the shared care protocol for children and adolescents here. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

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SUMMARY

1. ADHD is a heterogeneous behavioural syndrome characterised by the core symptoms of hyperactivity, impulsivity and inattention. While these symptoms tend to cluster together, some people are predominantly hyperactive and impulsive while others are inattentive.
2. Methylphenidate, atomoxetine lisdexamfetamine, and dexamfetamine are licensed as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD) in children (over 6 years of age) and adolescents when remedial measures alone prove insufficient.
3. The National Institute for Clinical Excellence (NICE) ADHD guidelines[1] state that treatment should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD. Young people with ADHD should normally be transferred to adult psychiatric services if they continue to have significant symptoms of ADHD or other coexisting conditions with adult services carrying out a comprehensive assessment of the person with ADHD.
4. ADHD continues into adulthood in approximately one third of patients. Studies have shown that stimulants work on core symptoms in adults with ADHD. Although unlicensed for use in adults NICE recommends methylphenidate as first line treatment of adults diagnosed with ADHD - with atomoxetine (licensed for continuation from adolescence into adulthood) and dexamfetamine (unlicensed) as alternatives if methylphenidate is ineffective. Dexamfetamine should be considered a third-line option. . NICE guidance was issued in 2008, before lis-dexamfetamine became available in the UK. Lis-dexamfetamine is the only licensed stimulant in adult patients and has a product licence as a first line treatment option in this age group. It has similar average effect sizes to

methylphenidate and dexamfetamine and shares a similar side effect profile. It has the advantage of being administered once daily. It can be considered as an alternative first line treatment to methylphenidate in adults.

5. NICE recommends that continued prescribing and monitoring of drug therapy may be performed by general practitioners, under shared care arrangements ensuring clear lines of communication between primary and secondary care are maintained.
6. When a consultant adult psychiatrist feels that the patient may benefit from continued care by the primary care team then he/she may seek the agreement of the GP concerned to share care providing the following conditions are met:
    a. the patient's condition is stable
    b. the dose of ADHD treatment is stable (this includes ensuring that a patient is stable following a switch from an immediate to a prolonged release preparation)
    c. the GP is provided with sufficient information to ensure they are confident to adequately monitor the patient
    d. Support and advice regarding all aspects of therapy will be provided by the specialist team

   If a GP is not confident to undertake these roles then he or she is under no obligation to do so.
7. If patients from abroad come to stay temporarily in Oxfordshire and formulations previously prescribed are not covered by these guidelines they will need to obtain their medication from their country of origin. Patients from abroad moving permanently to the UK should be assessed and offered a UK licensed product if appropriate. Medicines for ADHD that are only available abroad should not be prescribed / imported. As there are different thresholds for diagnosis of ADHD in other countries any patients prescribed medication within this guidance must fit into ICD 10 diagnostic criteria for ADHD to receive treatment.

2. BACKGROUND

For a diagnosis of ADHD, based on a complete history and evaluation of the patient, symptoms of hyperactivity/impulsivity and/or inattention should:

- meet the diagnostic criteria in ICD-10 (hyperkinetic disorder)[1] **and**
- be associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and/or direct observation in multiple settings, **and**
- be pervasive, occurring in two or more important settings including social, familial, educational and/or occupational settings

Current treatments for ADHD include a range of social, psychological, and behavioural interventions, which may be focused on the child/patient, parents &/or caregivers, or teachers.
NICE recommends that when deciding to treat children or young people with medicines, professionals should consider:

- methylphenidate for ADHD without significant co morbidity
- methylphenidate for ADHD with co-morbid conduct disorder
- 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 has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses
- In consultation with a regional tertiary specialist treatment centre dexamfetamine may be considered in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine

NICE Clinical Guideline 72 (attention deficit hyperactivity disorder: diagnosis and management) was published in 2008 and has not been revised to include lisdexamfetamine yet. Lisdexamfetamine is a prodrug of dexamfetamine.. It has similar average effect sizes to methylphenidate and dexamfetamine and shares a similar side effect profile. It has the advantage of being administered once daily. In Oxfordshire, young people and adults can be prescribed lis-dexamfetamine according to its product licence (children aged 6 years and over: when response to previous methylphenidate treatment is considered clinically inadequate and adults: a first line treatment option)..

General Treatment Principles

- In order to optimise drug treatment, the initial dose should be titrated against symptoms and side effects over 4-6 weeks during which symptoms and side effects should be recorded at each dose change by the prescriber after discussion with the person with ADHD by phone or direct contact.
- Dose titration should be slower if tics or seizures are present in people with ADHD
- If side effects are troublesome a reduction in dose should be considered
- Treatment response for all drugs should be reviewed at least annually including: comprehensive assessment of clinical need; benefits and side effects - taking into account views of patient and carers; the effect of missed doses, planned dose reductions and brief periods of no treatment. It has been recommended that treatment with stimulants should be interrupted at least yearly to determine whether continuation is needed[2]

RESPONSIBILITIES and ROLES[3]

Specialist responsibilities

1. .

Adult psychiatrists

- To accept referrals from GPs for new patients who require assessment for a possible diagnosis of ADHD
- To accept referrals from CAMHS where an 18 year old may need transitioning into adult services (as above)

NEW REFERRALS:

1. To carry out a full assessment of newly referred adults and provide a diagnosis of ADHD if appropriate.
2. To decide on and prescribe the most appropriate drug treatment and discuss benefits and side effects with the patient and/or carer and provide written information where appropriate. In the case of atomoxetine this should also include an explanation of the very rare risk of adverse hepatic reactions, what symptoms to look out for and what action to take should they occur.
3. To carry out and record all necessary baseline physical measurements as follows:
   - Height and weight
   - Baseline cardiovascular status including blood pressure and pulse, a history of exercise syncope, undue breathlessness and other cardiovascular symptoms, family history of cardiac/unexplained death. An ECG should be carried out if indicated
4. The initial dose should be titrated against symptoms and side effects over 4-6 weeks. Symptoms and side effects should be recorded at each dose change. The patient's progress should be reviewed regularly (this may be by telephone if appropriate).
5. To measure blood pressure and pulse following every dose increase, then at 3 and 6 months and every 6 months until the patient is discharged back to the GP.
6. To measure weight every 6 months until the patient is discharged back to the GP.
7. Newly diagnosed adult patients who have been stabilised on treatment should be discharged back to the care of their GP (based on the current contract)

REFERRALS FROM CAMHS

1. To assess, review and monitor ADHD and its treatment in young people reaching 18 (as above) who require ongoing secondary care treatment for other conditions meeting criteria for clusters 4-17.
2. To continue to prescribe ADHD treatments until the patient's ADHD is stable, at which time the patient should be referred back to the care of their GP for ongoing ADHD treatment. Ongoing secondary care treatment for conditions meeting criteria for clusters 4-17 may be necessary.

General Practitioner responsibilities

1. To reply to the request for shared care as soon as practicable.
2. To ensure a full understanding of the responsibilities for managing a patient on methylphenidate, atomoxetine, lisdexamfetamine, or dexamfetamine including identification of side-effects in line with the relevant Summary of Product Characteristics (SPC).
3. To provide repeat prescriptions after stabilisation.
4. Methylphenidate, lisdexamfetamine and dexamfetamine are controlled drugs, subject to safe custody and specific regulations for prescribing. Prescriptions for these medicines are only valid for dispensing within 28 days from the date of signature and, unless there are exceptional circumstances, each prescription should be for no more than 30 days' supply.
5. To monitor for any signs of diversion, misuse or abuse of methylphenidate, lisdexamfetamine and dexamfetamine.
6. To agree a monitoring schedule with the specialist to ensure that that all of the monitoring in the tables below will be undertaken by one or other party at the appropriate time.
7. To undertake such monitoring as agreed with the specialist, recording the results and communicating them to the specialist.
8. To ensure the compatibility of methylphenidate, atomoxetine, lisdexamfetamine or dexamfetamine with newly-prescribed concomitant medication.
9. To report any evidence of change in symptom control to the specialist.
10. To ask the patient whether they are experiencing adverse effects and liaise with the specialist if necessary.
11. To report to and seek advice from the specialist on any aspect of patient care which is of concern to the GP and which may affect treatment. Refer anyone who develops signs of heart disease to a cardiologist.
12. Report adverse events to the specialist and the MHRA.
13. Follow specialist advice (backed up by supporting information) on any changes in treatment.
14. To notify the specialist of the patient's failure to attend appointments.
15. Be aware that school policies on the use of medicines differ and consult with the specialist if a child/adolescent changes to a school with a policy that affects the use of multiple daily doses of medicines.

Patient's/Carer's role
1. To attend all appointments with the patient's GP and specialist. 2. To report any adverse effects to their specialist or GP whilst under treatment. 3. To share any concerns they have in relation to treatment. 4. To ask the specialist or GP if they do not have a clear understanding of their treatment. 5. To take the handheld physical health monitoring charts to each appointment (with the specialist or GP).

ONGOING PHYSICAL MONITORING SCHEDULE

(ref: NICE guideline no 72: ADHD, September 2008 (last updated Feb 2016), Lilly communication – Important safety information on Strattera and risks of increased BP & HR, 5.12.11, SPCs, and Oxford Health DTC decision, Aug 2012 ratified by CEC Nov 2012)

Adult monitoring

	Frequency		**Intervention**
Weight	6 monthly	If there is evidence of weight loss, measure the BMI. Record weight on a chart	Strategies to reduce weight loss, or manage decreased weight gain include: • taking medication with or after food rather than before meals • eating additional meals or snacks early morning or late evening when stimulant effects have worn off • obtaining dietary advice and eating high-calorie foods of good nutritional value Review treatment if weight loss persists.
Pulse	6 monthly (and before and after each dose change)	Record on a chart	If there is sustained resting tachycardia (or a significant increase in pulse eg 20 bpm) or

			arrhythmia refer to a cardiologist consider reducing the dose.
Blood pressure	6 monthly (and before and after each dose change)	Record on a chart	If blood pressure is raised above normal, or there is a clinically significant increase (eg 15-20mmHg), measured on 2 occasions refer to a cardiologist and consider reducing the dose.

SUPPORTING INFORMATION – refer to relevant SPCs for full details

METHYLPHENIDATE (first line treatment for all ages)

Licensed indications http://www.emc.medicines.org.uk
Methylphenidate is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD) in children (over 6 years of age) and adolescents when remedial measures alone prove insufficient. NB the product licence does not include adults

Formulations

Immediate Release Tablets – 5mg, 10mg, and 20mg

Prolonged release formulations:
Concerta® XL18mg, 27mg, 36mg, 54mg tablets – designed to replace three times daily dosing with the immediate release preparations (22:78 release profile)

Delmosart prolonged release 18mg, 27mg, 36mg, 54mg tablets – designed to replace three times a day dosing with immediate release preparations (22:78 release profile).

Xaggitin XL prolonged release 18mg, 27mg, 36mg, 54mg tablets – designed to replace three times a day dosing with immediate release preparations (22:78 release profile).

Xaggitin XL and Delmosart are both bioequivalent to Concerta XL – **Xaggitin XL and Delmosart replace Concerta XL on the formulary for all new patients who require a preparation with a 12 hour duration of action**. Patients already prescribed Concerta XL should have their prescription changed to Xaggitin XL or Delmosart at their next review.

Medikinet® XL – 5mg, 10mg, 20mg, 30mg, 40mg, 50mg, 60mg capsules- designed to be similar to twice daily dosing with immediate release formulations (50:50 release profile).

Equasym® XL – 10mg, 20mg, 30mg capsules - designed to be similar to twice daily dosing with immediate release formulations (30:70 release profile).

Xaggitin XL, Delmosart, Concerta XL Equasym XL and Medikinet XL are more expensive formulations of methylphenidate than immediate release preparations, but may be useful in certain situations, for example to avoid the need to take medicines to school.

Product	Maximum Licensed Dose*
Methylphenidate – ordinary release	60mg daily in divided doses
Xaggitin XL, Delmosart, Concerta XL	54mg once daily with or after breakfast
Equasym XL	60mg once daily before breakfast
Medikinet XL	60mg once daily with or after breakfast

*NICE[3] guidance indicates that according to response, doses of immediate release methylphenidate up to a total maximum of 90mg/day (Xaggitin XL/ Delmosart / Concerta XL equivalent = 108mg) in children and young adults (in the case of children and young people after consultation with a tertiary or regional centre) and 100mg/day in adults may be indicated.

Stimulant dose equivalents[3] IR-MPH: immediate-release methylphenidate; Xaggitin XL, Delmosart, Concerta XL, Equasym XL and Medikinet XL:

IR-MPH	Xaggitin XL / Delmosart / Concerta XL	Equasym XL	Medikinet XL
5	-	-	5
10	-	10	10
15	18	-	15 (10 + 5)
20	-	20	20
30	36	30	30
40	-	40 (2 x 20)	40
45	54	-	45 (40 + 5)
50	-	50 (20 + 30)	50
60	72* (2 x 36)	60 (2 x 30)	60
90	108 (2 x 54)	90 (3 x 30)	90 (60 +30)

Dosage and Administration

Careful dose titration is necessary at the start of treatment with methylphenidate. This may be achieved using an immediate release formulation taken in divided doses or an prolonged release preparation. The recommended starting daily dose is 5 mg once daily or twice daily (e.g. at breakfast and lunch), increasing if necessary by increments of 5-10 mg in the daily dose according to tolerability and degree of efficacy observed. If twice daily dosing is impracticable a prolonged release preparation may be used.
Evidence shows that adults with ADHD do better on higher doses (in terms of mg/kg) than children/adolescents.

Methylphenidate is a Schedule 2 Controlled Drug and is therefore subject to the regulations for controlled drugs (See BNF for more details). Supplies should be limited to no more than 30 days.

Contraindications to methylphenidate

Psychiatric	Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder. Diagnosis or history of severe and episodic (Type 1) Bipolar (affective) disorder (that is not well controlled).
Endocrine	Hyperthyroidism or thyrotoxicosis; phaechromocytoma
Cardiac	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
	Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders
Pregnancy	Pregnancy; breast feeding
Ophthalmic	Glaucoma
Monoamine Oxidase Inhibitors (MAOI)	Patients currently taking or who have taken within the preceding 2 weeks, a non-selective, irreversible monoamine oxidase inhibitor

Cautions:

- **Medical conditions that might be compromised by increases in blood pressure or heart rate**
- Epilepsy
- Tourette's syndrome and tics

- Behavioural disturbance and thought disorder may be exacerbated in psychotic children
- Anyone on methylphenidate who develops signs of heart disease should be referred to a cardiologist[4]
- During long term therapy check full blood count only if leucopenia/ thrombocytopenia/ anaemia is suspected

Interactions:

Drug	Action	Management
Alcohol	May increase methylphenidate levels and exacerbate some of its CNS effects	Advise avoidance of alcohol or use with caution in patients with a history of alcohol use
Anticoagulants	anticoagulant effect of coumarins may be increased	Monitor INR if methylphenidate is started or stopped
Phenytoin, phenobarbitone, primidone	Concentrations of antiepileptics may be increased	This is not an established interaction and is based on a handful of case reports only. However, be alert for an increase in antiepileptic side effects and take levels or reduce the dose if appropriate
Antidepressants	Metabolism of some SSRIs and TCAs may be inhibited and levels increased	Concomitant use may be therapeutically beneficial, however be alert for an increase in side effects and reduce doses if necessary.
Monoamine oxidase inhibitors	Possible hypertensive crisis may result from the combination	Methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors
Clonidine	Adverse effects on blood pressure and pulse may occur	The combination has not been systemically evaluated so the combination should only be used very cautiously.
Antihypertensive drugs	Methylphenidate may decrease the effectiveness of antihypertensives	Monitor blood pressure

Adverse effects of methylphenidate (for full list see Summary of Product Characteristics (SPC)):

Incidence	Adverse Effect	Management
very common (>10%)	Nervousness & Insomnia	Mainly at beginning of treatment and can be controlled by dose adjustment
common (≥1% to <10%)	Abdominal Pain, nausea & vomiting	Mainly at the beginning of treatment and may be helped by taking with food
	Headache, drowsiness, dizziness, dyskinesia, rash, and dry mouth, headache, drowsiness, decreased appetite	These effects are usually transient
	Changes in BP and heart rate	Usually an increase (monitor BP & pulse)
	Dizziness, dyskinesia	
	Decreased appetite, moderately reduced weight gain and slight growth retardation	For children and young people, plot height and weight on growth charts and review regularly. For adults consider monitoring body mass index if weight loss occurs
	Arthralgia	
Less common (≥0.1% to <1%)	Blurred vision, apathy, confusion tics, worsening of pre-existing tics, psychotic disorders, mood changes	If tics occur, consider whether they are stimulant related and whether tic-related

		impairment outweighs the benefits of ADHD treatment. Development of new, or worsening of pre-existing psychiatric symptoms should be monitored at every dose change and at least 6-monthly.
Rarely (≥0.01% to <0.1%)	difficulties in visual accommodation, angina pectoris	
very rarely (<0.01%)	abnormal liver function, leucopenia, thrombocytopenia, and anaemia.	**I**f there are signs and symptoms of liver dysfunction or of haematological abnormalities, discontinue methylphenidate and perform appropriate blood tests. There is no evidence for regular blood testing during methylphenidate treatment.

Time to response with methylphenidate:
Within a few hours or days. May take a few weeks for the full effect.

Onset and duration of action differ depending on the preparation used:

	Dose	% if IR in tablet	% of MR in tablet	Duration of action
IR methylphenidate	5-60mg in divided doses daily (Max 90mg)	100	0	2-4 hours
Xaggitin XL / Delmosart / Concerta XL	18-54mg daily (max 108mg)	22	78	12 hours
Equasym XL	10-60mg daily (max 90mg)	30	70	8 hours
Medikinet XL	10-60mg daily (max 90mg)	50	50	8 hours

ATOMOXETINE

Strattera®(Eli Lilly) 10mg, 18mg, 25mg, 40mg, 60mg, 80mg, 100mg capsules and 4mg/ml oral solution

Licensed indications http://www.emc.medicines.org.uk
Atomoxetine is licensed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (over 6 years of age), adolescents and in adults (diagnosed according to ICD-10 criteria). If symptoms persist into adulthood atomoxetine is also licensed to continue from adolescence into adulthood as long as clear treatment-benefit has been shown.In adults, the presence of symptoms of ADHD that were pre-existing in childhood should be confirmed.

Dosage and Administration

- Administer once daily in the morning with or without food. When atomoxetine administered as single daily dose, therapeutic benefit has been seen to persist for 24 hours throughout morning and evening.
- Patients experiencing unwanted effects taking atomoxetine as single daily dose may benefit from taking two evenly divided doses– the first in the morning and second in the late afternoon/early evening.

	Starting dose	Recommended maintenance dose
<70kg	0.5mg/kg/day	1.2mg/kg/day
>70kg	40mg/day	80mg/day

- Maximum recommended total daily dose is 100mg. The safety of single doses > 120mg and total daily doses > 150mg have not been systematically evaluated but NICE[3] guidelines indicate that doses up to 120mg/day may be necessary where there is a poor response to treatment (in consultation with a

tertiary or regional centre in the case of children or young people). Side effects should be monitored carefully
- As no distinct withdrawal effects have been identified, atomoxetine can be discontinued without the need for tapering of the dose in cases of severe adverse effects. Otherwise the recommendation is to taper the dose when stopping treatment.

Contraindications
Atomoxetine is contraindicated in patients with:

- Known hypersensitivity to atomoxetine or other capsule / oral solution ingredients
- A concomitant MAOI or those who have discontinued an MAOI within the last two weeks.
- Narrow- angle glaucoma, phaeochromocytoma or a history of phaeochromocytoma
- Severe cardiovascular or cerebrovascular disorders which would be expected to deteriorate following a clinically significant increase in blood pressure (e.g. 15-20mmHg) or heart rate (e.g. 20 beats per minute).Severe cardiovascular disorders may include severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies. Severe cerebrovascular disorders include cerebral aneurysm or stroke.

Cautions with atomoxetine:

Caution	**Advice**
Patients with hypertension, tachycardia, cardiovascular or cerebrovascular disease	Atomoxetine can affect heart rate and blood pressure. Most patients taking atomoxetine experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) that may not be clinically important. However, combined data from controlled and uncontrolled ADHD clinical trials show that some patients (approximately 6-12% of children and adults) experience clinically relevant changes in heart rate (20 beats per minute or greater) and blood pressure (15-20 mmHg or greater). Analysis of these clinical trial data showed that approximately 15-32% of patients experiencing clinically relevant changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases. As a result of these findings, patients who are being considered for treatment with atomoxetine should have a careful history and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure and heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. Patients who develop symptoms suggestive of cardiac disease during atomoxetine treatment should undergo a prompt specialist cardiac evaluation.
Patients with congenital or acquired long QT or a family history of QT prolongation[5]	There have been case reports of QT interval prolongation. Therefore atomoxetine should be used with caution in this group of patients.
Cerebrovascular effects	Patients with additional risk factors for cerebrovascular conditions (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with atomoxetine.

Jaundice/laboratory evidence of liver injury	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. All suspected hepatic reactions should be investigated and LFTs taken. Routine monitoring of liver function is not recommended. The reactions are seemingly idiosyncratic in nature therefore routine monitoring is unlikely to be helpful in minimising the risk.
Growth and development retardation	For children and young people, plot height and weight on growth charts and review regularly. For adults consider monitoring body mass index if weight loss occurs. Consideration should be given to dose reduction or interrupting therapy in patients who are not growing or gaining weight satisfactorily
Suicidal ideation and psychotic/manic symptoms	Patients treated for ADHD should be carefully monitored for appearance or worsening of suicide related behaviour, hostility, emotional lability and symptoms suggestive of psychosis or mania developing[5] as these have been reported as uncommon adverse events
Seizures	Seizures are a potential risk with atomoxetine. It should be introduced with caution in patients with a history of seizure. Discontinuation should be considered in any patient developing a seizure or if there is an increase in seizure frequency where no other cause is identified[5]
Pregnancy and lactation	Clinical data lacking – avoid

Interactions with atomoxetine

Incidence	Adverse Effect	Management
CYP2D6 inhibitors e.g. fluoxetine, paroxetine	May markedly increase atomoxetine levels	Dose adjustment and slower titration of atomoxetine may be necessary in those patients who are also taking CYP2D6 inhibitor drugs. Monitor for any increase in atomoxetine adverse effects
Drugs that affect noradrenaline e.g. venlafaxine, imipramine, mirtazapine, pseudoephedrine, phenylephrine	Potential for additive or synergistic pharmacological effects	Monitor for adverse effects
Drugs which can increase blood pressure	Possible additive effects on blood pressure	Monitor blood pressure when drug is started
Antihypertensive drugs	Atomoxetine may potentially increase blood pressure and therefore decrease the effectiveness of antihypertensive medication	Monitor blood pressure
Salbutamol (or other beta$_2$ agonists) – high dose nebulised or oral or intravenous administration	May cause increase in heart rate and blood	Monitor BP and pulse

	pressure due to additive side effects	
QT interval prolonging drugs – (such as neuroleptics, class IA and III anti-arrhythmics, moxifloxacin erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium, or cisapride),	Potential for an increased risk of QT interval prolongation when administered with other QT prolonging drugs	No extra monitoring indicated unless ongoing QTc problem
Drugs that lower seizure threshold. e.g. antidepressants, neuroleptics, mefloquine, bupropion, tramadol.	Seizures are a potential risk with atomoxetine	Consider using alternative treatments that do not lower the seizure threshold where possible, otherwise use with caution at the lowest effective doses.

Adverse effects with atomoxetine include (for full list see SPC):

Very common (>10%):	headache, abdominal pain, somnolence, nausea, vomiting, appetite decreased, blood pressure increased, heart rate increased
Common (≥1% to <10%):	dizziness, insomnia, constipation, fatigue, mood changes
Uncommon (≥0.01% to <1%):	suicide related events, aggression, hostility, and emotional lability, tremor, , syncope, tachycardia, migraines, QT prolongation, blurred vision
Rarely (<0.01%):	abnormal liver function*, seizures, , urinary hesitation and retention

Sexual dysfunction (erectile and ejaculatory dysfunction) and dysmenorrhoea should be monitored[3]
Refer to SPC for full list of adverse effects.

**see additional information in cautions section above*

Time to response for atomoxetine
Onset of action - three to four weeks, sometimes longer.

LISDEXAMFETAMINE (2nd or 3rd line in children and adolescents; 1st or 2nd line in adults)

- Elvanse ® 20mg, 30mg,40mg 50mg 60mg and 70mg capsules.

Licensed indications: Elvanse is indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate.

Dose and titration:
The starting dose is 30 mg taken once daily in the morning. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 20 mg once daily in the morning.
The dose may be increased by 10 or 20 mg increments, at approximately weekly intervals. Elvanse should be administered orally at the lowest effective dosage. The maximum recommended dose is 70 mg/day; higher doses have not been studied.

- Elvanse Adult ® 30mg, 50mg, 70mg capsules.

Licensed indications: Elvanse Adult is indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in adults.

Dose and titration: The starting dose is 30 mg taken once daily in the morning. The dose may be increased by 20 mg increments, at approximately weekly intervals. Elvanse Adult should be administered orally at the lowest effective dosage.

The maximum recommended dose is 70 mg/day; higher doses have not been studied

Caution should be exercised when prescribing lis-dexamfetamine to those at risk of stimulant misuse or diversion.

Lis-dexamfetamine is a schedule 2 controlled drug and is therefore subject to the regulations for controlled drugs (see BNF for more details). Supplies should be limited to no more than 30 days.

Known contraindications

- Symptomatic cardiovascular disease including moderate to severe hypertension and advanced arteriosclerosis structural cardiac abnormalities
- Hyper excitability or agitated states
- Hyperthyroidism, thyrotoxicosis
- Glaucoma
- During or for 14 days after treatment with an MAO inhibitor

Lisdexamfetamine should be used with caution in the following situations:

Caution	Advice
• History of cardiovascular disease or abnormalities	Avoid or take specialist cardiology advice.
• Psychosis or bipolar disorder	Monitor for aggressive behaviour or hostility during initial treatment
• History of drug or alcohol abuse	
• May lower seizure threshold	Discontinue if seizures occur
• Anorexia	
• Tics and Tourettes syndrome (use with caution)	discontinue if tics occur
• Susceptibility to angle-closure glaucoma	
• Avoid abrupt withdrawal.	
• Acute porphyria	

Drug interactions:

MAOIs	Contraindicated – do not co-prescribe. May cause severe headaches or other signs of a hypertensive crisis.
SSRIs and SNRIs	May cause serotonin syndrome
Antihypertensives	Amfetamines may decrease the effectiveness of guanethidine or other antihypertensive medications
Opioid analgesics	Amfetamines potentiate the analgesic effect of narcotic analgesics
Antipsychotics such as chlorpromazine and haloperidol	Block dopamine receptors and may inhibit the central stimulant effects of amfetamines.

Adverse effects of lis-dexametamine include (for full list see SPC):

Very common:	decreased appetite, weight decreased, insomnia, headache
Common:	dry mouth, diarrhoea, nausea, vomiting, tachycardia, irritability, fatigue
Uncommon:	agitation, dysphoria, bruxism, mania, hallucination, dyskinesia, mydriasis, blood pressure increased

Refer to SPC for full list of adverse effects.

DEXAMFETAMINE – 3rd line treatment

Dexedrine® (Auden Mackenzie Pharma Ltd) 5mg tablets
Amfexa (Flynn Pharma Ltd) 5mg, 10mg, and 20mg tablets
Dexamfetamine oral solution 1mg/ml (Martindale Pharma)

Adderall® (Shire US) - a sustained release preparation which contains a mixture of amfetamine/dexamfetamine - is not available in UK. American patients who come to live in Oxfordshire as temporary residents will be asked to obtain their own supply from US. If required, the dose equivalent from Adderall to dexamfetamine would be 1:1 but the latter needs to be taken in divided doses. Any patients treated for ADHD in Oxfordshire need to fit ICD 10 diagnostic criteria.

Licensed Indications:
For ADHD in children and adolescents aged 6 – 17 years old when response to previous methylphenidate is considered inadequate.

Dosage and Administration:

Age	Usual Starting Dose	Maximum dose
3-5yrs (hospital responsibility to prescribe)	2.5mg daily increased if necessary by 2.5mg at weekly intervals[13]	
>6yrs	5mg once or twice a day (breakfast and lunch) increased if necessary at weekly intervals by 5mg. Maintenance dose is given in two to four divided doses	Usual upper limit is 1mg/kg daily up to 20mg daily (though some children have needed 40mg or more for optimal response)

Adults	5mg twice a day increased by 5-10mg weekly as necessary	NICE[3] indicates that treatment of adults may require up to 60mg daily in 2-4 divided doses

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Caution should be exercised when prescribing dexamfetamine to those at risk of stimulant misuse or diversion Dexamfetamine is a Schedule 2 Controlled Drug and is therefore subject to the regulations for controlled drugs (See BNF for more details). Supplies should be limited to no more than 30 days.

Contraindications to dexamfetamine
Patients with symptomatic cardiovascular disease, structural cardiac abnormalities and/or moderate or severe hypertensive disease; patients with advanced arteriosclerosis; during or for 14 days after treatment with an MAO inhibitor; patients with a history of drug abuse or alcohol abuse; patients with hyperthyroidism, glaucoma, porphyria or hyperexcitability; patients with Gilles de la Tourette syndrome or similar dystonias; patients with hypersensitivity to dexamfetamine or any of the excipients

Cautions
- Concomitant guanethidine use
- Mild hypertension
- Family history of dystonias
- Tics - discontinue if tics develop
- Epilepsy (dexamfetamine may reduce the seizure threshold)
- Growth and development - monitored during treatment with dexamfetamine and interrupt treatment if weight gain is lower than expected
- Impaired kidney function
- Unstable personality
- Drug dependence and tolerance to doses
- Stopping treatment - abrupt cessation may produce fatigue and mental depression so treatment should be stopped gradually
- Co-morbid bipolar disorder

Interactions with dexamfetamine:

Drug	Action	Management
MAOI	Can result in potentially fatal hypertensive crisis	Do not co-prescribe
SSRI	May lead to serotonin syndrome Fluoxetine and paroxetine may reduce dexamfetamine levels	Consider if patient reports any unusual side effects Prescribe alternative SSRI
Tricyclic Antidepressants	May increase risk of CV side effects	No extra monitoring indicated
Beta-blockers	May result in severe hypotension	Caution when co-prescribing
Acidifying agents eg ascorbic acid, ammonium chloride	Reduced absorption, increased excretion resulting in reduced levels	No action is generally necessary however consider the possibility of an interaction if therapeutic efficacy is reduced
Alkalising agents e.g. sodium bicarbonate, acetazolamide	Increased absorption, decreased excretion resulting in increased dexamfetamine levels	No action is generally required, however if side effects increase consider stopping the alkalising agent or reduce the dose of dexamfetamine
Alcohol	CNS adverse effects may be exacerbated	Advise avoidance of alcohol or use with caution in patients with a history of alcohol use
Phenothiazines	May inhibit the actions of dexamfetamine	Do not co-prescribe

Adverse effects of dexamfetamine include:

Very common:	Decreased appetite, reduced weight gain and weight loss during prolonged use in children, insomnia, nervousness
Common:	Arrhythmia, palpitations, tachycardia, abdominal pain, nausea and vomiting, dry mouth, changes in blood pressure and heart rate, arthralgia, vertigo, headache, abnormal behaviour, anxiety, depression,

Refer to SPC for full list of adverse effects.

Time to response:
Within a few hours or days. May take a few weeks for the full effect. Onset: 20-60 minutes, duration 3-6hours

CONTACT DETAILS

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GP	Dr	Tel:
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