SHARED CARE GUIDELINE: Methylphenidate, atomoxetine, dexamfetamine and lisdexamfetamine in the management of Attention Deficit Hyperactivity Disorder (ADHD)

The shared care protocol covers the initiation and review of treatment in children and adolescents with ADHD. THIS PROTOCOL DOES NOT COVER THE INITIATION OF NEW TREATMENT IN ADULT PATIENTS.

The protocol however can be extended to cover the ongoing therapy for existing patients once they have reached 18 years of age.

**General Principles**

**Shared Care Responsibilities:**
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. *(BNF, 68, September - March 2015, p. 5)*

**Aims:**
1. The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.
2. Specific shared care guidance should be available for any high cost or high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.
3. Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.
4. Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies of any guideline in this series are available from members of the Greater East Midlands Commissioning Support Unit (GEMS) Prescribing & Medicines Optimisation Team.

**Date of Issue:** December 2015
**Review Date:** December 2016
Principles of shared care
The General Medical Council published their Good Practice In Prescribing And Managing Medicines and which came into effect 25th February 2013. A section of the guidance provides recommendations for the sharing of care which applies to any instance when care is shared between different services.

**Good practice recommendation 35.**
- Decisions about who and who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on patients best interest rather than on convenience or the cost of the medicine and associated monitoring or follow-up

**Good practice recommendation 36.**
- Shared care requires the agreement of all parties including the patient. Effective communication and continuing liaison between all parties to a shared care agreement is essential.

**Good practice recommendation 37.**
- If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.

**Good practice recommendation 38.**
- If you delegate assessment of a patients’ suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required.

**Good practice recommendation 39.**
- In both cases, you will be responsible for any prescription you sign.

**Good practice recommendation 40.**
- If you recommend that a colleague, for example a junior doctor or general practitioner, prescribes a particular medicine for a patient, you must consider their competence to do so. You must satisfy yourself that they have sufficient knowledge of the patient and the medicine, experience (especially in the case of junior doctors) and information to prescribe. You should be willing to answer their questions and otherwise assist them in caring for the patient, as required.

**Good practice recommendation 41**
- If you share responsibility for a patient’s care with a colleague, you must be competent to exercise your share of clinical responsibility.

You should:
- a) Keep yourself informed about the medicines that are to be prescribed for the patient
- b) Be able to recognise serious and frequently occurring adverse side effects
- c) Make sure appropriate clinical monitoring arrangements are in place and that the patient and the healthcare professionals involved understand them
- d) Keep up to date with relevance guidance on the use of the medicines and on the management of the patient’s condition

**Good practice recommendation 42**
- In proposing a shared care arrangement, specialists may advise the patient’s general practitioner which medicine to prescribe. If you are recommending a new or rarely prescribed medicine you should specify the dosage and means of administration and agree a protocol for treatment. You should explain the use of unlicensed medicines and departures from
authoritative guidance or recommended treatments and provide both the general practitioner and the patient with sufficient information to permit the safe management of the patient’s condition.

Good practice recommendation 43

- If you are uncertain about your competence to take responsibility for the patients continuing care you should seek further information or advice from the clinician with whom the patient’s care is shared or from another experienced colleague. If you are still not satisfied you should explain this to the other clinician and to the patient and make appropriate arrangements for their continuing care.

Introduction

In September 2008 the National Institute for Health and Clinical Excellence (NICE) published its clinical guideline 72 on diagnosis and management of Attention Deficit Hyperactivity Disorder (ADHD) in children, young people and adults.

The main conclusions from the guideline in relation to the pharmacological management of the condition are:

- 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 made according to DSM-IV criteria or the guidelines in ICD-10.
- In pre-school age children – drug treatment is not recommended. Healthcare professionals should offer parents or carers of pre-school children with ADHD a referral to apparent-training/education programme as first-line treatment.
- In school age children 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 school age children and young people with severe ADHD and severe impairment – offer drug treatment first line – also offer parents a group based training programme.
- Drug treatment should only be started by a healthcare professional with expertise in ADHD.
- Treatment should be based on comprehensive assessment.
- Drug treatment should always be part of comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions.
- GPs may continue prescribing and monitoring drug treatment under shared care arrangements.
- Do not use antipsychotics for the management of ADHD in children and young people.
- Methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for the management of ADHD.
- Drug choice is the responsibility of the healthcare professional with expertise in ADHD and should be based on:
  - Co-morbidities e.g. tics, tourettes syndrome, epilepsy.
  - Different adverse effects of drug treatments
  - Potential problems with compliance e.g. arrangements for midday dose to be administered at school.
  - Potential risk of drug diversion and misuse
  - Preferences of child/young person and their parent/carer.
- NICE advises:
  - Consider methylphenidate for ADHD without significant co morbidity
  - Consider methylphenidate for ADHD with co morbid conduct disorder
- Consider methylphenidate or atomoxetine in the presence of tics, Tourettes syndrome, anxiety disorder, and stimulant misuse or stimulant diversion.
- Consider atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerate dose or the child/young person is intolerant to low or moderate doses of methylphenidate.
- If there is a choice of more than one drug use the drug with the lowest overall cost.
  - If using methylphenidate, consider:
    - Modified-release preparations for convenience, their pharmacokinetic profile, improving adherence, reducing stigma (because the drug does not need to be taken at school) and reducing problems of storing and administering controlled drugs in schools.
    - Immediate-release preparations if more flexible dosing is required or during initial titration to determine correct dosing levels
  - Consider dexamfetamine when symptoms are unresponsive to the maximum tolerated dose of methylphenidate or atomoxetine.

### Lisdexamfetamine

- Lisdexamfetamine was launched in the UK in 2013 licensed to be used as part of a comprehensive treatment programme for the treatment of attention deficit disorder in children aged over 6 years of age when response to previous methylphenidate treatment is considered to be clinically inadequate. Lisdexamfetamine is a prodrug that is converted in the blood to dexamfetamine. Lincolnshire’s Prescribing and Clinical Effectiveness Forum (PACEF) has approved lisdexamfetamine for use within its licensing authorisation as an option for treatment.

### Drug Details

<table>
<thead>
<tr>
<th>Approved generic name - <strong>Methylphenidate</strong></th>
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</thead>
<tbody>
<tr>
<td>Brand Name - Concerta XL, Equasym XL, Medikinet, Medikinet XL, Ritalin</td>
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<td>Form and strength: standard release and modified release preparations</td>
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<table>
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<tr>
<td>Brand Name - Strattera</td>
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<tr>
<td>Form and strength: 10mg, 18mg, 25mg, 40mg, 60mg and 80mg capsules</td>
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<table>
<thead>
<tr>
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<tr>
<td>Form and strength: 5mg tablets</td>
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<table>
<thead>
<tr>
<th>Approved generic name - <strong>Lisdexamfetamine</strong></th>
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<tbody>
<tr>
<td>Brand name – Elvanse</td>
</tr>
<tr>
<td>Form and strength: 30mg, 50mg and 70mg capsules</td>
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</table>
Specialist Responsibilities

The specialist secondary/tertiary care service will:

1. Provide a comprehensive baseline physical assessment as stipulated in NICE guidance to include:
   - A full mental health and social assessment
   - A full history and physical examination, including:
     - Assessment of history of exercise syncope, undue breathlessness and other cardiovascular symptoms
     - Heart rate and blood pressure (plot on centile chart)
     - Height and weight (plot on growth chart)
     - 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.

2. Routine blood tests and ECGs are not recommended unless there is a clinical indication.
3. Interpret or arrange interpretation of electrocardiogram (ECG) if applicable.
4. Initiate therapy following full discussion with the patient/carer of different treatment options, benefits and risks. The choice of initial drug treatment and any changes to the choice of treatment is the responsibility of the specialist service.
5. Provide relevant, age appropriate, written information to the child/young person/parent/carer about diagnosis, assessment, support, self-help, psychological treatment, drug treatment and possible side effects.
6. Liaise with GP, School and any other agency involved with the child/young person, providing a comprehensive treatment programme for the child/young person. This must include frequency of specialist review following stabilisation and be aware of ongoing issues relating to prescribing when reaching young adulthood.
7. Titrate dose according to schedule adjusting dose as appropriate and undertake monitoring of clinical response and side effects. In certain circumstances agreement may be reached between the specialist service and the GP for the GP to continue to titrate the dose according to response.
8. During titration ensure the:
   - Gradual increase of the dose until there is no further improvement in symptoms, behaviour, education and or relationships and side effects are tolerable. Methylphenidate and dexamphetamine should be titrated over 4-6 weeks.
   - Parents and teachers record symptoms and side effects at each dose change (for example on conners’10-item scale
   - Review progress regularly (for example, weekly telephone contact and at each dose change).
   - Dose titration is slower if tics or seizures are present
   - Dose reduction is considered if side effects become troublesome
9. After titration and dose stabilisation carry out prescription and monitoring under locally agreed shared care arrangements with primary care
10. Send a letter to the GP, once a patient is stabilised on treatment suggesting that shared care should be considered for this patient. This letter should contain the following information.
    - Patient details including name, address date of birth and NHS number.
    - Details of treatment including drug name, dose, date treatment commenced and any further dose titration that is required (if applicable).
Details and the results of any investigations/ base line checks that have been carried out prior to commencement of treatment. This should include blood pressure, pulse rate, weight and height.

Date of patient’s last clinic visit and date of next clinic visit.

Name and contact details of consultant, key worker (if appropriate) and main carer.

Appendix A is an example of the letter but format and content may vary depending on which specialist service is responsible for the treatment.

11. Specialist review should be undertaken either by an ADHD specialist or, if agreed by the person with ADHD and their specialist, in primary care under a locally agreed shared care arrangement after titration and dose stabilisation

12. Review the patient at least annually to assess their need for continued treatment. The annual specialist review of drug treatment should include a comprehensive assessment of the following:

- Routine monitoring of height, weight, blood pressure and heart rate.
- Clinical need, benefits and side effects.
- The views of the person and those of a parent, carer, teacher, spouse, partner and close friends as appropriate.
- 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.
- Coexisting conditions should be reviewed, and the person treated or referred if necessary.
- The need for psychological, social and occupational support for the person and their parents or carers (as appropriate) should be assessed.

13. Issue a letter/clinic report to the GP after each review appointment providing a summary of review findings, confirmation of continuing treatment or treatment changes, confirmation that relevant monitoring has taken place or an explanation as to why it has been deemed necessary or unnecessary, assessment of the child/young person’s progress and confirmation that further prescriptions should be issued and the time of the next review.

14. Respond to any request from the GP to review the patient due to adverse effects of therapy.

15. Report any adverse effects of therapy to the Medicines and Health care products Regulatory Agency (MHRA).

16. Remain alert for the potential for misuse of methylphenidate and dexamfetamine, by observing the frequency and quantity of prescriptions issued and be alert to changes in family circumstances.

17. Advise the GP on continuing or stopping the medication following medical review of the patient and associated drug therapy.

18. Notify the GP if the patient is failing to attend for appropriate monitoring and advise GP on appropriate action. If the patient and their family fail to attend on two consecutive occasions the specialist will contact the patient’s GP and advise them not to issue any further prescriptions and the patient will be discharged from the specialist service.

19. For patients aged 17-18 years manage withdrawal of treatment prior to discharge or refer to appropriate adult services. Reassess a young person treated in CAMHS or paediatric services at school leaving age to determine if treatment needs to be continued. If it does arrange for transition to adult services (usually by age 18) giving details of the anticipated treatment and services required.

20. Will inform the patient’s GP if the ongoing responsibility for patient care is to be transferred to another consultant/ specialist service and to ensure both parties are aware of this change.
Methylphenidate, dexamfetamine and lisdexamfetamine are schedule 2 controlled drugs and therefore all controlled drug prescription writing legislation set down in the section of “Controlled Drugs and Drug dependence” in the British National Formulary (BNF) applies.

GP Responsibilities
The GP will:
1. Prior to referral to the specialist service determine the severity of behavioural and/or inattention problems suggestive of ADHD and how they affect the child or young person and their parents or carers. If problems are having an adverse impact on development or family life and persist with at least moderate impairment following either a period of up to 10 weeks watchful waiting or referral into a parent training/education programme then refer to secondary care either a paediatrician, child psychiatrist or specialist from the Children & Adolescents Mental Health Service. CAMHS.
2. Refer directly to secondary care if the behavioural and/or inattention problems are associated with severe impairment.
3. Notify the consultant in writing, without undue delay whether or not they agree to share care.
4. Provide any information requested by the specialist in relation to previous history of QTC prolongation or concurrent medication.
5. Prescribe the drug therapy as part of the shared care agreement once patient is stabilised. In certain circumstances the GP, following a request from the consultant specialist may agree to further titrate the dose according to the patient’s response.
6. Monitor the patients overall health and well-being on a needs led basis.
7. Monitor patients for side effects including heart rate, BP and weight as stipulated in monitoring section of the NICE clinical guideline 72. (see monitoring section page 14)
8. Monitor those patients prescribed atomoxetine for signs of depression.
9. Monitor patient’s suicidal thoughts or behaviour. If warning signs are detected treatment should be discontinued and urgent advice sought from specialist.
10. Remain alert for the potential for misuse of methylphenidate and dexamfetamine, by observing the frequency and quantity of prescriptions issued and be alert to changes in family circumstances.
11. Report adverse effects of therapy to the consultant and the medicines and health care products Regulatory Agency (MHRA).
12. Act on advice provided by the consultant if patient does not attend for appropriate monitoring.
   If the patient and their family fail to attend on two consecutive occasions then the GP will be advised not to issue any further prescriptions.
13. Can re-refer patients and their families back to secondary care following discontinuation of treatment as outlines in point 11 if the family can show they are willing to engage with both the specialist service and the monitoring requirements for the proposed treatment.
14. Alert the specialist if there are any concerns about the patient’s response to treatment or the ability of the patient to tolerate treatment.
15. Alert the specialist if there are any issues identified relating to poor concordance/compliance e.g. irregularities in the collection of repeat prescriptions.

Referral Criteria
The patients will be stabilised on a suitable dose of methylphenidate, atomoxetine, dexamfetamine or lisdexamfetamine before prescribing responsibility is transferred to the GP.
The specialist service will continue to supply treatment until the GP is prepared to accept responsibility for shared care.
**Licensed Indications**

Methylphenidate hydrochloride, atomoxetine, dexamfetamine and lisdexamfetamine are all licensed for the treatment of Attention Deficit Hyperactivity Disorders. Their license states that treatment should be initiated by a specialist physician experienced in managing the condition or in the case of dexamfetamine use should be under specialist supervision. There are licensing variations between the various substances and products. Refer to summary of product characteristics for further details. **Methylphenidate, dexamfetamine and lisdexamfetamine are not licensed for the management of ADHD in adults aged over 18 years. Atomoxetine, methylphenidate and lisdexamfetamine are not licensed for use in children under the age of 6 years of age.**

**Recommended Dosage and Administration**

**Methylphenidate**

**Standard formulations** e.g. generic methylphenidate or branded products Ritalin or Medikinet require careful dose titration.

*Child 6-18 years.* - The recommended starting dose is 5mg daily or twice daily increasing as necessary in weekly increments of 5-10mg to an effective dose. Usual maximum recommended dose is 60mg in two or three divided doses. Dose may be increased beyond the licensed daily dose of 0.7mg/kg up to 2.1mg/kg daily in 2-3 divided doses (up to a maximum of 90mg daily), under the direction of a specialist. Discontinue if no response after 1 month.

At higher doses monitor carefully for adverse effects.

*Adults over 18 years – unlicensed use.* 5mg three times daily increased if necessary at weekly intervals according to response. Maximum dose 100mg daily in 2-3 divided doses.

**Modified release formulations** – vary in the ration of immediate release to extended release methylphenidate that they contain, and also have differing pharmacokinetic profiles resulting in some delivering higher levels of methylphenidate at the start of the day and some provide a therapeutic effect lasting that of a school day 8 hours where others provide an effect lasting up to 12 hours.

**Concerta XL** – The formulation is 22% immediate release and 78% extended release. For those patients who have not previously taken methylphenidate the starting dose is for a child 6-18 years, 18mg once daily. Dose should be carefully titrated in increments of 18mg once a week to a maximum daily dose of 54mg/day taken as a single daily dose in the morning. If patients have previously taken methylphenidate Concerta XL please refer to manufactures information for equivalent doses. Discontinue if no response after 1 month.

**Equasym XL** - This contains immediate release and extended release methylphenidate in the ratio 30:70. For those patients who have not taken methylphenidate before the starting dose is for a child 6-18 years, 10mg once daily in the morning increasing gradually at weekly intervals if necessary, usual maximum 60mg daily but may be increased to 2.1mg/kg daily (max 90mg)- unlicensed dose) under direction of specialist. For those patients currently on immediate release methylphenidate careful dose titration will be required when switching to a modified release formulation. Discontinue if no response after 1 month.

**Medikinet XL** - This formulation consists of 50% extended release and 50% immediate release methylphenidate. In those patients not currently taking methylphenidate the starting dose for child 6-18 years is 10mg once daily in the morning with or after breakfast increasing gradually to a maximum of 100mg, if required. For those patients currently on immediate release methylphenidate careful dose titration will be required when switching to a modified release formulation.

**Atomoxetine**

Child over 6 years of age and adolescent with body weight under 70kg, initially 500micrograms/kg daily for seven days then increased according to response to usual maintenance dose of 1.2mg/kg
daily, but may be increased to 1.8mg/kg daily (maximum dose 120mg daily – unlicensed) under
direction of a specialist.
Child and adolescent with body weight over 70kg, initially 40mg daily for seven days then increased
according to response to usual maintenance dose of 80mg daily; but may be increased to
1.8mg/kg/day up to a maximum dose of 120mg daily (unlicensed) under the direction of a specialist.
These higher doses should only be used after review of poor response to drug treatment and in
consultation with a tertiary or regional centre. At higher does monitor carefully for adverse effects.
Total daily dose can be given either a single dose in the morning or in two divided doses with the last
dose given no later then early evening.
**Atomoxetine is now licensed for use in adults when the presence of symptoms of ADHD that
were pre-existing in childhood are confirmed. Initiation of treatment in adults is not covered
under this shared care protocol.**

**Dexamfetamine**
Child 6-18 years initially 2.5mg 2-3 times daily increased if necessary at weekly intervals by 5mg
usual max 1mg/kg (up to 20mg) daily.
Maintenance dose is given in 2-4 divided doses.
Use in adults is unlicensed.
**Lisdexamfetamine dimesylate**
Children aged 6 years or older initially 30mg once daily in the morning. The lowest effective dose
should be used. The dose can be increased by 20mg increments at approximately weekly intervals to
a maximum recommended daily dose of 70mg. Treatment should be stopped if the symptoms do not
improve after appropriate dosage adjustment over a one month period.
Use in adults is unlicensed.

**Background Pharmacology**
Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed behavioural
disorders of childhood, affecting 1-5% of school aged children. Its basic symptoms include
developmentally inappropriate levels of attention, concentration, activity, distractibility and impulsivity.
It causes problems in at home, in school, with peer relationships and may have long term adverse
effects on self confidence, academic performance, vocational success and social development.
Drugs licensed for the treatment of this disorder should be used as part of a comprehensive treatment
programme.
Drugs used can be divided into two groups.
Central Nervous Stimulants
Methylphenidate – is a central nervous stimulant.
Dexamfetamine - is a sympathomimetic amine with a central stimulant and anorectic activity. On set
of action is 60-90 minutes with peak serum concentration being reached 3 hours after oral
administration.
Lisdexamfetamine dimesylate is a pharmacologically inactive prodrug of dexamfetamine. After oral
administration lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed
primarily by red blood cells to dexamfetamine.
Both methylphenidate and dexamfetamine are controlled drugs and subject to the requirements of the
misuse of drugs regulations. As a prodrug of dexamfetamine it is expected that lisdexamfetamine will
also be classed as a schedule 2 controlled drug. In the interim the Home Office and the Royal
Pharmaceutical Society have advised that Lisdexamfetamine should be treated as a schedule 2 CD
All three drugs potentially have a resale value as drugs of abuse. These are all amphetamine related
substances and are effective in increasing attention and concentration and reducing impulsive and
restless behaviours. Secondary effects include increased school performance, improved peer relations and reduced aggression.

Atomoxetine is a highly selective and potent noradrenaline reuptake inhibitor, although the precise mechanism by which it works on ADHD is unknown. It is not a psychostimulant and is not an amphetamine derivative. It is effective in increasing attention and concentration and reducing impulsive and restless behaviours. It may also improve sleep and have an effect on early morning behaviours. It provided 24 hour control of ADHD symptoms.

### Adverse Effects (please refer to BNF and product SPC for more details)

**Methylphenidate**
- Abdominal pain, nausea, vomiting, diarrhoea, dyspepsia, dry mouth, anorexia, reduced weight gain, tachycardia, palpitation, arrhythmias, changes in blood pressure, cough, nasopharyngitis, tics (very rarely tourettes syndrome), insomnia, nervousness, asthenia, depression, irritability, aggression, headache, drowsiness, dizziness, movement disorders, fever, arthralgia, rash, pruritus, alopecia, growth restriction. Less commonly constipation, dyspnoea, abnormal dreams, confusion, suicidal ideation, urinary frequency, haematuria, muscle cramps, epistaxis, rarely angina, sweating and visual disturbances. Very rarely hepatic dysfunction, myocardial infarction, cerebral arteritis, psychosis, seizures, neuroleptic malignant syndrome, tolerance and dependence, blood disorders including leucopenia and thrombocytopenia, angle-closure glaucoma, exfoliative dermatitis and erythema multiforme, supraventricular tachycardia, bradycardia and convulsions also reported.

**Atomoxetine**
- Anorexia, dry mouth, nausea, vomiting, abdominal pain, constipation, dyspepsia, flatulence, palpitation, tachycardia, increased blood pressure, postural hypotension, hot flushes, sleep disturbances, dizziness, headache, fatigue, lethargy, drowsiness, irritability, tremor, rigors, urinary retention, enuresis, prostatitis, sexual dysfunction, menstrual disturbances, conjunctivitis, dermatitis, pruritus, rash, sweating, weight changes, less commonly suicidal ideation, aggression, hostility, emotional lability, cold extremities, mydriasis, very rarely angle-closure glaucoma also reported hepatic disorders, psychosis, hypoaesthesia, anxiety, depression, seizures and Raynaud’s phenomenon.

**Dexamfetamine**
- Nausea, diarrhoea, dry mouth, abdominal cramps, anorexia (increased appetite also reported) weight loss, taste disturbance, ischaemic colitis, palpitations, tachycardia, chest pain, hypertension, hypotension, cardiomyopathy, myocardial infarction, cardio vascular collapse, cerebral vasculitis, stroke, headache, restlessness, depression, hyperreflexia, hyperactivity, impaired concentration, ataxia, anxiety, aggression, dizziness, confusion, sleep disturbances, dysphoria, euphoria, irritability, nervousness, malaise, obsessive-complusive behaviour, paranoia, psychosis, panic attack, tremor, seizures, neuroleptic malignant syndrome, anhedonia, growth restriction in children, pyrexia, renal impairment, sexual dysfunction, acidosis, rhabdomyolysis,/mdratriasis, visual disturbances, alopecia, rash, sweating, urticaria, central stimulants have provoked choreoathetoid movements and dyskinesia tics and Tourette syndrome in predisposed individuals, very rarely angle closure glaucoma.

**Lisdexamfetamine**
- Nausea, decreased appetite, vomiting, diarrhoea, dry mouth, abdominal cramps, dyspnoea, sleep disturbances, tics, aggression, headache, dizziness, drowsiness, mydriasis, labile mood, weight loss, pyrexia, malaise, growth restriction in children. Less commonly anorexia, tachycardia, palpitation, hypertension, logorrhoea, anxiety, paranoia, restless depression, dysphoria, dermatillomania, mania, hallucination, sweating, tremor, visual disturbance, sexual dysfunction, rash. Very rarely angle closure glaucoma also reported cardiomyopathy, euphoria, seizures, central stimulants have
provoked choreoathetoid movements and dyskinesia and Tourette syndrome in predisposed individuals.

As a black triangle drug all adverse reactions should be reported through the yellow card system accessible online at www.mhra.gov.uk/yellowcard.

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**Drug Interactions** *(please refer to BNF and product SPC for more details)*

**Methylphenidate**
Monoamine Oxidase Inhibitors (MAOIs) contraindicated in those being treated with MAOI’s or those who have had treatment in preceding two weeks due to risk of hypertensive crisis.
Warfarin – may increase the anticoagulant effect
Anticonvulsants – may increase plasma levels of phenobarbitone, primidone.
Alcohol – may increase CNS effects of methylphenidate.
Anti- hypertensives – may decrease effectiveness.
Haloperidol anaesthetics – risk of sudden blood pressure increase during surgery. If surgery planned methylphenidate should not be used on day of surgery.
Dopaminergic drugs – caution recommended if using with dopamine antagonists such as antipsychotics or dopamine agonists such as tricyclic antidepressants as action of methylphenidate is to increase extracellular dopamine levels.
Centrally acting alpha-2 agonists e.g. clonidine - serious adverse reactions have been reported including sudden death – avoid concomitant use.

**Atomoxetine**
Monoamine Oxidase Inhibitors (MAOIs) Atomoxetine should not be used in combination with a MAOI. It should not be used within a minimum of two weeks after discontinuing therapy with a MAOI and treatment with an MAOI should not be initiated within two weeks after discontinuing treatment with atomoxetine.
Increases risk of ventricular arrhythmias with tricyclic antidepressants, methadone, amiodarone, disopyramide, parenteral erythromycin, moxifloxacin, and mefloquine, antipsychotics that increase the QTC interval, sotalol and diuretics.
Use with caution in patients on concomitant drugs that may lower the seizure threshold e.g. antidepressants, mefloquine, bupropion, tramadol and neuroleptics.

**Dexamfetamine**
Tricyclic antidepressants may increase risk of cardiovascular adverse effect.
Beta-blockers used concurrently may result in severe hypertension.
Lithium may antagonise effects of dexamfetamine.
Concurrent use of MAOIs or use within the preceding fourteen days may precipitate a hypertensive crisis.
Antihistamines may delay absorption of ethosuximide, phenobarbitone and phenytoin.
Acute dystonia has been noted with concurrent administration of haloperidol.
Phenothiazines may inhibit the actions of dexamfetamine.
Alcohol can increase CNS effects of dexamfetamine and patients should be advised to abstain from alcohol during treatment.

**Lisdexamfetamine**
Ascorbic acid can acidify urine, increase urinary excretion of lisdexamfetamine and reducing its half-life.
Sodium bicarbonate and other agents that alkalise the urine decrease urinary excretion and can prolong the half life.
Monamine oxidase inhibitors (MAOI’s) should not be administered during or within 14 days of MAOI’s as can increase the release of norepinephrine and other monoamines leading to severe headaches and other signs of hypertensive crisis.
Antihypertensives – may decrease effectiveness of guanethidine and other antihypertensive medications.
Could potentiate the analgesic effect of narcotic analgesics.
Chlorpromazine and haloperidol inhibit central stimulant effects of amphetamines.
Lithium may block anorectic and stimulatory effects of amphetamines.
May elevate plasma corticosteroid levels.

Precautions (please refer to Summary of product characteristics and current edition of the BNF for more detail)

**Methylphenidate**
Should be used with caution in patients with history of epilepsy (discontinue or seek specialist advice if increased seizure frequency), psychotic disorders anxiety or agitation, tics or a family history of Tourette syndrome, susceptibility to angle-closure glaucoma; avoid abrupt withdrawal.

**Atomoxetine**
Should be used with caution in patients whose underlying medical condition 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 such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during atomoxetine treatment should undergo a prompt specialist cardiac evaluation.

Atomoxetine should only be used with caution in those with congenital or acquired long QTC or a family history of QTC prolongation. The risk increases if atomoxetine is used concomitantly with other drugs that produce QTC prolongation, drugs that cause electrolyte disturbances and those that inhibit cytochrome P450 2D6.

Patients should be monitored for the appearance of, or worsening of suicide related behaviour, hostility, psychotic or manic symptoms and emotional lability.
Seizures are a potential risk therefore atomoxetine should be introduced with caution in patients with a history of seizure. Discontinuation should be considered in any patient developing seizure or if there is an increase in seizure frequency.
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 risk of hepatic disorders and told how to recognise symptoms.
Hepatic impairment - halve dose in moderate impairment, quarter dose in severe impairment.

**Dexamfetamine**
Use with caution in patients with anorexia, mild hypertension (contra-indicated if moderate or severe) psychosis or bipolar disorder, monitor for aggressive behaviour or hostility during initial treatment, history of epilepsy discontinue if seizures occur), tics and Tourette’s syndrome (use with caution) – discontinue if tics occur, monitoring growth in children and susceptibility to angle closed glaucoma. Avoid abrupt withdrawal, data on safety and efficacy of long-term use not complete, acute porphyria. Special caution for use in children- monitor height and weight as growth restriction may occur in prolonged therapy. (Drug free periods may allow catch up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity)

**Lisdexamfetamine**
Use with caution in those with anorexia, history of cardiovascular disease or abnormalities including mild hypertension, heart failure, recent MI and ventricular arrhythmia. Evaluate cardiovascular status before starting treatment.
Use with caution in those with psychotic disorders, bipolar disorder, monitor for aggressive behaviour or hostility during drug treatment, history of drug or alcohol abuse, may lower seizure threshold (discontinue if seizures occur) tics and Tourettes syndrome (use with caution and discontinue is tics occur.
Use with caution in those with susceptibility to angle-closure glaucoma, avoid abrupt withdrawal, acute porphyria.
Special caution for use in children- monitor height and weight as growth restriction may occur in prolonged therapy. (Drug free periods may allow catch up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity)
Renal impairment.

**Contraindications (please refer to Summary of product characteristics and current edition of the BNF for more detail)**

**Methylphenidate –**
Not to be used in patients with severe depression, suicidal ideation, anorexia nervosa, drug or alcohol dependence, psychosis, uncontrolled bipolar disorder, hyperthyroidism or thyrotoxicosis, cardiovascular disease (including heart failure, cardiomyopathy, severe hypertension, arterial occlusive disease, angina, and arrhythmias), structural cardiac abnormalities, phaeochromocytoma, glaucoma, vasculitis, cerebrovascular disorders.
Hypersensitivity or intolerance to methylphenidate or excipients
Pregnancy - no information available avoid use unless potential benefit outweighs risk.
Breast feeding – limited information available – avoid..

**Atomoxetine –**
Do not use in patients with narrow angle glaucoma
Should not be used if patient concurrently taking monoamine oxidase inhibitors (MAOIs).
Hypersensitivity or intolerance to atomoxetine or excipients
Should not be used in patients with phaeochromocytoma or history of phaeochromocytoma.
Should not be used in patients with severe cardiovascular or cerebrovascular disorders.
Pregnancy - no information available avoid use unless potential benefit outweighs risk.
Breast feeding – avoid use present in milk in animal studies.

**Dexamfetamine –**
Not to be used in patients with marked anxiety disorders, hyperexcitability, psychosis, history of drug or alcohol abuse, cardiovascular disease (including moderate to severe hypertension), structural cardiac abnormalities, advanced arteriosclerosis, hyperthyroidism, glaucoma and in pregnancy and breast feeding.
Contra-indicated in Tourettes syndrome but is used with caution by specialists. Any prescribing in this situation is unlicensed.
Hypersensitivity or intolerance to dexamfetamine or excipients.

**Lisdexamfetamine –**
Not to be used in those with symptomatic cardiovascular disease including moderate to severe hypertension and advanced arteriosclerosis, hyperexcitability or agitated states, hyperthyroidism.
Not to be used if breast feeding.
Pregnancy – manufacturer advises use only if potential benefit outweighs risk.

**Monitoring**

**Responsibility of specialist service prior to commencement of treatment**
Children and young people 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 centile chart)
- Height and weight (plotted on growth chart)
- Family history of cardiac disease and examination of the cardiovascular system.

- An ECG if there is a 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 abuse and drug diversion
- Enquiry about history of seizures or tics.

**Monitoring required during drug treatment**

Blood pressure and heart rate should be monitored before and after each dose change, and every three months. **If sustained tachycardia, arrhythmia or systolic BP greater than 95th centile (or a clinically significant increase) is measured on 2 occasions contact paediatrician for advice and consider dose reduction.**

Height should be monitored every 6 months.

Weight should be measured at 3 & 6 months after treatment started and then 6 monthly thereafter.

Both height and weight measurements should be plotted on growth centile chart and should be regularly reviewed by the specialist responsible for treatment.

During treatment NICE states that people taking methylphenidate, dexamfetamine or atomoxetine, do not need routine blood tests and ECGs unless there is a clinical need.

For children and young people taking methylphenidate and dexamfetamine, healthcare professionals/parents and carers should monitor changes in the potential for drug misuse and diversion which may come with changes in circumstances and age. In these situations modified release methylphenidate or atomoxetine may be preferred.

In young people sexual dysfunction and dysmenorrhoea should be monitored as potential side effects of atomoxetine.

**Reference values for blood pressure measurements**

The Journal of hypertension 27(9):1719-1742 September 2009 contains reference blood pressure charts for children and adolescents. This can be accessed via The British Hypertension Society website following the link below:

http://www.bhsoc.org/resources/children-young-people/

Appendix B contains the Nottinghamshire Guideline for the assessment and management of Hypertension in Paediatric Patients which also contains reference tables for blood pressure centiles by gender, age and height percentiles.
At normal doses atomoxetine can be associated with treatment emergent psychotic or manic symptoms e.g. hallucinations, delusional thinking, mania or agitation) in children or adolescents without a previous history. If such symptoms occur contact consultant medical team urgently for advice and consider discontinuing or withdrawing treatment. Patients and their carers should be informed of risk of suicidal thoughts/behaviour and advised to contact the specialist team for urgent advice if these occur or if there is worsening of irritability, agitation or depression.

Development of seizures. Discontinue treatment and seek urgent advice from specialist.

Hepatic disorders. Be alert to possibility of jaundice or laboratory evidence of liver injury. If either occurs discontinue treatment and seek urgent specialist advice. In these circumstances treatment must not be restarted. Patients and carers should be advised of risk of liver damage 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.

**Indication of Likely Cost of Therapy in Primary Care**

Approximate annual cost at licensed dose.

**Methylphenidate**

- **Methylphenidate** 5-60mg in one to two divided doses £37 -£396
- **Medikinet** 5-60mg in one to two divided doses £37 - £394
- **Ritalin** -5-60mg in one to two divided doses £41-£481
- **Concerta XL** 18-54mg once daily £375-£884
- **Equasym XL** 10-60mg once daily £300-£840
- **Medikinet XL** 10-60mg once daily £289 - £808

**Atomoxetine**

- **Strattera** 10/18/25/40/60mg one tablet daily £812

**Dexamfetamine**

- **Dexedrine** 2.5mg-40mg daily, £160-£2,574
- **Lisdexamfetamine** 30-70mg daily £758 - £1,081

Guide prices from September 2015 edition of MIMS
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Tel 01476 560759

Dr Anne Thompson
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Tel 01476 560759

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CAMHS, Ash Villa
Greylees
Sleaford
Tel 01529 488061

United Lincolnshire Hospitals Trust Community Paediatric Services
Boston
Dr E Ikhena
Boston Health Centre
Tel 01205 360880 ext 208
Grantham
Dr J Clarke
Grantham Hospital
Tel 01476 464500

Shared Care Guideline: Methylphenidate, atomoxetine, dexamfetamine and lisdexamfetamine in the management of Attention Deficit Hyperactivity Disorder (ADHD) – V.01
Lincoln
Dr F Johnson
Lincoln County Hospital
Tel 01522 5125512 Ext 3177

For advice regarding medication
Specialist Mental Health Pharmacy Service
Gervas House
Long Leys Road
Lincoln
LN1 1EJ
Tel No 01522 577000 ext. 7563

References:
2. NICE Clinical Guideline 72 - Attention deficit hyperactivity disorder. Diagnosis and management of ADHD in children, young people and adults.
9. Summary of product characteristics Strattera 10mg,18mg,25mg,40mg,60mg & 100mg hard capsules. Eli Lilly and Company limited. Updated 19.12.2014.

Compiled on behalf of Lincolnshire Partnership Trust Medicines Management Committee, United Lincolnshire Hospitals Community Paediatric Service and NHS Lincolnshire by:

Cathy Johnson
Interface Lead Pharmacist, NHS Lincolnshire

Updated November 2014
Shiraz Haider
Chief Pharmacist, LPFT

Dr Fosade Johnson
Consultant, ULHT Community Paediatric Service

Shared Care Guideline: Methylphenidate, atomoxetine, dexamfetamine and lisdexamfetamine in the management of Attention Deficit Hyperactivity Disorder (ADHD) – V.01
Appendix A Invitation to shared care.

Shared Care Protocol for treatment of Attention Deficit Hyperactivity Disorder in Childhood

Section 1: Agreement for transfer of prescribing to GP

<table>
<thead>
<tr>
<th>Patient details/addressograph</th>
<th>Name ..............................................................................................................</th>
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<tbody>
<tr>
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<td>Address .....................................................................................................</td>
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<td>DOB .......................................................... Hospital No ..............................</td>
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Drug name and dose:
The following tests, investigations have been carried out:

<table>
<thead>
<tr>
<th>Blood pressure:</th>
<th>Date:</th>
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<tbody>
<tr>
<td>Pulse:</td>
<td>Date:</td>
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<tr>
<td>Weight: (including centiles)</td>
<td>Date:</td>
</tr>
<tr>
<td>Height: (including centiles)</td>
<td>Date:</td>
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<tr>
<td>Diagnosis of ADHD made on (date):</td>
<td></td>
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<tr>
<td>Medication started on (date):</td>
<td></td>
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<tr>
<td>Patient stabilised on (drug/dose):</td>
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</tr>
<tr>
<td>Patient’s last clinic visit on (date):</td>
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<tr>
<td>Patient’s next clinic visit on: then every months</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Consultant:</th>
<th>Agreement to shared care, to be signed by GP and Consultant before transfer of care to GP.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>Consultant Signature:  ...........................................................................................................</td>
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<tr>
<td>Contact Number:</td>
<td>Date: ..........................................................</td>
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<tr>
<th>GP</th>
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<td>Address:</td>
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<tr>
<td>Contact Number:</td>
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<tr>
<th>Main Carer / parent / guardian:</th>
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<tr>
<td>Contact Number:</td>
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<table>
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<tr>
<th>Key worker if appropriate:</th>
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<tbody>
<tr>
<td>Contact Number:</td>
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The GP has the right to refuse to agree to shared care, in such an event the total clinical responsibility will remain with the consultant. The GP should then discuss alternative arrangements with the responsible consultant.
**Hypertension**

<table>
<thead>
<tr>
<th>Title of Guideline (must include the word “Guideline” (not protocol, policy, procedure etc))</th>
<th>Guideline for the assessment and management of Hypertension in Paediatric Patients</th>
</tr>
</thead>
</table>
| Contact Name and Job Title (author) | David Broodbank ST7 Paediatrics  
Corinne Langstaff Paediatric Nephrology Consultant |
| Directorate & Speciality | Family Health – Paediatric Nephrology |
| Date of submission | September 2013 |
| Date on which guideline must be reviewed (this should be one to three years) | September 2016 |
| Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis) | Children and Young People presenting to Nottingham Children’s Hospital With Hypertension |
| Abstract | This guideline describes the Assessment and Management of Hypertension in Paediatric patients. |
| Key Words | Hypertension, High Blood Pressure, Child, Young Person, Renal, |
| Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues? | 2a |
| Evidence base: (1-5) | 1a meta analysis of randomised controlled trials  
1b at least one randomised controlled trial  
2a at least one well-designed controlled study without randomisation  
2b at least one other type of well-designed quasi-experimental study  
3 well –designed non-experimental descriptive studies (ie comparative / correlation and case studies)  
4 expert committee reports or opinions and / or clinical experiences of respected authorities  
5 recommended best practise based on the clinical experience of the guideline developer |
| Consultation Process | Children’s Renal Unit guideline review,  
Paediatric Clinical Guidelines Group |
| Target audience | Clinicians and healthcare professionals caring for children and young people treated for Hypertension at Nottingham University Hospitals NHS Trust |

This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.

<table>
<thead>
<tr>
<th>Version Number</th>
<th>Date Produced</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension Guideline V1</td>
<td>May 2008</td>
<td>Dr D Wood, Dr S Rhodes</td>
</tr>
</tbody>
</table>
| V2 | Sept 2013 | Dr David Broodbank  
Dr Corinne Langstaff |
Document History

Major changes from previous guideline:

1. Inclusion of definitions of hypertension in line with 4th report
2. Reduction in detail regarding presentation, history and examination
3. Clarification of section on lifestyle management
4. Inclusion of section on management of hypertensive crisis
5. Update of centile charts as per 4th report and inclusion of centile charts for neonates.
6. Addition of section on specific anti-hypertensive agents
7. Addition of separate algorithms for patients with acute severe / symptomatic hypertension and asymptomatic hypertension
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<td>Appendix 4 – Measuring of blood pressure</td>
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<td>Appendix 5 – Causes of hypertension</td>
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1. **Introduction**

Hypertension in children is common, occurring in 5% of the paediatric population. Although often asymptomatic, a significant proportion of children will have an underlying cause so investigation is usually justified. The measurement of blood pressure itself in children is challenging and hypertension will only be identified if children have their blood pressure checked appropriately. The long-term health risks for hypertensive children and adolescents can be substantial and so it is important to seek out and treat hypertension.

2. **Definitions (Fourth Report³)**

- **Hypertension**: Average systolic blood pressure (SBP) and / or diastolic blood pressure (DSP) greater or equal to the 95th percentile for age, sex and height on three or more occasions.

- **Severe Hypertension** (also described as stage 2 hypertension): Average of 3 readings SBP and / or DSP >5mmHg above the 99th percentile.

- **Prehypertension (or high normal blood pressure)**: Average SBP and /or DSP greater or equal to the 90th percentile but below the 95th percentile.

- **Adolescents (aged 10-19 years)** with blood pressure above 120/80mmHg should be considered prehypertensive.

- **White Coat Hypertension**: A patient with BP levels above the 95th percentile in clinic or hospital, who is normotensive outside a clinical setting. Ambulatory BP monitoring (ABPM) is usually required to make this diagnosis.

3. **Presentation**

Hypertension may present as an asymptomatic incidental finding, during screening in at risk groups or as:

- Congestive cardiac failure
- Headache
- Cerebrovascular incident
- Hypertensive encephalopathy
- Facial nerve palsy
- Failure to thrive

The history and examination needs to seek out these features and also look for features of any of the above causes. This guideline is not intended to provide and exhaustive list of all the clinical features of the many causes of hypertension.
4. **Investigation**

Investigations are aimed at identifying the cause of hypertension if this is not already known, assessing the presence of any co-morbidities and identifying any end-organ damage. Investigations will be directed by clinical findings but below is a suggested scheme:

**All Children**

- **To identify a cause**
  - Urinalysis for protein / blood / infection
  - Full blood count
  - U&Es, creatinine
  - Renal ultrasound (with renal vessel doppler if available)
  - Thyroid function tests
  - Urine catecholamines
  - Plasma renin and aldosterone (sample should be taken directly to the laboratory for immediate separation and freezing. Do not put in pod.)

- **To identify co-morbidities**
  - Fasting lipids
  - Glucose

- **To assess for end-organ damage**
  - ECG
  - Echocardiogram (presence of left ventricular hypertrophy, may also identify a cause eg. Coarctation of aorta)
  - Retinal examination (in those with severe or long standing hypertension)
  - (U&Es and urinalysis are also part of the end-organ assessment)

**If indicated**

- Urine pregnancy test
- Urine toxicology screen
- Urine steroid profile

Renovascular disease should be considered in children if peripheral renin/aldosterone is elevated or basic renal imaging is suggestive. It should also be considered if hypertension remains difficult to control despite the use of two agents, even if other investigations are normal. These cases should be discussed with paediatric nephrology.

If possible, blood and urine samples should be taken prior to commencing treatment. However, treatment should not be delayed unnecessarily.
5. Management

5.1 Goals of Therapy
1. To reduce blood pressure to <95th percentile
2. To reduce blood pressure to <90th percentile in those with co-morbidities
3. To consider aggressive blood pressure control (<50th percentile) in some patient groups (e.g. those with chronic kidney disease)

5.2 Lifestyle advice
This may be all that is required in prehypertensive children and should be given to all children with hypertension
- Dietary advice regarding healthy eating (including reducing salt intake). All children with hypertension and pre-hypertension should be referred to a dietician.
- Regular physical activity (30-60 minutes/day)
- Weight reduction if overweight or obese (see management of obesity in children and young people guidelines)
- Interventions to improve sleep if sleep apnoea identified.
- Advice regarding alcohol, caffeine and drugs
Note that lifestyle interventions are more successful if the whole family participate.

5.3 Pharmacological Intervention indicated in:-
- Symptomatic hypertension
- Secondary hypertension
- Hypertension with associated target-organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite non pharmacologic measures

Selection of an appropriate anti-hypertensive depends upon the age of the patient, the clinical scenario and the presence of any contraindications. This guidance intends to highlight some important points about each drug class but is not intended to replace a full clinical assessment or the advice contained within the BNFc.

Paediatric nephrology is

General Principles
- Once daily dosing regimes are preferable when possible to aid compliance
- Younger children (<1 yr) may need multiple daily dosing to increase dose flexibility e.g. propranolol rather than atenolol or captopril rather than enalapril.
- Doses should be commenced at the starting dose in the BNFc and then gradually titrated until the desired blood pressure is achieved (see goals of therapy).
- In infants or those with impaired cardiac function it may be necessary to initiate antihypertensive medication in hospital with BP monitoring – these patients should be discussed with a paediatric nephrologist.

Calcium Channel Blockers (eg. nifedipine, amlodipine)
- Can be used as first or second line agents in most cases of hypertension if not contraindicated (eg. diabetes mellitus (nifedipine))
- Amlodipine tablets can be dispersed in a known volume of water and a proportion taken. This avoids the need to order expensive special medications which also have a short shelf life.
- Nifedipine has a short half-life and so can lead to relatively large fluctuations in BP. Amlodipine is therefore preferable for long term treatment, though
modified release preparations of nifedipine are an acceptable alternative in patients able to swallow tablets.

- Patients under 6 years of age may have an increased ability to clear amlodipine. Dividing the daily dose into two divided doses in this age group may therefore improve efficacy, though this has not been robustly demonstrated to be beneficial.

**Beta Blockers** (eg propranolol, atenolol)
- Can be used as first or second line agent in most cases of hypertension if not contraindicated (eg. asthma, portal hypertension)
- Cases of phaeochromocytoma need concurrent alpha-blockade

**ACE Inhibitors** (eg.captopril, enalapril, lisinopril)
- Good first line agent in cases of chronic kidney disease providing renal artery stenosis has been excluded.
- Electrolytes and creatinine must be checked 7 – 10 days after initiating or increasing an ACE inhibitor dose because of the risk of renal impairment and hyperkalaemia
- Counsel teenage girls regarding the contraindication in pregnancy
- Counsel regarding the importance of stopping medication whilst unwell with diarrhoeal or vomiting illnesses
- Enalapril and lisinopril tablets can be crushed and made into a suspension. This removes the need for expensive Special Preparations.
- Angiotensin 2 receptor blockers (eg. Losartan) may provide an alternative in those who are unable to tolerate ACE inhibitors or can be used in addition.

**Diuretics** (eg.furosemide)
- May be the most appropriate treatment for hypertension in the context of fluid overload –for example, glomerulonephritis.
- Counsel regarding the importance of stopping medication whilst unwell with diarrhoeal or vomiting illnesses

6. **Algorithms for management of specific categories of hypertensive child:**

6.1 **Hypertensive crisis** (seizures, encephalopathy or cardiac failure)

6.2 **Symptomatic** (eg. Headaches, facial nerve palsy) or **severe hypertension** (Average SBP and / or DSP >5 mmHg above the 99th percentile).

6.3 **Asymptomatic hypertension** (Average systolic blood pressure (SBP) and / or diastolic blood pressure (DSP) greater or equal to the 95th percentile for age, sex and height on three or more occasions).
6.1 **Hypertensive crisis**: seizures, encephalopathy or cardiac failure

These children will require admission to an HDU or PICU setting (or another appropriately equipped ward e.g. tertiary nephrology ward) for close blood pressure monitoring and intravenous anti-hypertensives.

**Admit** to high dependency area for:
- Neurological observations
- *Consider* intra-arterial blood pressure monitoring
- *Consider* intracerebral pathology which might be causing raised intracranial pressure – if suspected, investigate and DO NOT aim to lower blood pressure until this cause has been excluded.

**Use IV treatment to reduce BP slowly:**
- 1/3 of total BP reduction over the first 12 hours
- Next 1/3 total BP reduction over second 12 hours
- Final 1/3 of BP reduction over next 24 hours
- If blood pressure drops suddenly then treat with fluid bolus

**Convert** to oral agents as BP improves

**Intravenous Options:**
- Labetalol
- Sodium Nitroprusside

See PICU pharmacopeia for dosing regimes and BNFc for cautions / contraindications

**Special considerations:**
If proven / suspected phaeochromocytoma consideration should be given to alpha-blockade and patients should be managed in conjunction with paediatric oncologist.
6.2 **Symptomatic hypertension and/or acute severe hypertension:**
Average SBP and/or DSP >5 mmHg above the 99th percentile

**Admit** to a ward able to monitor blood pressure frequently
- Discuss management with a paediatrician experienced in the management of acute severe hypertension
- Ensure hypertension NOT secondary to intracerebral pathology in which case lowering BP could be dangerous

**Set a BP threshold** for PRN treatment appropriate for the patient e.g. 10 mm Hg above 95th percentile on 2 occasions 15 mins apart

**Control BP**
- Use Nifedipine up to 250 micrograms/kg/dose (maximum dose: 5 mg) if not contraindicated* (nb frequent small doses are safest)
- Aim to **reduce blood pressure slowly** (1/3 of the blood pressure reduction over the first 12 hours of treatment)
- Ensure immediate medical review if the blood pressure drops markedly or the patient becomes symptomatic
- Consider **fluid overload** as the cause of hypertension in which case a diuretic may be a more appropriate treatment

Re-check BP every 30 minutes
Consider second dose of nifedipine if BP remains raised above threshold
**Discuss with paediatric nephrologist if unable to control BP**

Once BP improving:
- Convert to a long acting anti-hypertensive (see below)
- Investigations as above

**Nifedipine contraindications:**
- Shock
- Advanced aortic stenosis
- Encephalopathy / cranial hypertension

**Cautions**
- Impaired cardiac function
- Diabetes (may affect blood sugars)
6.3 **Asymptomatic hypertension**: Average systolic blood pressure (SBP) and/or diastolic blood pressure (DSP) greater or equal to the 95th percentile but less than 5 mm over the 99th percentile for age, sex and height on three or more occasions.

May be treated as an outpatient

- Investigations as above
- Lifestyle advice as above
- Select a pharmacological treatment

Refer patients with:
- Secondary hypertension – to a paediatrician experienced in the management of childhood hypertension
- Hypertension despite 2 antihypertensive agents – to a centre with experience in the use of angiography in a child with hypertension

7. **Audit Points**

1. Is blood pressure being measured correctly in inpatient and outpatient situations?
2. Have patients had appropriate investigations to elicit secondary causes of hypertension?
3. Have investigations been undertaken prior to commencing treatment if appropriate?
4. Is blood pressure being maintained within the recommended parameters?
5. Has an appropriate choice of antihypertensive agent been made?

8. **References**

4. Mattoo, T. Hypertension in infants between one month and one year of age. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013.
Appendix 1
Blood pressure centiles by gender, age and height percentile

<table>
<thead>
<tr>
<th>Age, y</th>
<th>BP Percentile</th>
<th>Systolic mmHg</th>
<th>Diastolic mmHg</th>
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</tbody>
</table>

Note: The 90th percentile is 1.5 SD, the 50th percentile is 0.5 SD, and the 5th percentile is 2.5 SD below the mean.

By convention, the BP 95th percentile must be converted to a height z-score given by 95% 1.645 (the tabled value is 1.585, 0.825, 0.525, 0.250, 0.125, 0.050, and 0.025). This height percentile is then computed from the methodology in Appendix B as described in Appendix C for children with height percentiles other than these. The following steps 1 through 4 are as described in Appendix C.

Downloaded from www.pediatrics.org by on February 11, 2009
<table>
<thead>
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<th>Age Group</th>
<th>BP Percentile</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
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</table>

*The tables for this study were provided by the University of Nottingham, School of Medicine, Department of Child Health, and are used with permission. The tables are based on data from the British Society for Paediatric Gastroenterology, Hepatology, and Nutrition (BSPGHAN) and the National Institute for Health and Care Excellence (NICE). The tables are intended for use in the United Kingdom and are not applicable to other countries.*
### Appendix 2 - Neonatal blood pressure centiles

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<tr>
<th>Post-conceptual age</th>
<th>50th percentile</th>
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</tr>
<tr>
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<td>40 weeks</td>
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<tr>
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<tr>
<td>MAP</td>
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<tr>
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<tr>
<td>SBP</td>
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<tr>
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<td>70</td>
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<tr>
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</table>

This table provides estimated values for blood pressures after two weeks of age in infants from 26 to 44 weeks post conceptual age. The 95th and 99th percentile values are intended to serve as a reference to identify infants with persistent hypertension that may require treatment.

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure.

Reproduced from: Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management, and outcome. Pediatr Nephrol
## Appendix 3
90th and 95th percentiles of mean day- and night-time systolic and diastolic BP, stratified according to gender and height

### BOYS

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<tr>
<th>Height (cm)</th>
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<th>90th pct</th>
<th>95th pct</th>
<th>90th pct</th>
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### GIRLS

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<th>90th pct</th>
<th>95th pct</th>
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</table>
Appendix 4 - Measuring Blood Pressure

Manual blood pressure measurement using a sphygmomanometer is the gold standard. Blood pressure may be measured using an automated oscillometric device or a manual cuff and auscultation. Oscillometric devices may overestimate blood pressure so any high blood pressure measured this way should be checked manually. The use of a Doppler technique is preferable in very young children as the Korotkov sounds are less reliably heard in this group.

- **Cuff size:** The largest cuff which can fit on the arm should be used. The cuff should be 2/3 the length of the upper arm and the bladder should be 80-100% the circumference of the arm. Errors due to too large a cuff are unlikely but if the cuff is too small blood pressure can be overestimated.

- **Environment:** The child should be rested for at least 5 minutes. The brachial artery should be at the level of the heart and blood pressure should be measured in the right arm when possible. The sphygmomanometer should also be at the level of the heart.

- **Technique:** The brachial artery should be palpated to obtain an approximate systolic BP. Auscultation should then be performed with the first Korotkov sound (K1) being taken as systolic BP. Diastolic BP is recorded at the disappearance of Korotkov sounds (K5) In some children this may not occur in which case the muffling of sounds (K4) may be recorded.

- **Doppler:** The Doppler probe is placed over the brachial artery and the cuff inflated until the signal disappears. The point at which the signal returns is the systolic blood pressure. The diastolic pressure cannot be identified with this method.

- **Automated:** Oscillometric devices have the advantage of reducing inter-observer error and were also used in the construction of the centile charts. However, they still require the correct size cuff and **any child with a BP above the 90th centile should have it re-checked manually.** Not all oscillometric machines have been validated in children. Note that the default maximum pressure is usually 200mmHg which is too high for a child. The **maximum pressure should be set at 20 – 30 mmHg above baseline prior to use.**

- **Ambulatory:** Ambulatory blood pressure monitoring is helpful to determine true blood pressure. This is available in a number of centres including Nottingham, Sheffield and Leicester. Results should be reviewed by a clinician experienced in interpretation of 24 hour blood pressure monitoring.
Appendix 5 - Causes of Hypertension
Hypertension may be either primary (no underlying cause identified and formerly known as essential) or secondary to an underlying cause. Of those with an underlying cause the majority will be renal or reno-vascular in nature. Hypertension in children should be investigated with primary hypertension being a diagnosis of exclusion.

The causes of hypertension can be considered by age of presentation:

<table>
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<th>Newborn – 1 year</th>
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<th>5-10 years</th>
<th>10-20 years</th>
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</thead>
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<td>Renal artery stenosis</td>
<td>Reflux nephropathy</td>
<td>Primary Hypertension</td>
</tr>
<tr>
<td>Renal vein or artery thrombosis</td>
<td>Middle aortic syndrome</td>
<td>Glomerulonephritis</td>
<td>Reflux nephropathy</td>
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<td>Congenital renal disease (ARPKD, dysplasia etc)</td>
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<td>Cystic renal disease</td>
<td>Glomerulonephritis</td>
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<td>Endocrine tumours</td>
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<td>Wilm’s tumour</td>
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<tr>
<td>Bronchopulmonary dysplasia</td>
<td>Cystic kidney disease</td>
<td>Endocrine tumours</td>
<td>Other parenchymal renal disease e.g. Liddle’s syndrome</td>
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<tr>
<td>Patent ductus</td>
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<td>Endocrine tumours</td>
<td>Primary hypertension</td>
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<tr>
<td>Intraventricular haemorrhage</td>
<td>Monogenic hypertension (e.g. Liddle’s syndrome)</td>
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<tr>
<td>Hydrocephalus</td>
<td>Wilm’s tumour</td>
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<td>Brain tumour</td>
</tr>
<tr>
<td>Drugs</td>
<td>Brain tumour</td>
<td></td>
<td>Intracerebral bleed</td>
</tr>
</tbody>
</table>