GP SUMMARY

Evidence Review: Pharmacological therapy of ADHD in adults

Introduction

Attention deficit hyperactivity disorder (ADHD) is among the most common psychiatric disorders in childhood, and it is now well-recognised that symptoms usually persist into adulthood. Adults with ADHD have much higher rates of substance misuse, unemployment, relationship difficulties and criminality, and often present with co-morbid psychiatric disorders. The current NICE Guidelines, published in 2008, were fundamental in recognising the disorder in adults, and providing recommendations for pharmacological therapy and properly managed transition of patients to adult services.
Since their publication, however, new medications have been introduced and disappointingly few health authorities have adequately met the need for transitional services. This presents challenges for GPs, who may be requested to prescribe for adult patients with ADHD, and in recognition of this, the DPC requested a review of the latest evidence. This summary provides key information from the evidence review and includes links to other relevant guidance or sources of information.

Pharmacological Treatment Options

Medications for ADHD may be classed in one of 2 categories: (psycho)stimulants or non-stimulants.

NICE Recommendations

Current NICE Guidelines recommend drug therapy as first-line in adults with ADHD, and suggest that this should be continued for as long as it is clinically effective. This is a change from the previous guidelines which recommended stopping treatment during adolescence. The guidelines advise that psychological interventions such as cognitive behavioural therapy lack data to support efficacy, but may be considered for adults when:

- the person has made an informed choice not to have drug treatment
- drug treatment has proved to be only partially effective or ineffective or the person is intolerant to it
- people have difficulty accepting the diagnosis of ADHD and accepting and adhering to drug treatment
- symptoms are remitting and psychological treatment is considered sufficient to target residual (mild to moderate) functional impairment.

Methylphenidate (stimulant) is the recommended initial choice of pharmacological therapy for adults with ADHD, with **dexamfetamine** (stimulant) or **atomoxetine** (non-stimulant) as second-line options.
Atomoxetine would be the preferred initial choice if there is a risk of misuse or diversion.
Antipsychotic medications are not recommended for treatment of ADHD symptoms.
For further details refer to www.nice.org.uk/guidance/cg72 (includes a treatment pathway and information for the public).

To aid adherence and minimise risks of abuse, longer-acting formulations (i.e. once or twice daily) are usually recommended for adults.

Current Treatment Options

Table 1 at the end of this document summarises the medications currently licensed in the UK for the treatment of ADHD. Not all are licensed for use in adults, but there are more licensed options available now than there were at the time of publication of the NICE Guidelines. Changes that have occurred since publication of the NICE Guidelines (new medications, or changes to licensing of established medications) are highlighted in red in the table.

Although overall the NICE Guidelines remain well-founded, the evidence review has highlighted some areas of change that should be considered, as they may give reason to deviate slightly from the recommendations.

- Methylphenidate remains unlicensed for initiation in adults. However, a number of studies have been published in recent years lending support to the efficacy of methylphenidate, particularly long-acting formulations, in this patient group. Some long-acting formulations are now licensed for continuation of treatment into adulthood (refer to Table 1 below).
- Lisdexamfetamine has become available as another option for treatment. This is a long-acting pro-drug of dexamfetamine, and has the advantage of being licensed for both initiation and continuation in adults, with ample robust evidence to support its efficacy and safety in the adult population. Although higher cost, it could rival methylphenidate as a first-line stimulant drug of choice, and would certainly seem a preferable option to dexamfetamine, which by contrast is not licensed for use in adults and is lacking in recent evidence to lend any further support to its use in this patient group.
- Over recent years, atomoxetine has gained more data to support its efficacy and safety in adults, and is now licensed for initiation or for continuation therapy in this patient group. This, along with its advantages as a non-stimulant, may increase its popularity. However, limited evidence suggesting possible inferiority of non-stimulants to stimulants in efficacy, along with higher costs compared to methylphenidate may still prevent it becoming a routine first-line choice.
- Another non-stimulant, guanfacine, has also recently become available, and is therefore another potential option. However it is only licensed in children (≤17 years) and evidence to support its use in adults is lacking. It is not currently supported for prescribing by non-specialists within the DPC area.

Other Treatment Options
Although not specifically mentioned by NICE for use in adults, there are also a selection of drugs not licensed for ADHD, but available in the UK for other indications, that may also be recommended following specialist referral. These include modafinil, bupropion, venlafaxine, clonidine (licensed preparation available in the USA), reboxetine and tricyclic antidepressants (e.g. imipramine).
They are typically lower cost than licensed ADHD options, but evidence to support their efficacy is very limited. GPs may choose to prescribe these treatments at their professional discretion, but should take into consideration guidance from the General Medical Council on prescribing unlicensed medicines (http://www.gmc-uk.org/Prescribing_guidance.pdf_59055247.pdf).

Safety

ADHD treatments are generally well-tolerated but there are some adverse effects and safety concerns to be considered. For full details refer to the product summary of product characteristics (www.medicines.org.uk).

Adverse effects
Side-effects of stimulants (methylphenidate, dexamfetamine, lisdexamfetamine) are usually mild and transitory, and include headache, reduced appetite, palpitations, nervousness, insomnia, and dry mouth. More serious potential adverse effects include increased blood pressure/heart rate, weight loss, and reduced growth rate in children or adolescents.

Atomoxetine may cause headache, dry mouth, raised blood pressure and heart rate, somnolence, and nausea/vomiting. Orthostatic hypotension and syncope have been reported

(due to its effect on noradrenergic tone), and rarely severe liver injury. As with stimulants decreased appetite is very common, and this has been associated with growth retardation in terms of height and weight gain, although this effect does not seem to continue long-term. Sexual dysfunction (erectile and ejaculatory dysfunction) and dysmenorrhoea are also potential side effects of atomoxetine.

In contrast to other treatments, guanfacine may cause weight gain.

Specific Safety Issues
A 2009 review of methylphenidate by the European Medicines Agency addressed concerns of its long-term use, specifically cardiovascular and cerebrovascular safety, psychiatric adverse effects, and effects on growth and sexual maturation in children. The review concluded that the risk-benefit balance remained positive but, bearing in mind the lack of long-term data, made a number of recommendations for summaries of product characteristics, and for pre-treatment screening and ongoing monitoring in patients. Further information is available from an MHRA Drug Safety Update (https://www.gov.uk/drug-safety-update/methylphenidate-safe-and-effective-use-to-treat-adhd).

The risk of treatment-emergent psychotic or manic symptoms associated with atomoxetine was also highlighted in this Drug Safety Update (https://www.gov.uk/drug-safety-update/atomoxetine-risk-of-psychotic-or-manic-symptoms-in-children-and-adolescents) and the summary of product characteristics now includes a relevant warning to consider stopping atomoxetine if these symptoms occur.

Cautions
The table below summarises particular cautions which need to be considered for ADHD treatments:

Caution	**Which drug(s)?***
Tic disorders	Methylphenidate Lisdexamfetamine Dexamfetamine
Epilepsy/seizure disorders	Methylphenidate Atomoxetine
Psychiatric disorders	All
Driving	All (but particularly dexamfetamine and lisdexamfetamine, as amphetamine is one of the drugs for which a 'threshold limit' has been set in drug-driving laws). Note: overall ADHD treatments demonstrate positive effects on driving behaviour in patients with ADHD.
Abuse potential (misuse and/or diversion)	Greatest risk: Dexamfetamine Methylphenidate immediate-release Limited risk: Methylphenidate prolonged-release Lisdexamfetamine

*From treatments licensed for ADHD

Patient Monitoring
Before starting any drug treatment for adults with ADHD, NICE guidelines recommend a full assessment to include:

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

  - weight
  - family history of cardiac disease and examination of the cardiovascular system
- an ECG if there is past medical or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination
- risk assessment for substance misuse and drug diversion (where the drug is passed on to others for non-prescription use).
- Potential for interactions with recreational drugs, including possibly cannabis

On an ongoing basis, NICE recommend that healthcare professionals should consider using side effect rating scales throughout treatment, and that in adults taking a stimulant, patients' weight should be measured every 6 months. They also recommend 3 monthly checks of blood pressure and heart rate, to be recorded on a centile chart.
They do not recommend routine blood tests, liver function tests and ECGs for any of the treatments unless there is a clinical need.
However, due to specific cardiovascular risks associated with its use, higher risk patients on guanfacine may require more regular ECGs (refer to SPC).

An annual review is recommended for all patients receiving ADHD treatments, which should consider:

- Clinical need (N.B. Annual drug holidays are recommended to assess whether ongoing treatment is required. These are typically carried out during school holidays for children, but may be more difficult for adults with the constant pressures of daily life).
- Benefits (N.B. Evidence suggests that concerns about development of tolerance to treatments are unfounded).
- Side effects
- Effect of missed doses, dose reductions, or brief periods without medication
- Preferred pattern of use
- Coexisting conditions and possible need to treat/refer
- Need for psychological, social and occupational support

Further Information

- The Southern Health Pharmacological Treatment of Attention Deficit Hyperactivity Disorder in Adults Guidelines are particularly recommended as they consider the NICE Guidelines alongside more recent developments to provide a useful summary of management of adults with ADHD. Available via http://www.southernhealth.nhs.uk/knowledge/clinical-support-services/medicines-management/policies/
- NICE Guidelines CG72 Attention deficit hyperactivity disorder: diagnosis and management. Available via www.nice.org.uk (full update due 2018 - see https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0798)
- UKMi Medicines Q&A: Can methylphenidate be used for adults with attention deficit hyperactivity disorder (ADHD)? Available via www.sps.nhs.uk
- British Association of Psychopharmacology Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder (2014) summarise current literature and provide consensus recommendations for treatment of ADHD in children and adults. Available via www.bap.org.uk/guidelines
- The European Network Adult ADHD: European consensus statement on diagnosis and treatment of adult ADHD (2010).

A copy of the full evidence review and references is available on request from formulary@uhs.nhs.uk.

Table 1: Summary of medications available in the UK for treatment of ADHD

Generic name	Brand names*	Licensing status	Mode of action	Estimated average cost of 28 days treatment[Ŧ]
Methylphenidate (immediate-release) tablets	Ritalin, Medikinet	For children aged 6 years and over. Not licensed in adults.	Stimulant. Thought to inhibit dopamine and noradrenaline reuptake.	£19.53
Methlyphenidate prolonged-release tablets/capsules	Concerta XL, Matoride XL, Medikinet XL 10mg/20mg/30mg/ 40mg/50mg/60mg	For children aged 6 years and over. **Licensed for continuation in adolescents whose symptoms persist into adulthood**, but not licensed for initiation in adults		£43.81
	Equasym XL, Medikinet XL 5mg	For children aged 6 years and over. Not licensed in adults.		£44.33
Atomoxetine capsules/oral solution	Strattera	For children aged 6 years and over, adolescents and **adults (initiation** or continuation).	Non-stimulant. Noradrenaline-selective reuptake inhibitor.	£61.94 (capsules) £138.83 (oral solution)
Dexamfetamine sulfate tablets	Amfexa	For children and adolescents aged 6 to 17 years. Not licensed in adults.	Stimulant. Centrally-acting sympathomimetic.	£123.75 (prescribed generically) £92.82 (prescribed as Amfexa)
Lisdexamfetamine tablets	Elvanse	For children aged 6 years and over. Licensed for continuation in adolescents whose symptoms persist into adulthood.	Stimulant. Pro-drug, metabolised to dexamfetamine.	£70.70
	Elvanse Adult	For adults. Not licensed for children and adolescents.		£70.70
Guanfacine prolonged-release tablets	Intuniv	For children and adolescents aged 6 to 17 years. Not licensed in adults.	Non-stimulant. Selective, alpha-2a adrenergic agonist.	£98.84

*Examples of brand names as listed in electronic Medicines Compendium. May not be comprehensive.
Ŧ Costs estimated based on median calculated from usual dose range (prices from Drug Tariff or MIMS Sept 2016)
Red font indicates where changes have occurred since publication of the NICE Guidelines (new medications, or changes to licensing of established medications)

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