How is standard ADHD medication used in clinical practice and how is this supported by research?

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Abstract

ADHD is a common neurodevelopmental disorder. It is important for the clinician to keep up-to-date with the new developments in using ADHD medications effectively, while empowering patients and parents to make informed choices. The aim of this paper is to assist the clinician in deciding which medication or formulation to recommend in different circumstances. Ten simple principles of administering ADHD medication are outlined, along with comprehensive tables and a flow chart. An up-to-date summary of the research supporting current practice is presented.

How is standard ADHD medication used in clinical practice?

1. When should ADHD medication be considered?

- The NICE guideline (1) recommends that medication is used as a first-line treatment in children and young people with severe ADHD and also for those with moderate ADHD and persisting significant impairment following a parent-training/education programme or group psychological treatment.
- Medication should always be a part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions.
- The decision to start medication should be made by a specialist in paediatrics, child and adolescent psychiatry or learning disability.
- Drug treatment is not recommended for pre-school children (1).

2. What medications are available to treat ADHD in the UK?

- Currently methylphenidate, dexamfetamine (stimulants), and atomoxetine (non-stimulant) are available as standard ADHD medications. Methylphenidate and atomoxetine are licensed for use from 6 years of age. Dexamfetamine is licensed from 3 years of age but the BNF (7) only recommends its use from the age of 6 years.
- See table 1 for standard medications, available strengths, frequency of administration, titration and maximum recommended doses.

3. Identifying goals of treatment with parent and/or patient

- Identify the goals/targets to be achieved with ADHD medication; this needs to be agreed with the parent/carer and the child/young person, where applicable. It is also important to involve the school teacher.

- The primary goal is to control the symptoms of ADHD. As a result of this, secondary effects may be improvements in academic performance, social skills, challenging behaviour and family relations but these may depend very much on a comprehensive approach, involving far more than the medication alone.

4. Choosing the right treatment – Methylphenidate or Atomoxetine?

The choice of medication should take into consideration the different properties of the available drugs and preparations, co-morbid conditions (for example, sleep disorders), the adverse-effect profile, potential for drug misuse or diversion, and the preferences of the patient and carers.

Methylphenidate

- Consider Immediate Release (IR) methylphenidate (generic methylphenidate, Ritalin® or Medikinet®) (1) in the following circumstances.
- During initial titration to determine correct dosing level
- If more flexible dosing is required.
- Modified-release methylphenidate might achieve the following (1).
    a. Improved compliance.
    b. Reduced stigma by avoiding the necessity for medication at school.
    c. Avoiding the problems of medication storage and administration at school.
    d. A more even, consistent and longer-duration response.
- Use Equasym XL or Medikinet XL once a day in the morning if there is a need to cover the school day. IR methylphenidate can be tried after the school day to cover the evening period.
- Use Concerta® XL to cover the school day and evening at home.
- Always use brand names when prescribing modified-release preparations of methylphenidate because different brands have different profiles/durations of action (see Table 1). Follow the guidelines for prescribing controlled drugs (see paper on Shared Care Guidelines in this journal).
- The child/young person can have drug holidays during weekends/school holidays, if their behaviour at home is manageable and there is no interference with achieving agreed goals/targets. However, drug holidays are not routinely recommended.

Atomoxetine

- Consider atomoxetine in the following circumstances.
    a. When all-day cover is needed and if there are significant ADHD symptoms during early morning and/or late evening.
    b. When there are unacceptable adverse effects with methylphenidate.
    c. If there is inadequate response to the maximum tolerated dose of methylphenidate.
    d. A strong family preference for a non-stimulant (3).
    e. Risk of drug "diversion".

Other indications include tics, substance abuse or comorbid anxiety.

- The child/young person cannot have drug holidays: atomoxetine should be taken every day.

Dexamfetamine

Dexamfetamine can be used as an alternative in children who do not respond to methylphenidate or atomoxetine (7).

- If there is a choice of more than one drug, use the drug of lowest overall cost (1).

5. Titration of medications

- Titration is best carried out by using a 'start low and go slow' regime. Start with a small dose and build up gradually over a period of 4 weeks, whilst monitoring for both clinical response and adverse effects (see table 1).

- Regarding methylphenidate: warn parents that doses that are too high may lead to a withdrawn, depressed, tearful state which can be reversed immediately by reducing the dose. It is not usually necessary to stop the drug.
- Regarding atomoxetine: explain to parent/carer and young person, when applicable, that it may take 6 weeks or longer to achieve the full effect of the medication (3). It would be wise to continue treatment up to 12 weeks before deciding to discontinue because of lack of response.

6. Provide appropriate and relevant written information to the parent/carer and child/young person, when applicable

- Leaflets/books
  - Provide parents/carers with basic information leaflets about ADHD, e.g. The Royal College of Psychiatrists parent information sheets.
  - There are several self-help guide books for parents, children and young people.
- Websites and support groups
  - Parents/carers can access reliable information from local/national support groups. ADDISS, a national support group, is a useful resource and can be accessed at www.addiss.co.uk
  - It is important to warn parents/carers about websites propagating negative information about ADHD and medications. Reputable websites include www.addiss.co.uk and www.rcpsych.ac.uk/mentalhealthinfo
- Travel advice about controlled drugs
  - Methylphenidate and dexamfetamine are controlled drugs. Parents/carers and young people should receive advice when travelling abroad with these medications.
  - A doctor's letter stating that the individual has ADHD and needs to have the medication regularly should be carried; it is advisable to take a simple leaflet or a booklet about the condition, just in case.

7. Initiating and monitoring treatment: response and adverse effects

- Carry out a pre-treatment check before commencing medication. Check for cardiovascular conditions in the child and family (see papers on NICE guidelines & standard treatments, and the paper on CVS adverse effects in this issue).
- Follow the NICE guidelines; check weight and height (plot on growth chart), blood pressure and pulse rate (plot on centile chart).
- Inform parent/carer of adverse effects of medication and monitor for adverse effects.
- Use well-established instruments/questionnaires to monitor progress
  - 'Dundee Difficult Times of the Day Scale' (D-DTODS) is completed by parent and teacher to assess difficult behaviour and monitor pattern of response to treatment throughout the day.
  - Conners Parent and Teacher Rating Scales and Clinical Global Impression – Improvement scale (CGI-I), to monitor response.
  - ADHD-Rating Scale (ADHD-RS)

8. Liaison with school regarding progress

- School teacher/SENCo (Special Educational Needs Coordinator); telephone discussion as and when needed.
- Consider using SKAMP rating scale to measure classroom behaviour and response to medication.
- Professionals meetings at school as required.

9. Shared care with an expert paediatrician/child and adolescent psychiatrist

- Follow the local shared-care guidelines.

10. Review of medication regularly and manage comorbid conditions, if present

- Review at least 6 monthly/yearly once the treatment response is established.
- If stimulant medication is used, ask whether there is a marked change in the morning after the medication is given; if not, then question whether the medication should be continued.
- Drug treatment should be continued as long as it is clinically effective and this should be reviewed at least annually (1).
- Discontinue methylphenidate if there is no response after one month.
- Always ensure associated comorbid conditions are managed appropriately.

Table 1

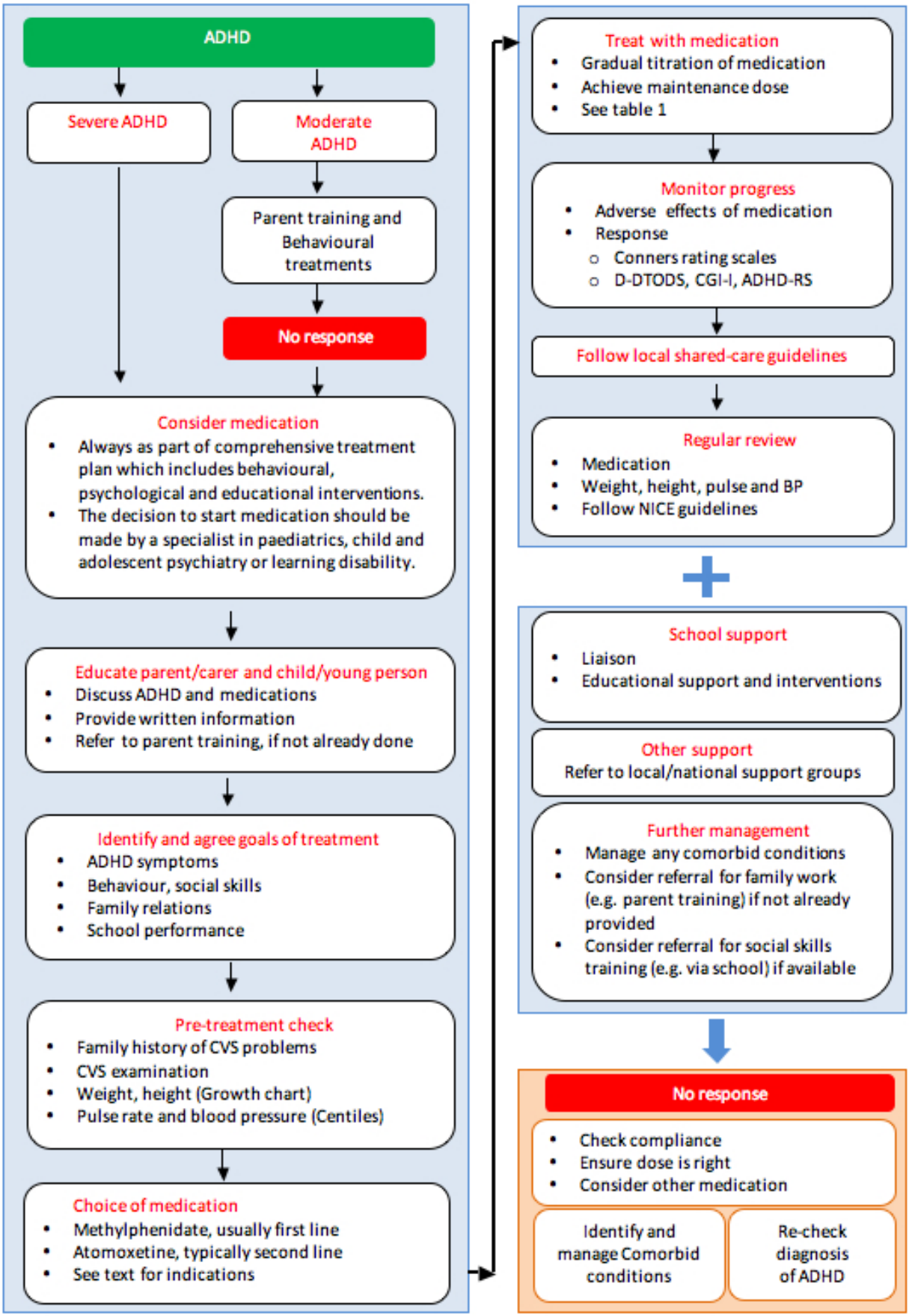
Medication	Stimulant					Non-stimulant
	Short acting Dexamfetamine	Short acting MPH*	Long acting MPH*			Long acting Atomoxetine
	Generic Dexamfetamine	Ritalin® Medikinet® Generic Methylphenidate	Medikinet® XL	Equasym® XL	Concerta® XL	Strattera®
Formulation	Tablet	Tablet	Capsule ***Can be sprinkled (7)	Capsule ***Can be sprinkled (7)	Tablet	Capsule
IR:ER ratio of MPH** See table 2	-	IR 100%	IR 50% ER 50%	IR 30% ER 70%	IR 22% ER 78%	-
Duration of action	Up to 4 hrs (2)	Up to 4 hrs (2)	Up to 8 hrs (4)	Up to 8 hrs (3)	Up to 12 hrs (3)	Up to 24 hrs (5, 6)
Doses available	5mg	Ritalin 10mg Medikinet 5mg, 10mg, 20mg	5mg, 10mg 20mg, 30mg 40mg	10mg 20mg 30mg	18mg 27mg 36mg	10mg, 18mg, 25mg, 40mg, 60mg, 80mg
Equivalent daily doses of MPH (1) (Not equivalent in profile/ duration of action)	5mg	10mg	10mg	10mg	-	-
	(5mg of dexamfetamine is equivalent to 10mg of IR MPH) (2)	15mg	-	-	18mg	
		20mg	20mg	20mg		
		30mg	30mg	30mg	36mg	
		40mg	40mg			
		45mg			54mg	
		60mg	60mg	60mg	72mg	
Titration Start low and go slow Age : 6-18 years	2.5mg 2 to 3 times a day and increase by 5mg per day at weekly intervals (7)	Start with 5 mg 1-2 times daily, increase by 5-10mg/day at weekly intervals (7)	Start with 5-10mg/day and increase weekly by 10mg increments	Start with 10mg/day and increase weekly by 10mg increments	Start with 18mg/day and increase by 9-18mg at weekly intervals	< 70 kg - start with 0.5mg/kg/day for 7 days and increase to 1.2mg/kg/day, according to response (7)
						>70 kg - start with 40mg/day for 7 days and increase to 80mg/day, according to response (7)
Frequency of doses/day	2 or 3 times a day	2 to 3 times a day	Once a day in the morning with or after breakfast (4)	Once a day in the morning before breakfast (7)	Once a day in the morning with or without food	Once a day or 2 divided doses/day
Maximum dose per day**** Age : 6-18 years	1mg/kg/day (8) 20mg/day (1, 7)	Licensed maximum 60mg/day	Licensed maximum 60mg/day	Licensed maximum 60mg/day	Licensed maximum 54mg/day	<70 kg - 1.8mg/kg/day 120mg/day (7)
	Up to 40mg/day may occasionally be required (1)	Up to 2.1mg/ kg/ day or 90mg/day (1, 7)	Up to 2.1mg/ kg/day or 90mg/day (1,7)	Up to 2.1mg/ kg/day or 90mg/day (1, 7)	Up to 2.1mg/ kg/day or 108mg/day (1, 3, 7)	>70 kg – 120mg/day (7)

***MPH** – methylphenidate; ****IR: ER ratio** – proportion of **I**mmediate **R**elease and **E**xtended **R**elease components of methylphenidate in the long-acting preparations.
*****Sprinkle** – this means the content of the capsule can be opened onto tablespoon full of apple sauce, then swallowed immediately without chewing, for children with swallowing difficulties.
******Maximum dose per day** - Take advice from a specialist while using maximum dose per day, when it is unlicensed.

Table 2 Modified-release methylphenidate: Strengths of tablets/capsules and proportion of immediate release (IR) to extended release (ER)

Medication	Medikinet® XL (capsule) IR:ER 50:50					Equasym® XL (capsule) IR:ER 30:70			Concerta® XL (tablet) IR:ER 22:78		
Tablet/capsule strength	5mg	10mg	20mg	30mg	40mg	10mg	20mg	30mg	18mg	27mg	36mg
IR proportion (Immediate Release) MPH	2.5mg	5mg	10mg	15mg	20mg	3mg	6mg	9mg	4mg	6mg	8mg
ER Proportion (Extended Release) MPH	2.5mg	5mg	10mg	15mg	20mg	7mg	14mg	21mg	14mg	21mg	28mg

Flow chart on how standard ADHD medication is used in clinical practice



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Part 2: How are these recommendations supported by research on treatment outcomes. (This section is by Dr Dave Coghill.)

Notwithstanding the fact that there has been a significant interest in the treatment of ADHD over the past few years, few of the recently published papers have had a major impact on treatment protocols. There are, however, some exceptions. One of the most influential and widely-quoted studies is the Multimodal Treatment of ADHD study (MTA study) in which four treatment arms were compared (medication, behavioural, combined and treatment as usual in the community). Comparison of the medication arm, in which the medication was carefully titrated and monitored, and the community arm, in which medication was often given but not as carefully titrated or monitored, demonstrated just how important it is to have a carefully crafted approach to prescribing in ADHD (1). Comparison of the three active treatment arms was initially interpreted as demonstrating the superiority of medication over behavioural treatment (2). However, a reanalysis of the MTA data demonstrated that for those children and young people who met the criteria for hyperkinetic disorder (severe pervasive impairing ADHD) medication treatment was clearly superior to behavioural treatment, whereas for those with less severe forms of ADHD the two treatment approaches were similar in effectiveness (3).

When thinking about which order the different medications should be considered it would be good to be able to use data from direct head-to-head comparisons of the different medications. Unfortunately there are few such studies and it is therefore necessary to use indirect comparisons of standardised data from different studies. The most common method of making such comparisons is to use effect sizes. These are a standardised measure of the strength of action of a treatment (also see paper on "ADHD and Other Medications" in this issue, in which effect sizes are defined and discussed). In clinical trials of medications for ADHD, both stimulants (short and long acting) and atomoxetine have been associated with moderate to large effect sizes. The effect sizes for stimulants are generally larger (mean ranges between 0.8 and 1.0) than those for atomoxetine (0.7) (4). However recent clinical trials with atomoxetine that have been longer in duration (up to 12 weeks) have reported effect sizes up to 1.3 (5). It is important to put these effect sizes into context as they are considerably greater than those seen with other psychiatric drugs (e.g. SSRI antidepressants 0.5, antipsychotics 0.25).

When using long-acting methylphenidate preparations it is essential to acknowledge that the three licensed long-acting methylphenidate preparations; Equasym XL, Medikinet XL and Concerta® XL each have different proportions of immediate-release and extended-release methylphenidate and the extended-release component also differs with respect duration of action (see Table 1). Studies have demonstrated that these differences translate into different profiles of action across the day and that these are very closely related to the pharmacokinetic profiles of each preparation (6, 7). It is therefore very important that clinicians familiarise themselves with these different profiles and make use of them to tailor treatment to individual needs.

For patients who have problems in the evening it may be helpful to consider atomoxetine, as studies have suggested that, even when given once daily, the effects of atomoxetine can continue throughout the evening and into the morning (8). Recent evidence suggests that the effects of atomoxetine continue to develop over the first few months of treatment. It is therefore sensible to continue with treatment for at least 12 weeks before conceding a lack of effect (5, 9). Evidence is also starting to emerge to support the notion that atomoxetine impacts positively on quality of life as well as reducing symptoms (10). Unfortunately similar studies for stimulants are still to appear.

Where methylphenidate has been tried but resulted in an inadequate response at the maximum tolerated dose, it has become fairly routine to consider atomoxetine. It is worth noting however that only around 40% of methylphenidate non-responders respond to atomoxetine (11) compared to around 66% who will respond to dexamfetamine (12).

In this context it is interesting to speculate why dexamfetamine, which has been available for many years, is used so infrequently in the UK, whilst in the United States amphetamine products are much more widely used. Even though NICE excluded almost all of the clinical trials of dexamfetamine in ADHD because of their crossover design, there is considerable evidence to support the use of dexamfetamine as an alternative in children who do not respond to methylphenidate or experience significant adverse effects from this drug. The main drawback of dexamfetamine is that it is only available as an immediate-release preparation in Europe. This is particularly pertinent in view of the concerns about abuse potential. Studies do, however, suggest that the amphetamines are equally effective as methylphenidate with no additional safety or tolerability issues (13). In general 70% of patients will respond to methylphenidate, 70% will respond to amphetamines and between 90 and 95% will respond to one or the other (12). As noted above it is therefore more likely that a methylphenidate non-responder will respond to dexamfetamine than to atomoxetine. These findings may become more relevant in Europe in the near future if lisdexamfetamine, an amphetamine prodrug that is already marketed in North America, is licensed for use in Europe. Several published studies have supported the efficacy, tolerability and safety of lisdexamfetamine in the treatment of ADHD (14, 15) and studies in Europe are ongoing.

Two other treatments for ADHD that have been used off-label for many years have now been approved by the FDA for use in the United States (also see paper on "ADHD and Other Medications" in this issue). These are the two alpha-2 agonists, clonidine and guanfacine (both preparations are extended release). Randomised controlled trials have demonstrated both to be safe and effective in treating ADHD, although only the results of the guanfacine studies have been published (16, 17). The effect sizes for the alpha-2-agonists are smaller than those for stimulants. The adverse-effect profile of these drugs suggests that they may be particularly beneficial as adjunctive rather than stand-alone treatments. Again European studies of extended-release guanfacine are ongoing.

GP Comment.

What have I learned from this paper?

1. These are clear useful medicines-management guidelines on drugs for treating ADHD.

2. This practical guide should be very useful for the GP in the day-to-day management of patients with ADHD by offering a quick reference to the issues that matter, supported by reputable publications.

3. The large amount of information and the increasing numbers of medications/formulations used to treat ADHD can be very confusing; the flow sheets and table in this paper offer clear guidance and information.

4. A community-based mental health nurse would be able to liaise with the GP, schoolteachers and family during the ongoing treatment phase of medication.

5. It is reassuring to know that current practice in treating ADHD is supported by published research.

Dr. Peter Cliffe, GP, Surrey.

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