Medical management of ADHD in adults: part 1

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Abstract

Attention deficit hyperactivity disorder (ADHD) in adults is common, impairing and often unrecognised. Comorbidity is very common and may compound the impact of ADHD. It is important that a diagnosis of ADHD is made following a high-quality assessment. Symptoms and social outcomes can be improved by treatment, particularly medication. Non-pharmacological treatment may be more effective in those who are also on medication, and psychoeducation and environmental modifications are also important. Stimulants such as methylphenidate and lisdexamfetamine are recommended first choice medications. The choice of drug can be tailored to patients' circumstances, especially intended duration of action, then titrated week by week, according to response.

Key learning points

- Attention deficit hyperactivity disorder (ADHD) is clearly defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision.
- ADHD is a serious condition with high levels of functional impairment, mental health and somatic comorbidities, and increased mortality, particularly if untreated.
- Treatment, including stimulants such as methylphenidate and lisdexamfetamine and non-stimulants such as atomoxetine, is highly effective in reducing the core symptoms of ADHD and reducing a range of social impacts.
- Treatment may also mitigate some of the common comorbidities found in patients with ADHD.

Introduction

Attention deficit hyperactivity disorder (ADHD) is prevalent in adults (at least approximately 2.5%, compared with approximately 5.9% in children[1]) and carries an estimated 12.7-year reduction in life expectancy if untreated in adulthood.[2] ADHD has been described as 'the diabetes of mental health'[3] because of its significant public health impact. As well as distressing symptoms, untreated ADHD is associated with significant social impacts[4] on relationships, parenting, educational attainment, employment and income, accidents and injuries, driving infringements, risky sexual behaviour, substance and alcohol misuse and criminal behaviour. Treatment can be very effective with higher effect sizes[5] for medication than most other treatments in psychiatry. Medication is associated with reduced all-cause mortality after 2 years (39 treated vs 48 untreated per 10 000 individuals).[6]

In the UK, managing ADHD within a 'specialist' secondary or tertiary service model has led to very long waiting lists because referrals exceed the capacity of specialist ADHD clinics. To meet demand, services need to be 'mainstreamed',[7] and generalists (in mental health or primary care) need to become more familiar with management, at least for less complicated cases, and certainly for ongoing or 'shared' care. Across two articles, I share my experience and explore key issues in supporting people with ADHD.

Part 1 of this two-part series considers diagnostic criteria, non-pharmacological interventions and provides an overview of pharmacological management. Part 2 will consider the medicines in more detail.

Background

ADHD is a disorder defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR).[8] Diagnosis in adults requires at least five of nine 'core' listed symptoms (see table 1) of inattention, or five of the nine listed for hyperactivity/impulsivity. Symptoms must be *persistent* over time (not intermittent) with several present since childhood (prior to age 12 years), be *pervasive* across different areas of life (such as domestic, social, academic or occupational) and be a *problem* (ie, cause impairment, defined as 'interfere with, or reduce the quality of, social, school or work functioning'). Lastly, another diagnosis must not better explain the symptoms.

While symptoms, or traits, are 'normally distributed' in the population, ADHD has a clear (if somewhat empiric) DSM-5-TR definition and therefore has a specific medical meaning. It can be analogised to blood pressure; everyone has a blood pressure, but 'hypertension' has a defined (again somewhat empiric) threshold; the benefits of lifestyle on helping blood pressure and cardiovascular risk apply to the whole population, but we would only offer medicines to those with formally diagnosed hypertension. We only offer medicines to 'medically diagnosed' ADHD, but those who are 'sub-threshold' by DSM-5-TR criteria may still have needs and may benefit from other support. This group may be at risk of overdiagnosis, but we must remember that underdiagnosis is more widespread than overdiagnosis. Claims that some patients exhibit 'a bit of ADHD' have no medical validity and undermine how seriously the diagnosis is regarded, when formally made for others.

Table 1 DSM-5-TR definition of ADHD

Inattentive symptoms are where the patient often:	Fails to give close attention to details or makes careless mistakes in schoolwork, at work or with other activities
	Has trouble holding attention on tasks or play activities
	Does not seem to listen when spoken to directly
	Does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace (eg, loses focus, side-tracked)
	Has trouble organising tasks and activities
	Avoids, dislikes or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework)
	Loses things necessary for tasks and activities (eg, school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones)
	Is easily distracted
	Is forgetful in daily activities
Symptoms of hyperactivity-impulsivity are where the patient often:	Fidgets or taps with hands or feet, or squirms in seat
	Leaves seat in situations when remaining seated is expected
	Feels restless
	Is unable to engage in leisure activities quietly
	Is 'on the go' or acting 'as if driven by a motor'
	Talks excessively
	Blurts out an answer before a question has been completed
	Has difficulty waiting his or her turn
	Interrupts or intrudes on others

ADHD, attention deficit hyperactivity disorder; DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision.

ADHD is subject to similar misunderstandings which stigmatise other mental illnesses. It can be detrimental for patients with ADHD to have their condition trivialised or undermined in the media, not least by medical professionals. Often, assessment for ADHD has been delayed because symptoms have been attributed to a comorbidity such as anxiety or depression, and patients, particularly women,[9] have suffered a long and difficult journey to get the correct diagnosis after being given other labels which do not fully describe their symptoms.

Societal prejudice can cause patients to question the validity of their experiences and potentially miss out on useful intervention. Also, patients typically suffer other important symptoms which are usually present but not part of the definition of ADHD: mood instability, rejection sensitivity, low self-esteem, insomnia and wider examples of poor executive function may be far more disabling than symptoms of inattention or hyperactivity. Comorbidity is very common and may also compound the disability from ADHD.

Publicity about poor diagnostic assessments may undermine public confidence in the management of ADHD. It is important that clinicians are confident that the diagnosis has been made following a high-quality assessment, such as that defined by 'The adult ADHD assessment quality assurance standard' (see box 1).[10] It is outside the scope of this article to debate whether ADHD diagnoses should require a higher standard of assessment than that for other mental illness diagnoses. General practitioners (GPs), who may be asked to take over repeat prescriptions, need to be able to recognise a good quality assessment[11] and to judge whether initiation of medication has followed good practice, as considered in this review.

Non-pharmacological management

The National Institute for Health and Care Excellence (NICE) guideline (NG87)[12] recommends a 'comprehensive, holistic shared treatment plan that addresses psychological, behavioural and occupational or educational needs' and that medication should be considered when there is 'a significant impairment in at least one domain *after* environmental modifications have been implemented and reviewed'.

Psychoeducation is important[13]: it may help patients to unpack a lifetime of distress and confusion. The explanatory framework of ADHD can help them to understand their strengths and weaknesses, express and explain themselves better to others, find better coping strategies and stop berating themselves for being unable to perform like others. 'Reasonable adjustments' at work

Box 1 Adult ADHD AQAS essential components for diagnostic assessment[10 11]

- Presenting concern(s)
- Full psychiatric history
- Neurodevelopmental evaluation
- Medical history for potential differentials and contraindications to treatment
- Semi-structured interview with open questions and elaboration, avoiding over-reliance on checklists or questionnaires
- Explicit detailing of which DSM-5 symptoms of inattention, hyperactivity and impulsivity are persistent, pervasive and problematic
- Discussion of independent evidence (informant-based and other objective data such as school reports) used to support the diagnosis
- Consideration of differential diagnoses and comorbidity

ADHD, attention deficit hyperactivity disorder; AQAS, assessment quality assurance standard; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

or study (which are a right under the UK's Equality Act 2010), and supportive, understanding interpersonal relationships can help greatly.

Psychotherapy may be helpful, although it may be difficult to obtain on the National Health Service in the UK, resulting in greater emphasis on medication. There is some evidence for Cognitive Behavioural Therapy and Mindfulness, but medication is more effective in reducing ADHD symptoms. Psychotherapy may be particularly helpful for psychological comorbidities (eg, anxiety) and may be more useful for ADHD in those already on medication.[1]

'Pills [alone] do not build skills'.[14] Coaching, peer support and lay resources can be very helpful but require signposting. A recent review by Faraone *et al*[15] lists 19 international professional organisations providing resources, mainly for clinicians. Social prescribers or care navigators may helpfully signpost local services.

Optimising lifestyle is recommended, including sleep, regular daily routines, moderating alcohol, a balanced diet and regular exercise. There is evidence of benefit for exercise[16] and contested evidence has been reviewed[17 18] for omega-3 supplements, vitamin D, mineral deficiencies and exclusion of artificial food additives or a 'few foods diet'. Low magnesium is associated with ADHD,[19] but causation remains unproven. The authors of a very small, open-label study that reported some improvement in ADHD symptoms from a magnesium supplement suggested that further evaluation was warranted.[20] Magnesium may be involved in several poorly understood neuroprotective effects[21] but may have biologically plausible effects in ADHD as an N-methyl-D-aspartate receptor inhibitor, a role shared by memantine, which has been assessed to have potential benefits for ADHD in small-scale clinical trials in adults[22] and children.[23] Biofeedback, digital technologies and transcranial magnetic/trigeminal nerve stimulation have limited evidence so far.

Pharmacological treatment

The evidence base for medication for ADHD shows high efficacy in short-term (<1 year) trials,[24] but longer-term trials are lacking. Many trials are sponsored by manufacturers, and there are few head-to-head trials. Many would argue that the trials are at significant risk of bias and the measured outcomes are typically patient-reported symptoms, rather than objective outcomes such as time off work[25]—but there are observational studies which suggest positive real-world long-term improvements in 'mood disorders, suicidality, criminality, substance use disorders, accidents and injuries, traumatic brain injuries, motor vehicle crashes and educational outcomes',[26] and hospital admissions.[27]

A European systematic review by Dijk *et al* that included children, adolescents and adults,[28] concluded that 'treating ADHD is generally cost-effective compared to no treatment', even without counting the cost to wider society from accidents, work productivity and so on, but calls for better data. Treating adults in the 18 months following diagnosis incurs additional prescribing costs, but one cohort study by Adamou *et al*[29] showed these could be partly offset by costs of healthcare while untreated (using the 18 months before diagnosis as a comparator).

Most drugs for ADHD enhance norepinephrine activity in some way. Both methylphenidate and lisdexamfetamine inhibit the dopamine transporter and norepinephrine transporter (NET) increasing synaptic dopamine and norepinephrine in the striatum and prefrontal cortex, noting that the NET also transports dopamine and is particularly expressed in the prefrontal cortex. This may be the main mechanism of action,[30] but there are other effects suggesting important differences, such as lisdexamfetamine having effects on serotonin. It is also unclear why the effects of atomoxetine (which is also a NET inhibitor) are slower to become apparent than with stimulants. There are comprehensive reviews of the pharmacology of stimulants[31] and the neurobiology[15] of ADHD for those interested. Of note, stimulants do not improve productivity in neurotypical people.[32]

Medication for ADHD can be considered in terms of stimulants and non-stimulants. A large network meta-analysis by Cortese *et al*[33] shows stimulants are more effective than non-stimulants. Some patients find stimulants dramatically effective from the first dose; patients may describe a 'lightbulb moment' where they suddenly appreciate what it can be like to not have ADHD, that is, to be generally organised, productive, calm, considered. While the optimal dose may be effective as soon as it is absorbed, several titration steps may be needed to reach this dose over a period of several weeks or months. Non-stimulants may take longer to demonstrate clinical effects (atomoxetine may take 8–12 weeks to reach maximum efficacy).

Considerations when starting any medication for ADHD

Treatment goals

Negotiating clear treatment goals with patients (preferably Specific, Measurable, Achievable, Relevant, Timed) may help them to be realistic about what medication can achieve; understanding patients' priorities may help clinicians determine optimal treatment; and goals can facilitate a 'measurement-informed approach' to assess response. Simple patient-centred goals may be: 'what things about ADHD would you like to 'fix' the most?' Also, functional impairment self-rating scales can be useful to judge the response to treatment, such as the Adult ADHD Quality of Life survey,[34] Weiss Functional Impairment Rating Scale[35] or others.[36] Such scales help to focus on the core symptoms of ADHD which may be more likely to respond to treatment than an aspirational goal which could depend on other factors. Life skills and habits may take longer to 're-learn' and may be less suitable as goals by which to judge treatment. However, patients may struggle with completing detailed rating scales at regular intervals. It may help to share with the patient a record of initial treatment goals and baseline function for later comparison.

Without specified treatment goals, assessment of progress may become based on subjective global impression: this may be less accurate due to day-to-day events and recall biases. Medication which takes longer to achieve an effect may also be subject to a 'levelling over time' bias, causing the patient to underestimate progress.

However, the response to medication may be so dramatic that it validates patients' previous life experience as stemming from a disability, allowing them to 'finally make sense' of their life. The patient may have a 'grief' reaction when considering past mistakes, plans they never managed to complete, relationships and opportunities they lost, etc, which all could have been avoided. They may become angry that the diagnosis and treatment were not available to them previously. Treatment may bring a 'honeymoon period' with high expectations—yet, despite much benefit, treatment may disappoint them by not solving everything, especially if there is significant comorbidity which may not respond to medication (eg, autism). This adjustment period during the start of treatment may contribute to mood fluctuations which might complicate assessment of response.

Comorbidity

Psychiatric[37] and somatic[38] comorbidities are common in ADHD and may contribute significantly to symptoms and choice of treatment. For example, stimulants might help comorbid autonomic dysfunction (eg, gastroparesis, constipation, postural orthostatic tachycardia syndrome[39]) or obesity (suppress appetite, improve impulse control, improve organisation to follow better diet) and perhaps chronic pain[40] and fatigue.[41] Insomnia is a

common comorbidity: stimulants may make sleep worse, although paradoxically some patients sleep better on stimulants. Melatonin helps insomnia in children with ADHD or autism,[42] but evidence for adults is lacking. Small studies have assessed the effect of clonidine on sleep in younger people and adults with nightmares, but it is not licensed for this in the UK.[43 44] Although some patients with tics may be made worse by stimulants, overall, there is not much effect[45]; clonidine (off-label) and guanfacine may also help tics or Tourette's syndrome. Conversely, treatment for the comorbidity may help ADHD.

Some comorbidities, such as bipolar disorder, substance misuse, severe depression, epilepsy or hypertension, may be serious enough to require treatment before considering medication for ADHD. Once controlled, even serious comorbidities are usually not a sufficient reason to withhold treatment for ADHD. Sometimes a comorbidity such as severe depression may be improved or easier to treat once the ADHD is treated.

Bipolar disorder may co-occur in over 10%[46] of those with ADHD, and some patients with bipolar disorder may have been misdiagnosed as ADHD. Bipolar disorder may present in young people around the same time as starting stimulants. Stimulants and atomoxetine can be associated with a manic episode, although it is less clear[47] whether stimulants cause mania, rather than trigger it in patients who may be predisposed. It is important to be vigilant for any features in the personal or family history which may suggest bipolar disorder, before and after starting medication. If bipolar disorder is diagnosed, ADHD medication should be stopped; once the patient is on an effective mood stabiliser ADHD medication may be reconsidered[48] (if the patient still meets diagnostic criteria for ADHD once the bipolar disorder is controlled).

Autism is a common comorbidity with ADHD, but it seems that treating ADHD in those with autism leads to a similar reduction in ADHD symptoms as treating ADHD in those without autism.[49] However, ADHD medication is unlikely to help with symptoms of autism per se.

Substance (and alcohol) use disorder (SUD) is a common comorbidity. A recent expert consensus review by Young *et al*[50] emphasises that SUD must not be an excuse to avoid treating ADHD, although it is desirable that the SUD is stable, and the patient is working towards abstinence. Unfortunately, for SUD and ADHD, services are often separated, yet treating one may help the other. Stimulants remain preferred to atomoxetine because of effectiveness, unless the risk of non-medical use of stimulants is significant.

Risk of misuse

The risk of stimulant abuse is lower for long-acting than short-acting stimulants as their speed of onset produces less of a 'high'. Lisdexamfetamine may have additional advantages as a pro-drug: if dissolved and injected it does not have a significantly faster speed of onset.

The risk of diversion should be considered. However, at a population level most non-medical use is by family members or friends, many of whom suspect they have ADHD, and 'is associated with no, or minor, medical effects'.[51] In the UK, stimulants are classified as Controlled Drugs and it is recommended that only 30 days' supply should be prescribed at a time.

Alcohol may alter the metabolism of methylphenidate leading to greater plasma concentrations.[52] In practice, many patients who want to drink moderately at social events in the evening will have already cleared their daytime doses of stimulant. Alcohol may be discouraged due to exacerbation of symptoms of ADHD (eg, disinhibition, poor concentration) as much as because of medication. There is no data on interactions between alcohol and lisdexamfetamine or atomoxetine.

Cautions and contraindications

The Summaries of Product Characteristics (SPC) for stimulants and atomoxetine list many cautions and contraindications, many of which are common comorbidities, as above.

Some warnings may relate to historic concerns rather than evidence of harm. For example, each SPC for stimulants or atomoxetine warns about potential seizure risk; however, observational studies[53] show no increase in seizure rates between patients on stimulants compared with off stimulants. Epilepsy is more common in those with ADHD, and ADHD is more common in those with epilepsy. This may have explained earlier studies which suggested seizures were associated with ADHD medication.[54] Treating ADHD is associated with lower seizure rates[53] perhaps due to better executive function allowing improved lifestyle or concordance with anticonvulsants.

Stimulants and atomoxetine are cautioned or contraindicated with cerebrovascular disease or a family history of sudden cardiac death. Cardiovascular assessment is recommended in the NICE clinical guideline (NG87).[12] NICE does not precisely define such an assessment but does provide a list of indications for cardiology referral: including any congenital heart disease or cardiac surgery, a family history of sudden death which may be cardiac, blood pressure in the hypertensive range and various symptoms (palpitations, dyspnoea, syncope) or signs (murmur, heart failure) of heart disease. NICE also states that an ECG is not necessary unless there are specific indications. The adult ADHD assessment quality assurance standard for assessment of ADHD[10] has a similar wording about assessing cardiovascular risk. It is controversial whether auscultation is necessary, and if it were, how competent a psychiatrist would be in detecting abnormalities. Some online assessment clinics ask the GP to perform cardiovascular examination or testing, but this is not part of the GP's contract. Such information may already be present in the GP records and could be obtained via patient-accessed records.

All the warnings about using medication for ADHD must be balanced against the benefits of treatment and the substantial risks of not treating ADHD. Advice from relevant specialists (eg, cardiologist) may be important.

Pregnancy and lactation

Whether to continue medication for ADHD in pregnancy needs to be carefully considered on an individual level, ideally before conception. Patients often feel calmer during pregnancy, perhaps due to higher levels of allopregnanolone, and may manage without ADHD medication. However, the desire to avoid any risks of exposing the fetus to medication must be balanced against the risks of untreated ADHD (eg, chaotic lifestyle, poor diet, risk taking, substance misuse, alcohol, smoking, risk of homelessness, inability to engage with services and mood disorders). There is little evidence for or against teratogenesis from stimulants, although one meta-analysis[55] of four cohort studies on a total of 2831 pregnancies exposed to methylphenidate suggests there may be a 25% increase in anomalies generally and a 50% increase in cardiac anomalies; miscarriage and preterm delivery may also be a concern, but all these are also associated with untreated ADHD. Patients may be directed to the BUMPS (best use of medicines in pregnancy) website for information (https://www.medicinesinpregnancy.org/). Clinicians may find the UK teratogenicity information service helpful (https://uktis.org/monographs/) as well as input from perinatal mental health and maternal medicine services.

Untreated ADHD carries a significant risk of postnatal depression.[56] ADHD medication may dramatically improve executive function to cope with demands of caring for a new baby: new chores, sleep deprivation, irregular meals, loss of routine. For the baby, the risks from small amounts of stimulant in breast milk

seem low and are likely to be offset by the benefits of improved maternal mental health. Timing medication doses to minimise excretion in milk is unrealistic, but short-acting stimulants may be preferred to allow napping in the middle of the day when the baby is asleep. Information for patients is available from the Breastfeeding Network (https://www.breastfeedingnetwork.org.uk/factsheet/adhd-and-breastfeeding/).

Atomoxetine and lisdexamfetamine have no conclusive data in pregnancy or lactation.

Social factors

Social factors may also influence the choice of drug: the need for a carer to administer medication, dietary choices to avoid gelatine or shellac as an excipient, the affordability of medication where relevant or proximity to a family member or friend who might divert supplies.

Conclusion

ADHD is a serious condition with high morbidity but responds well to treatment, which can be tailored to the patient's medical and psychosocial needs. Stimulants are effective first-line medications. The second part of the article covers individual drugs in more detail, including initiation and titration.

Acknowledgements I would like to thank Anna Wright for valuable comments from a patient perspective, and Drs Sally Cubbin and Ulrich Müller-Sedgwick.

Competing interests None declared. Refer to the online supplementary files to view the ICMJE form(s).

Provenance and peer review Commissioned; externally peer reviewed.

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DOI: 10.1136/dtb.2024.000019