

Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common condition with a high societal burden. The present guidelines summarise current literature, generating expert consensus recommendations for the treatment of ADHD in children and adults. These guidelines also provide a review of recent research in the fields of neuroimaging, neuropsychology and genetics of ADHD. Novel discoveries in these areas have informed physiological models for the disease. Since the publication of the previous British Association for Psychopharmacology guidelines in 2008, new drugs have been licensed and further compounds are being investigated. The publication of randomised controlled trials of psychological interventions has contributed to the range of treatment options for ADHD. As the disorder has been diagnosed more frequently there has been greater focus on comorbid conditions and how they impact treatment. Services have continued to develop for the treatment of ADHD in adults and care agreements have been introduced to facilitate access to treatment.

Keywords

ADHD, attention deficit and hyperactivity disorder, hyperkinetic disorder, BAP, ADD

Introduction

The British Association for Psychopharmacology (BAP) encompasses psychiatrists, psychopharmacologists and pre-clinical scientists interested in studying the effects of drugs on the brain. Since its foundation in 1974 the BAP has aimed to bridge the gap between experimental research and the development of new treatments for psychiatric illness. The publication of guidelines on different topics including depression, anxiety disorders and attention deficit hyperactivity disorder (ADHD) is a crucial part of this commitment to translate scientific evidence into diagnosis, treatment recommendations and service provision.

Who are these guidelines for?

In line with the general aims of the BAP guideline series, these guidelines are intended to translate recent research in the field of ADHD to promote improvements in diagnosis and treatment of this disorder.

These guidelines are aimed at all those who deliver clinical care, commission treatment or are otherwise involved in the diagnosis and treatment of children, adolescents and adults with ADHD, including psychiatrists, general practitioners,

psychologists, paediatricians, pharmacists, commissioners and user representatives. The guidelines encompass a comprehensive assessment of current literature on ADHD, ranging from aetiological research and neuroimaging to current trends in the development of treatment and services.

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Table 1. Categories of evidence and strength of recommendations.

Categories of evidence for causal relationships and treatment	
Ia:	Evidence from meta-analysis of randomised controlled trials
Ib:	Evidence from at least one randomised controlled trial
IIa:	Evidence from at least one controlled study without randomisation
IIb:	Evidence from at least one other type of quasi-experimental study
III:	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV:	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Categories of evidence for observational relationships	
I:	Evidence from large, representative population samples
II:	Evidence from small, well-designed, but not necessarily representative samples
III:	Evidence from non-representative surveys, case reports
IV:	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Strength of recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category II evidence
D	Directly based on category IV evidence or extrapolated from category III evidence
S	Standard of clinical care

Brief summary of consensus method

These guidelines were arrived at by consensus during a one-day conference of a group of nationally recognised experts in a wide range of aspects of ADHD in children, adolescents and adults. This meeting was in part sponsored by Janssen, Lilly and Flynn-Pharma but represented the independent views of the participants. Contributors received no fee or honorarium for participation. The guideline group included psychiatrists, psychologists, pharmacists, recognised clinical and preclinical researchers in the field and user representatives. Observers from pharmaceutical companies were invited to attend to provide clarification in terms of unpublished data from clinical trials or post-marketing surveillance of drug use, and information on individual marketing authorisation for specific drugs; but were not permitted to participate in the proceedings nor in drafting the guidelines. Selected speakers presented summaries of the current published literature in specific areas with emphasis being placed on meta-analyses, systematic reviews and randomised controlled trials. Discussion followed each presentation with the aim of arriving at consensus based on the evidence presented. Evidence was appraised according to the criteria defined in Shekelle et al. (1999) (see Table 1). A draft guideline based on the slides of the presentations and the transcript of the session was circulated to all participants for comments. This guideline reflects the consensus views of participants; however the named authors take responsibility for the final document.

Strength of evidence and recommendations

The categories of evidence for causal relationships and grading of recommendations used in these guidelines follow the methodology of the *North of England Evidence-based Guideline Development Project* (Centre for Health Services Research, University of Newcastle upon Tyne and the Centre for Health Economics, University of York).

Recommendations are rated A to D according to category of evidence. A lower rating implies a less extensive or robust body of evidence but not necessarily lesser clinical importance. The category S represents a standard of care, which describes a consensus based on good practice standards rather than evidence.

Brief summary of historical context of previous and current guidelines

The previous BAP guidelines for treatment of ADHD were published in 2007 with the main focus on the transition between adolescence and adulthood, diagnosis and treatment of ADHD beyond the adolescent years. At that time there were no published European guidelines for ADHD in adults, and the 2007 guidelines provided a benchmark for the development of clinical services. They constituted a comprehensive reference source for clinicians wishing to establish evidence-based clinics for the treatment of ADHD in adults, and provided an independent scientific perspective on all facets of ADHD including symptoms, diagnostic criteria and treatment.

In 2008 the National Institute of Clinical Excellence (NICE) in the United Kingdom completed a full review of the diagnosis and treatment of ADHD across the lifespan, and published guidelines for the diagnosis and management of ADHD in childhood, adolescence and adulthood. These guidelines were a significant stimulus for the development of improved service provision for ADHD in the UK. Similar guidelines published in Germany (DGKJP, 2007) and Canada (CADDRA, 2011) had comparable effects in their respective countries (Seixas et al., 2012). A further detailed review and European consensus statement was also published by the European Network of Adult ADHD (ENAA), (Kooij et al., 2010). Despite this increased interest there is still a scarcity of services, particularly adult services, for those with ADHD.

The proportion of the population receiving treatment for ADHD in the UK and other Western countries is far lower than the estimated population prevalence of the disorder (I). A great number of patients who would benefit from treatment for ADHD, both children and adults, are never identified or treated (Gustavsson et al., 2011; Wittchen et al., 2011). At the time of writing, financial austerity measures have unfortunately led to cost cutting in health services across Europe. Nevertheless, in view of the current under-provision of services it remains important that ADHD continues to be considered a field for expansion of service provision.

Failure to treat adults with ADHD is costly to society (I). Untreated ADHD results in increased rates of unemployment (I) (Halmoy et al., 2009) and sickness absence (I) (de Graaf et al., 2008). There are associations with illicit drug use and alcohol addiction (Ia), lack of academic achievement (I) and higher rates of poor social adjustment and family or marital conflict (II) (Biederman et al., 2006; Fried et al., 2013; Kaye et al., 2013;

Wymbs et al., 2008). Recently, a large epidemiological study from Sweden showed an approximately four-fold increase in criminal convictions associated with ADHD, that was reduced during periods of targeted treatment for ADHD (Lichtenstein et al., 2012) (II). In addition, untreated ADHD can have a detrimental effect on the relatives of patients and their carers (Cadman et al., 2012).

Consensus points

1. The proportion of the population receiving treatment for ADHD in the UK and other Western countries is still lower than the estimated population prevalence of the disorder (I).
2. Untreated ADHD is costly to society. It produces increased rates of unemployment (I), it associates with illicit drug use and alcohol addiction (I), poor academic outcomes (I), higher rates of marital conflict (II) and increased criminality (II).

Scope of guidelines

BAP guidelines have usually been updated on a five-yearly basis. Following this tradition this document is an update to the previous guidelines published in 2007 (Nutt et al., 2007). It is the aim of the BAP guidelines to encourage evidence-based changes of clinical practice incorporating and summarising new research. Whenever evidence was limited this is acknowledged and a recommendation is reached by consensus.

In the previous guidelines ADHD was defined as a neurodevelopmental disorder, and recommendations for diagnosis and treatment for adults with ADHD were inferred from data relating largely to children. Although this has remained the case in certain areas, far more evidence is now available that is specific to adults with ADHD. In general, new research has corroborated the view that deficits found in adults are similar to those already identified in children, and that response to treatment is comparable (I).

A point of discussion at the time of the earlier guideline was whether ADHD is best conceptualised as a distinct category, or represents the extreme and impairing tail of one or more dimensional traits. The evidence for the later view has grown since 2007 (Chen et al., 2008; Levy et al., 1997; Toplak et al., 2009, 2012). However, for practical reasons it is still necessary for clinicians to think at least to some degree categorically when making decisions about diagnosis and treatment (Coghill and Sonuga-Barke, 2012).

Many areas of the guidelines have remained unchanged and are not repeated in this update. For example, diagnostic criteria still require the presence of significant impairment as well as symptoms. The symptom checklist for ADHD in the adult is reproduced here as it was in the last version (Table 2). The new DSM V has changed some of the criteria for ADHD; it acknowledges the disorder in adulthood as well as in childhood. Adults with ADHD can be diagnosed with five symptoms instead of the six required for children. In addition, it is now possible to have a diagnosis of ADHD in the presence of autism spectrum disorder (APA, 2013).

New scales and diagnostic tools have been developed, and some are freely available for use (Rosler et al., 2006).

Recent meta-analyses have calculated and compared effect sizes for most medications commonly used to treat ADHD in adults, which are generally in line with findings in children (discussed in

Table 2. BAP extended adults symptoms checklist.

BAP extended adult symptom checklist

1. Lack of attention to detail or carelessness
2. Inattention in tasks or activities the patient finds tedious
3. Difficulty listening
4. Failure to follow instructions
5. Starting many tasks while having difficulty finishing them
6. Poor organisational skills
7. Avoidance of, dislike of, or inability to expend sustained mental effort
8. Losing or misplacing things
9. Ready distractibility
10. Forgetfulness
11. Fidgeting
12. Restlessness or an inability to sit still in low-stimulation situations
13. Inappropriate or excessive activity or an internal feeling of restlessness or edginess
14. Difficulty keeping quiet; talking out of turn
15. Unfocused mental activity; difficulty turning thoughts off
16. Blurting out responses; poor social timing in dialogue
17. Trouble waiting if there is nothing to do
18. Interrupting or intruding on others
19. Irritability, impatience or frustration
20. Affective lability or hot temper

the treatment section). Other studies have demonstrated the value of adjunctive treatment with cognitive behavioural therapy and other types of psychological treatment. On the question of how and by whom services for adults with ADHD should be developed, many providers of psychiatric care have created specialist clinics for adults with ADHD or extended their transitional services to include older patients or those presenting for the first time as adults. Finally, these guidelines have been extended to include more information relevant to treatment of ADHD in children and adolescence, compared with the original 2007 version.

Neurodevelopmental background

Definition of ADHD

ADHD is a neurodevelopmental condition which can persist throughout the lifespan. At its core is a persistent and pervasive pattern of inattention and/or hyperactivity and impulsiveness. Both genetic and environmental factors play an important role, leading to alterations of multiple circuits in the brain and creating various pathways to symptoms, different individual deficit profiles and resulting impairments (Table 3).

Aetiology

Recent advances in the genetics of ADHD. As detailed in the previous guidelines, ADHD is a highly inheritable condition (I), (Burt, 2009; Todd et al., 2005). First-degree relatives of a child diagnosed with ADHD are 4–5 times more likely to have ADHD than the general population (Faraone et al., 2000), and there is up to a 10-fold risk among the siblings of children with combined-type ADHD (Brookes et al., 2008).

Table 3. Consensus: ADHD is a neurodevelopmental condition.

- ADHD is a neurodevelopmental condition, with multiple pathways to symptoms each marked and mediated by different deficit profiles (B)
- Research points at ADHD being the end of a spectrum of a population trait, more than a traditional category (A)
- ADHD trajectories start in childhood and can continue to adulthood (A)
- The status of an ADHD-like disorder of later onset has not yet been established (D)
- In the absence of specific biomarkers common to the entire group of ADHD patients, assessment and treatment are guided by clinical phenotypes (A)
- ADHD is a pathophysiologically complex and heterogeneous disorder (B)
- A sophisticated causal framework is needed that accounts for the causal heterogeneity in the condition and can integrate aetiological, neuroimaging and neuropsychological findings (D). The role of gene × environment interaction in the aetiology of ADHD and the role of the default mode network requires further investigation (D)

Early candidate gene studies focused on neurotransmitter systems and identified several genes involved in dopamine and serotonergic neurotransmission (Gizer et al., 2009). The strongest evidence remains for a small but significant effect of the 7-repeat allele of the dopamine D4 receptor gene (Li et al., 2006). Genetic variants within five genes reaching evidence for association with ADHD (serotonin 1b receptor, serotonin transporter, dopamine D4 and D5 receptor and the dopamine transporter) (Gizer et al., 2009) were previously estimated to account for 3.2% of phenotypic variance and 4.2% of heritability of ADHD (Kuntsi et al., 2006).

Genome-wide association studies (GWAS) show evidence of nominal association with ADHD of common genetic variants within sets of traditional candidate genes for ADHD (Neale et al., 2008, 2010), and converging evidence from different study designs suggest that genetic variation within a network of genes involved in neural growth increases risk for ADHD (Poelmans et al., 2011). GWAS have yet to identify common genetic variation that reaches grade Ia; however, it was recently estimated that 28% of the variance in ADHD is explained by currently available genome-wide genetic marker arrays (Yang et al., 2013). Given the current consortium sample size of 5840 cases and 11,552 controls, current findings indicate that we are on track to discover genome-wide significant genetic variants once samples increase to 10,000 cases and higher.

In addition, elevated rare copy numbers have been found in ADHD. Initial findings and replication studies indicate that this reaches Ia level of evidence (Elia et al., 2012; Stergiakouli et al., 2012; Williams et al., 2010, 2012). More specifically, there was evidence for association with duplications spanning the *CHRNA7* gene at chromosome 15q13.3. This finding was consistently replicated in an additional 2242 ADHD case subjects and 8552 comparison subjects from four independent cohorts from the United Kingdom, the United States, and Canada (Williams et al., 2012).

Environmental influences. The systematic review of Coghill et al. (2014; personal communication) identified prematurity as the only environmental factor with sufficient evidence

of a temporally ordered association with ADHD. For two factors – maternal smoking in pregnancy (although this effect seems likely to be mediated by genetic factors) and low birth weight – the evidence was suggestive but not conclusive. There was limited or insufficient evidence to make firm conclusions with respect a variety of other factors, including maternal alcohol use in pregnancy, maternal psychological status in pregnancy, severe head injury, duration of breastfeeding, severe early childhood deprivation, family psychosocial factors, early household gas/NO₂ exposure, childhood streptococcal infection and maternal use of other drugs in pregnancy. In most cases only single studies have assessed the interaction between individual genes and environmental factors, therefore the results of these should be considered tentative and need to be confirmed in further research. This is an important area for future development.

Structural neuroimaging in ADHD

Meta-analyses of imaging studies have detected differences in the neural structure of patients with ADHD: smaller right hemispheric grey matter volumes of the basal ganglia, including the putamen, the globus pallidus, and the caudate nucleus, possibly smaller grey matter volumes in total and right cerebral volume, cerebellum, corpus callosum, frontal lobes, prefrontal cortex, deep frontal white matter and temporal lobe and possible grey matter increased in the left posterior cingulate cortex/precuneus (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Makris et al., 2008; Nakao et al., 2011) (I). However, the precise nature and relevance of these differences remains contentious. In the three most recent meta-analyses of imaging studies of ADHD which considered the whole brain, the dopamine-rich basal ganglia was the only brain region found to be consistently reduced in grey matter.

Brain maturation

The pattern of cortical brain development in ADHD follows essentially the same trajectory as that of non-ADHD children, but appears to be delayed by an average of 2–3 years in ADHD subjects. The delay is particularly marked in the prefrontal cortex but is also evident in other parts of the brain, including the temporal lobe. Cortical normalisation mirrors clinical outcomes to an extent, with less symptomatic subjects showing more cortical normalisation than those with persistent symptoms (Shaw and Rabin, 2009). This evidence points to an ‘immaturity hypothesis’, where ADHD patients require more time to achieve the same developmental milestones than unaffected subjects (III).

Brain connectivity in ADHD

Research on brain connectivity by Castellanos and colleagues (2008) suggests that ADHD may be a disconnectivity syndrome. Both structural and functional connectivity appear to be affected (Konrad and Eickhoff, 2010). These studies have suggested that ADHD is associated with both reduced efficiency in long-range connections and decreased nodal efficiency (local connectivity). Interestingly, preliminary data suggest that those regions that are associated with decreased long-range functional connectivity (e.g. anterior limb internal capsule or the corpus callosum) are also associated with reduced structural connectivity.

These structural and functional abnormalities are likely to impact negatively on long-range communications among the various parts of the brain. Decreased nodal efficiency has been demonstrated most convincingly in the prefrontal, temporal occipital and associated subcortical regions. Some studies have also identified increased nodal efficiency, and it has been suggested that this may be a compensatory mechanism in some areas (e.g. inferior frontal gyrus) (Wang et al., 2009). Reduced coupling has been found with parietal and cerebellar regions during attention and response inhibition, which may reflect greater effort required by those with ADHD who cannot otherwise compensate for the coupling deficit. There has been particular interest in the potential role played by the default mode network in ADHD. Interestingly, there are two contrasting perspectives as to how these effects may be mediated, with Tian et al. (2006) suggesting hyper-connectivity and Castellanos et al. (2008) proposing hypo-connectivity. While there is little experimental data to support either view, the hypothesis put forward by Castellanos et al. – that the default mode network is normal at rest but fails to be attenuated when engaging in a task and interferes with the neuronal circuits underlying task performance – has face validity and deserves further investigation. Integration of these findings suggests that the decreased global efficiency of brain networks in ADHD may be associated with a loss of long-range connections which cascade into compensatory mechanisms.

The dopamine hypothesis

The dopaminergic system in ADHD has been investigated through a series of PET and SPECT studies over the last decade. Most studies have relatively small samples sizes, and some findings are controversial. Dopamine transporter availability in the striatum of adults and children with ADHD was found to be consistently reduced, indicating a problem in dopamine synthesis (Del Campo et al., 2012). Volkow et al. (2009, 2011) compared never-medicated adult ADHD patients ($n = 55$) with healthy controls ($n = 44$), and patients showed significantly lower availability of D2/D3 dopamine receptors and dopamine transporter (DAT). However, a considerable overlap of individual binding levels between patients and healthy controls was reported. The severity of ADHD symptoms also correlated with striatal dopamine receptor density (Volkow et al., 2009). DAT availability may change with medication status, with higher density in patients exposed to medication and lower in drug-naïve patients (Fusar-Poli et al., 2012). Table 4

Table 4. Key facts: neurodevelopmental background of ADHD.

- ADHD is a highly inheritable condition
- Prematurity is the main environmental factor associated with ADHD
- More research is needed to elucidate the role of other environmental factors
- Imaging studies have detected differences in the neural structure of patients with ADHD
- Brain maturation appears delayed and structural and functional connectivity are affected
- Dopaminergic pathways are implicated in ADHD
- An underlying hypothesis explaining all these findings has yet to be developed, more research is needed in this area

summarizes key facts about the neurodevelopmental background of ADHD.

Neuropsychology

Patients with ADHD display a heterogeneous range of neuropsychological profiles. Some appear relatively normal while others show different patterns of impairment. It could be said that neuropsychologically, ADHD is an umbrella term for a range of different but related pathophysiological entities. For instance, Sonuga-Barke et al. (2008) found that children and adolescents with ADHD could be distinguished from one another in terms of the extent to which they showed executive or timing or delay related deficits – with the majority of patients showing just one of these deficits and very few showing all three. Where deficits have been found, the areas involved have included executive function, selective and sustained attention, response inhibition, working memory and reward-related motivation. In some patients, deficits in executive function and temporal processing may overlap, while in others these are not present.

New studies have shown that the neurocognitive profiles of adults with ADHD are similar to those of children with ADHD, confirming the neurodevelopmental continuity in the trajectory of the condition (I). The current literature does not support the concept of a disease of later onset without symptoms in childhood. In clinical practice, many patients may not have been diagnosed in childhood but will report impairment since a young age. Table 5 summarises the effect sizes for neuropsychological deficits in a range of domains tests in children, adolescents and adults.

Since 2007 there have been a number of developments of significance. Evidence for executive function deficits of moderate size remains strong in children, adolescents and adults with an increase in the number of positive studies in adulthood. The number of studies of timing and state-regulation deficits has increased for children and adolescents, strengthening the case for deficits in each of these areas in childhood. The evidence is more mixed in relation to reward and punishment (Bush, 2011). There is now evidence for abnormalities in adult ADHD in terms of timing problems (Gilden and Marusich, 2009; Valko et al., 2010); reward (Strohle et al., 2008), although this is an area in need of more studies; delay processing (Scheres et al., 2008); and state regulation. However, the quality of the adult-related evidence in these domains is limited by the lack of systematic reviews or meta-analyses. The issue of neuropsychological heterogeneity has not been addressed directly in adult samples. Another difficulty to be considered when assessing neuropsychological profiles in ADHD is the impact of comorbidity on the testing. It is likely that results are affected by depression, anxiety and by learning disabilities when these co-occur with ADHD.

Diagnostic value of neuropsychological tests

Specific neuropsychological tests can be useful in the assessment of executive function in ADHD and as a research tool for endophenotypes. However, they should not be used in isolation to diagnose ADHD in the absence of a clinical evaluation by an experienced clinician (Sonuga-Barke et al., 2008). Tests for executive function have good positive predictive value but poor

Table 5. Quantitative studies column describes the existence of quantitative reviews published for the named test. **Strength of effect:** no effect, Cohen's $d < .2$, small effect, Cohen's $d .2-.4$; moderate effect Cohen's $d .4-.7$; large effect Cohen's $d .7-1.0$; very large effect Cohen's $d > 1.0$. Task domains in table; **Executive Function** (Sonuga-Barke et al., 2008) CPT = continuous performance test of sustained attention; SSRT = Stop signal reaction time measure of inhibitory control; WM-spati = visuo-spatial working memory; WM - verb = verbal working memory; ToL/H = Tower of London/Hanoi measure of planning; Trials-B = a measure of planning; **Timing:** (Toplak et al., 2006); Time (<sec) = measures of millisecond timing such as time discrimination tests; Time (>sec) = measures of multi-second timing such as interval reproduction; **State Regulation** (Sonuga-Barke et al., 2010): ISI effects = the effect of varying event rate on performance; Motivation : Reward = measure of sensitivity to the effects of adding rewards to tasks; Punishment = measure of sensitivity to sensitivity of adding punishments to tasks; Delay = measures of the effects of reward delay on performance and choice.

	Child/adolescent		Adult	
	Quantitative reviews	Strength of effect	Quantitative reviews	Strength of effect
CPT comm	Yes	Moderate	Yes	Moderate
CPT-omm	Yes	Moderate	Yes	Moderate
SST-RT	Yes	Moderate	Yes	Small
WM-spati	Yes	Moderate	Yes	Small
WM-verb	Yes	Moderate	Yes	Small
ToL/H	Yes	Moderate	Yes	Small
Trials-B	Yes	Moderate	Yes	Moderate
Stroop Intf	Yes	Small	Yes	Small
WCST-Per	Yes	Moderate	Yes	No effect
Time- (<sec)	No	Moderate	No	Small/moderate
Time- (>sec)	No	Moderate	No	Small/moderate
ISI effects	No	Moderate	No	Small
Reward	No	Small	No	No effect
Punishment	No	Small	No	No effect

negative predictive value (Nutt et al., 2007) for diagnosing ADHD. Therefore the use of these tests for the diagnosis of ADHD will lead to a high level of false negative cases. This is probably closely tied to the neuropsychological heterogeneity of ADHD. An added difficulty is the lack of standardisation of neuropsychological testing across studies and the paucity of research addressing the stability of these results over time as well as the lack of evidence relating to other neuropsychological markers. Two different responses appeared to this lack of diagnostic value of neuropsychological (in particular executive function) tests. Barkley and Fischer (2011) argued that the problem is the use of ecologically invalid laboratory tests to measure executive function and showed that questionnaire measures of executive function may be more useful, while Gupta et al. (2011) argued that what is required is an assessment that combines multiple neuropsychological domains including executive and non-executive tasks. It remains to be seen whether either of these approaches will resolve the role of neuropsychological testing in ADHD. An additional problem is a lack of clarity about the relationship between ADHD symptoms and neuropsychological deficits. While there are clear cognitive differences at the group level between those with high and low levels of ADHD symptoms, attempts to demonstrate meaningful associations between these two aspects of functioning are few, and where present do not provide clear support for causal relationships (Coghill et al., 2007).

Multi-domain assessments using a broad definition of executive function have appeared in the last few years for both children and adults. Some of these, such as the CANTAB, are computerised. One of its components – the Rapid Visual Information Processing task (RVIP) – has been shown to core test for ADHD

in endophenotype studies (Pironti et al., 2013). The Stop Signal Reaction Time tasks (SSRT) has also performed well in studies by several groups (Hart et al., 2013). This provides an opportunity to address the known heterogeneity of ADHD with the aim of identifying new subtypes of the disorder and clarify causal pathways. The utility and cost effectiveness of multi-domain assessments in everyday clinical practice is still to be determined. IQ testing is not a mandatory requirement in the evaluation of ADHD, but it can be useful in certain cases such as for educational or court assessments. ADHD patients may underperform in these tests, particularly in timed tasks and in those where impulsivity is a limiting factor.

Other uses of neuropsychological testing

A neuropsychological assessment should be considered where the impairment at home, education and/or work is disproportionately greater than what would be expected from symptoms alone. Given the apparent heterogeneity in neuropsychological deficits in ADHD, neuropsychological testing can play an important clinical role in identifying cognitive strengths and weaknesses in specific individuals, which can help the tailoring of interventions in school or college. For instance, if it can be established that a child has a working memory deficit it may be useful to supplement their core treatment with additional training in working memory. It may be possible in the future to use neuropsychological profiling to help develop personalised treatment approaches. Furthermore, many institutions require some type of neuropsychological assessment in order to establish the case for extra tutoring, counselling, and extension of academic deadlines or extra time in exams. Not all patients with ADHD will benefit

from these interventions, so testing can provide a framework to evaluate the type of support needed. Measuring neuropsychological change before and after treatment may be useful in highlighting areas of functioning that require further attention. Similarly, testing may greatly assist the overall assessment of ADHD defendants when preparing reports for court proceedings

Neurocognitive testing does not provide a baseline measure to assess symptom improvement with medication. Clinical impression and hyperactivity-inattention scales continue to be the standard method to evaluate symptomatology and adjust dosage. This is because it is still not clear which deficits underline the symptoms and impairments of ADHD, and attempts to link change in symptoms to change in cognitive performance during treatment for ADHD suggest that these relationships may be much more complex than previously assumed (Coghill et al., 2007). Potential biomarkers of the clinical response have recently been identified in a preliminary study of methylphenidate and atomoxetine (Schulz et al., 2012) using functional magnetic resonance while performing a go/no go task.

Summary

There is good evidence of altered neuropsychological function in ADHD in many domains, and there is not one single neuropsychological profile that separates ADHD from normality or from other conditions. This limits the diagnostic value of neuropsychological testing, although in the future it might be useful in identifying neuropsychological subgroups with specific clinical needs. Therefore direct studies of neuropsychological heterogeneity are necessary in order to quantify and corroborate evidence in children and adults. The impact of comorbidity on test performance needs to be considered. Neuropsychological instruments can be useful to assess learning impairments, in court settings and school, but currently a diagnosis of ADHD should not be based on cognitive impairment as detected by these tests. Table 6 summarizes key facts about neuropsychological testing in ADHD.

Electroencephalography in ADHD

The Food and Drug Administration (USA) has recently approved an EEG-based instrument as a diagnostic aid for ADHD in children

Table 6. Key facts: neuropsychology in ADHD.

- New evidence strengthens the case that ADHD is neuropsychologically heterogeneous (I)
- Neuropsychological studies of ADHD in the adult have doubled in number in recent years, but many uncertainties remain (I)
- Additional studies have confirmed that executive function deficits in adults are similar to those in children and that those deficits only affect a proportion of adults (I)
- New multi-domain batteries and ratings of everyday executive function are promising approaches to diagnosis but their practical value needs to be confirmed before they can be recommended for everyday clinical use (S)
- There are new research studies of timing/impulsive responding and impulsive choice driven by sensitivity to reward choice and state regulation in adults with ADHD but still little or no work on reward/punishment sensitivity (S)

to be used as part of a complete medical and psychological examination (FDA, 2013). The device calculates the ratio between theta and beta brain waves at rest. This ratio is higher in children with ADHD. A meta-analysis found that this biomarker correlated well with behavioural changes over time (Snyder and Hall, 2006). However, one randomised controlled trial in children failed to find a correlation between theta/beta ratio and symptomatology in children while performing a sustained attention task (Ogrim et al., 2012). Alpha and beta band activity in posterior regions has been reported to be reduced in ADHD children, although this finding is not homogenous, with a subgroup of ADHD children showing increased activity that correlated with greater severity of symptoms (Loo and Makeig, 2012). Although EEG markers are promising, they have several limitations. Firstly, as with neuropsychological assessments, the findings are heterogeneous; for example, up to 16% of children with ADHD will have normal theta/beta ratios. Secondly, various technologies and instruments were used in the electrographic studies of ADHD, which may explain the variation in results across studies. Finally, the presence of comorbidity may impact on the EEG observations, leading to misdiagnosis (Loo and Makeig, 2012). More research is required to clarify the role of an EEG in the diagnosis of ADHD.

Pharmacology of drug treatments for ADHD

Introduction

Until very recently, the psychostimulants *dl-threo*-methylphenidate (methylphenidate) and *d*-amphetamine, together with the selective noradrenaline reuptake inhibitor, atomoxetine, were the only drugs approved in Europe for the management of ADHD. As shown in Figure 1, the pharmacological characteristics of these drugs are highly restricted, both in terms of their neurochemical mediators and mechanisms of action. Noradrenaline and dopamine are the only neurotransmitters that have been implicated in the therapeutic actions of ADHD drugs. Although considerable prominence has been given to dopamine as the more important mediator of the therapeutic effect of ADHD drugs, the available evidence does not support this view. Guanfacine, which is a preferential α_{2A} -adrenoceptor agonist, and atomoxetine, a noradrenaline reuptake blocker, are both highly selective noradrenergic drugs that have proven efficacy in treating ADHD (Heal et al., 2012). In contrast, no drug with a selective dopaminergic mechanism of action has yet been shown to be beneficial in treating this disorder. This point is further supported by the finding that several drug candidates with potent dopamine reuptake inhibitory properties have been discontinued in clinical development in ADHD due to a lack of efficacy (Heal et al., 2012). The explanation is that in the prefrontal cortex (PFC), which is widely believed to be an important brain region for the therapeutic actions of ADHD drugs, dopaminergic innervation is sparse and the density of DAT sites on dopaminergic neurones is very low (Hitri et al., 1991). For this reason, a major portion of dopamine that is released from neurones in the PFC is sequestered into noradrenergic neurones via noradrenaline reuptake transporters (Moron et al., 2002; Stahl, 2003). Consistent with this observation, in vivo microdialysis experiments in rodents have demonstrated that the noradrenaline-selective reuptake inhibitor, atomoxetine (Bolden-Watson and Richelson, 1993; Bymaster

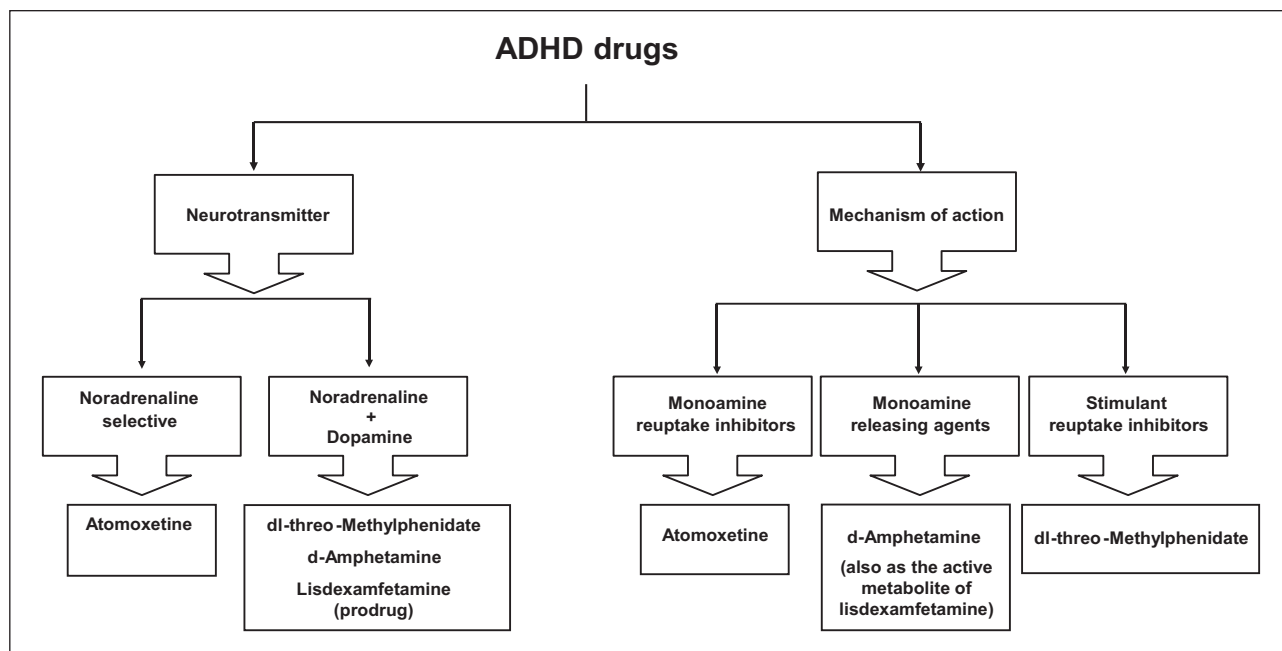


Figure 1. Pharmacological classification of ADHD drugs approved in Europe.

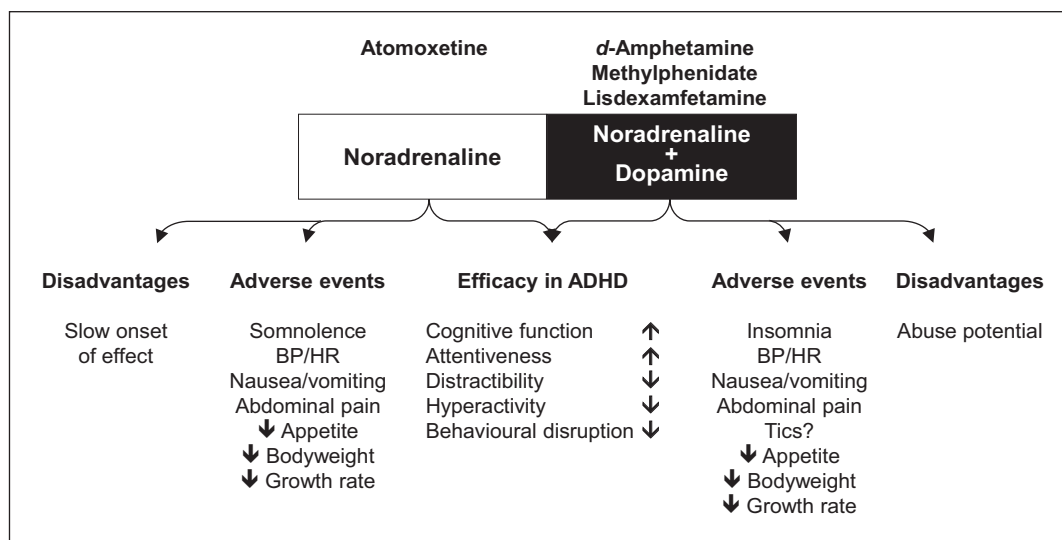


Figure 2. ADHD drugs – relationship between primary pharmacology, efficacy, safety and recreational abuse potential. BP=blood pressure, HR=heart rate.

et al., 2002) unequivocally increases the extraneuronal concentration of both noradrenaline and dopamine in the PFC (Bymaster et al., 2002; Swanson et al., 2006), whereas GBR 12909, which is a potent and selective dopamine reuptake inhibitor (Andersen, 1989), produced either minimal or no significant increase in the concentration of either catecholamine (Pozzi et al., 1994; Tanda et al., 1997). In summary, enhancement of dopaminergic and noradrenergic neurotransmission in the PFC is probably critical to the therapeutic efficacy of ADHD drugs.

As shown in Figure 2, the pharmacological actions of the ADHD drugs, which mediate their therapeutic effects, are identical to those responsible for producing their adverse events. For

each of the drugs, there will always be a fine balance between delivering greater efficacy by increasing the dose versus the emergence of unacceptable levels of adverse events. As discussed in several recent reviews (Heal and Pierce, 2006; Heal et al., 2012), there is a good correlation between the pharmacodynamics of drugs on catecholaminergic neurotransmission in the brain as determined by intracerebral microdialysis in rodents and their clinical efficacy and safety as ADHD treatments. Stimulants, which produce very large and profound increases in the extracellular concentrations of dopamine and noradrenaline in the PFC and dopamine in the striatum, are also the most effective medications that are available to physicians to treat ADHD.

New drugs

In terms of new drugs, the *d*-amphetamine prodrug, lisdexamfetamine (Elvanse®, Tyvanse®, Vyvanse®), and an extended-release formulation of guanfacine (Intuniv®), have been marketed recently. Both drugs are approved and have been available in North America for the treatment of ADHD for several years. In December, 2012, approval of lisdexamfetamine for the treatment of ADHD in children ≥ 6 years of age when there is inadequate response with methylphenidate was recommended by eight European countries: the UK, Denmark, Finland, Germany, Ireland, Norway, Spain and Sweden. Lisdexamfetamine, which can be administered once-daily, is a prodrug that is metabolised by red blood cells to yield its active metabolite, *d*-amphetamine, and L-lysine (Pennick, 2010). Lisdexamfetamine has been shown to be effective in the treatment of ADHD (evidence level Ia) in a number of randomised, double-blind, placebo-controlled trials that have been performed in children (Biederman et al., 2007a, 2007b) and adults (Adler et al., 2008), and also in open-label, long-term investigations (Findling et al., 2008; Weisler et al., 2009). The side-effect profile of this prodrug (Vyvanse® US Prescription Drug Label, 2012) is similar to that of *d*-amphetamine or methylphenidate (Heal et al., 2013), but there is evidence from studies performed in drug-experienced human volunteers that indicates its liability for recreational abuse may be substantially lower than that of immediate-release *d*-amphetamine (Jasinski and Krishnan, 2009a, 2009b). In a similar vein, Kollins et al. (1998) compared the subjective and reinforcing properties of a sustained release and immediate-release formulation of methylphenidate in healthy volunteers, and observed that the stimulant and reinforcing effects of the former were attenuated and transient compared with the latter, leading the authors to conclude that the sustained release formulation posed a reduced risk for recreational abuse. Lisdexamfetamine, despite its very low abuse potential, is likely to be a Controlled Drug in many European countries, but its level of scheduling has not yet been published.

Guanfacine is not available for treating ADHD in Europe. Results from clinical trials performed mainly in the combined (hyperactive/impulsive-inattentive) ADHD subgroup have shown that the preferential α_{2A} -adrenoceptor agonist, guanfacine, is an effective (evidence level Ia) ADHD treatment in children and adolescents (Scahill et al., 2001; Biederman et al., 2008). However, guanfacine appeared to be less efficacious in treating the minority of subjects with the inattentive subtype of this disorder. Response rates of 50–60% in children on guanfacine treatment (Biederman et al., 2008; Scahill et al., 2001) place it alongside the other non-stimulant drugs in terms of relative efficacy. However, no head-to-head studies have been performed in adults. α_{2A} -adrenoceptors are also important in the central regulation of blood pressure and induction of sedation. Hypotension, bradycardia and occasional reports of syncope together with somnolence, fatigue, sedation, upper abdominal pain, dry mouth, nausea and dizziness are reported adverse events for guanfacine (Intuniv® US Human Prescription Drug Label, 2012). In contrast to all other ADHD drugs, guanfacine may be associated with moderate weight gain.

Effectiveness of drugs

Psychostimulants are first-choice pharmacological treatment both in children and adults. Methylphenidate and dexamfetamines

reach level Ia with the non-stimulant atomoxetine and the smoke cessation agent bupropion. Clonidine and guanfacine reach level Ib. The only randomised controlled trial of modafinil in adults was negative (Arnold et al., 2012), despite positive results in children (Kahbazi et al., 2009). In the UK, methylphenidate is considered the psychostimulant of choice. In terms of effectiveness, a meta-analysis comparing drug versus placebo interventions suggested that the standardised mean differences for ADHD symptoms are 1.03 for dexamfetamine and 0.77 for methylphenidate (Faraone and Buitelaar, 2010). In terms of the relative effectiveness of methylphenidate versus atomoxetine, a recent meta-analysis of studies in children and adolescents suggested little difference (standardised mean difference of 0.09). However, a subgroup analysis within this meta-analysis indicated that a long-acting preparation of methylphenidate might be more effective than atomoxetine (standardised mean difference of 0.32).

Modified-release methylphenidate is preferred to instant-release formulations. For children, it reduces stigma as the child does not need to take any medication to school, avoiding storage and administration problems. In addition, it facilitates parental monitoring. In adults, modified-release preparations pose less risk of abuse and improve adherence. It is worth noting that the various brands of modified-release methylphenidate available differ in proportions of immediate release and delayed release, and are not bioequivalent (Table 7).

In terms of initial choice of treatment (Table 8), atomoxetine should be preferred if there are any contra-indications to stimulant treatment: in general, when treatment with methylphenidate has been ineffective, or not tolerated, in the presence of anxiety disorders or severe tics, or when there is a risk of misuse or diversion (evidence level IV). In children, risk of misuse by parents or siblings should be considered when making a therapeutic decision. In the presence of family history of cardiac problems (e.g. sudden cardiac or unexplained death of a first-degree relative before the age of 40 years) or any significant cardiovascular concerns (e.g. frequent syncope, especially exercise induced, excessive shortness of breath or exercise intolerance), further cardiac examination should be considered before starting ADHD medication. In the presence of family history of cardiac problems or any cardiovascular concerns, either atomoxetine or methylphenidate may be used cautiously – but should be monitored carefully.

Pre-treatment assessment

Before commencing treatment with psychostimulant drugs or atomoxetine, the following are required: full history with a basic physical exam including height, weight, pulse, blood pressure, and heart and lung auscultation (Table 9). If there is family or personal history of heart disease or the cardiovascular examination is abnormal an ECG is recommended. Risk of self-harm should also be assessed. In the case of atomoxetine, previous history of liver disease should be evaluated. It is not necessary to obtain basal liver tests in the absence of a positive history. If bupropion is used, previous history of bipolar disorder and epilepsy needs to be considered.

In adults and teenagers, a risk assessment for potential substance misuse and drug diversion is required when prescribing psychostimulants. This is not, however, necessary for atomoxetine, which has no abuse potential.

Drug diversion of psychostimulants is a particular concern in college and university settings (Franke et al., 2011; Sofuoglu,

Table 7. Stimulants and non-stimulant medications used in ADHD (adults and children), half-lives, formulations and trade names.

Drug	Half-life of chemical (approx. plus range)	Formulations (UK)	Trade name
Methylphenidate	Children 2.5 h (1.5–5) Adults 3 h (1.3–7.7) Longer with XL	Plain 5 mg, 10 mg, 20 mg Concerta XL 18 mg, 27 mg, 36mg **** Medikinet XL 5 mg, 10 mg, 20 mg, 30 mg, 40 mg Equasym XL 10 mg, 20 mg, 30 mg Others are available in other countries	Concerta® *** Medikinet® *** Equasym® *** Ritalin®
Dexamfetamine	10–12 h (variable, very sensitive to urinary pH)	Tablets 5 mg	
Atomoxetine	5.2 h 21.6 h in 2D6 poor metabolisers	Capsules 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg	Strattera®
Bupropion	14 (8–24 h) Longer on chronic dosing	Tablets 150 mg	Zyban®
Clonidine	12–16 h, up to 23h	Tablets 25 mcg, 100 mcg	Dixarit®, Catapres®
Modafinil	12–15hrs	Tablets 100 mg, 200 mg	Provigil®
Lisdexamfetamine*	Up to 1h, inactive and metabolised to dexamfetamine	*Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg (not all strengths available in all countries)	Elvanse®* (Europe) Tyvanse® (Eire) Vyvanse® (USA and Canada)
Guanfacine**	17 (10–30)	**Tablets 1 mg, 2 mg	Tenex®** Intuniv®**

*25 mg of Vyvanse is molecularly equivalent to 10 mg of dexamfetamine; Adderall contains roughly 75% dextroamphetamine and 25% levoamphetamine; lisdexamfetamine is a single-enantiomer (dextro) amphetamine.

**Not licensed in UK at time of writing. Presentations listed are available in other countries.

***The proportions of immediate release (IR) and modified release (MR) are different in the available methylphenidate XL formulations:

Concerta XL 28% IR, 72% MR

Equasym XL 30% IR, 70% MR

Medikinet XL 50% IR, 50% MR

****The Concerta XL products do not release the full methylphenidate content; 18 mg is equivalent to 15 mg IR methylphenidate, 36 mg to 30 mg IR methylphenidate and 54 mg to 45 mg IR methylphenidate.

Table 8. Consensus.

1. Stimulants are first-line treatment for adults with ADHD (A)
2. Atomoxetine is considered first-line treatment in patients with substance use disorders (S)
3. Drug treatment should be continued as long as clinically useful (S)
4. Careful titration and monitoring of side effects is required, particularly when using stimulants (A)
5. Drug holidays may be useful to ascertain the need of continuation of treatment (S)
6. Co-administration of drugs is relatively common in clinical practice for resistant cases but there is a lack of studies investigating its efficacy(S)

Research needs

1. More studies are required to elucidate the effects of 'flexible' dosing and co-administration of drugs
2. More pharmacological studies in humans are necessary to understand the full range of actions of ADHD medications in the brain and the individual variations that may limit efficacy or cause side effects

2010). Students entering university should be warned about the risks of lending or sharing their medication with other students, and should be advised to store psychostimulant medication in a safe location. The street value is thought to be higher for amphetamine than methylphenidate, and higher for instant-release formulations compared with slow release. Abuse of prescribed stimulants

is not widely reported in the UK and would require 'injection' or 'snorting' to provide the sensation of a 'high'. The risks of abuse can therefore be largely avoided by use of long-acting formulations of methylphenidate or amphetamine. The prodrug lisdexamfetamine has a very low abuse potential and is a good alternative to immediate-release dexamfetamine.

Table 9. Pre-treatment assessment table.

Psychostimulants	Atomoxetine
Full medical history	Full medical history
Weight, height, blood pressure and pulse	Weight, height, blood pressure and pulse
Cardiovascular exam (Auscultation)	Hx of liver illness
Family and personal history of cardiovascular illness	Hx of self-harm
Hx of self-harm	
Assessment of risk of abuse and diversion	

Treatment of ADHD in children and adolescents

Prevalence of treatment in children

Data from the most recent nationally representative British Child and Adolescent Mental Health Survey, carried out in 2004, found an ADHD prevalence rate of 2.2% in 5–16-year-olds (Sayal et al., 2010a). This relatively low prevalence reflects the application of strict DSM-IV symptom and impairment criteria. Only one-third of children meeting criteria for ADHD were receiving psychoactive drugs; the median duration of treatment was 20 months, and 93% of those taking medication were receiving methylphenidate (Sayal, 2010a). The strongest predictor for receiving pharmacological treatment was severity of symptoms, as conceptualised by also meeting criteria for ICD-10 Hyperkinetic disorder. The introduction of non-stimulant medication such as atomoxetine since 2004 may have subsequently altered this pattern of findings. In comparison with its prevalence, ADHD in children is still underdiagnosed in the UK. Healthcare Improvement Scotland has conducted two national surveys of ADHD care across Scotland. These surveys identified that in 2011 only 0.6% of school age children in Scotland currently receive treatment for ADHD. There was a five-fold variation in treatment rates across the country, and in most regions there had been little change in treatment rates since the original survey in 2007.

The NICE guidelines (2008) used the distinction between DSM-IV-defined ADHD criteria and ICD-10 Hyperkinetic disorders to distinguish between moderate and severe ADHD. In practice, hyperkinetic disorder can be conceptualised as a severe form of ADHD – it approximates to combined subtype ADHD with severe impairment in function. It is characterised by persistent and pervasive traits of all three core features (hyperactivity, impulsiveness and inattentiveness). In contrast, ADHD has broader criteria as all three features are not required; predominantly overactive/impulsive or inattentive subtypes are sufficient to meet diagnostic criteria. The DSM-IV system also treats pervasiveness differently; impairment rather than symptoms need to be present in more than one setting, such as home and school. In comparison with children with ADHD, children who meet criteria for both ADHD and hyperkinetic disorder have increased risk of neurodevelopmental delay (such as motor or language delays), greater severity of symptoms and impairments in academic and cognitive functioning and better response to medication treatment (Santosh et al., 2004; Tripp et al., 1999).

In terms of clinical assessment, it is useful to have working knowledge of both diagnostic classification systems. The first

question is whether a diagnosis of ADHD can be made. After this, further enquiry should be made about the presence of all three types of symptoms and severity of associated impairment to see whether criteria for hyperkinetic disorder are met. Next, assessment should be made for the presence of any comorbid disorders as this may guide treatment choices. To aid clinicians, NICE guidelines distinguished between moderate and severe impairment. A potential caveat of the hyperkinetic disorder conceptualisation is that severely inattentive children with moderate or mild hyperactivity might be overlooked. These will correspond to a subgroup of children with ADHD who are mainly impaired academically but who are not disruptive in the classroom or at home. The hyperkinetic/combined subtype cut-off and psychological treatments aimed at behavioural change may not be as useful for these children. This is important, as drug treatments for ADHD have beneficial effects on children's on-task behaviour and academic work completion (Prasad et al., 2013). There is a risk that access to pharmacological treatments could be delayed on the grounds of not fulfilling the criteria for hyperkinetic disorder. Professionals need to be aware of the existence of severely inattentive children. Scales and diagnostic tools should be developed to identify this group of children and to better assess ADHD specific impairment.

Adjunctive rating scales may be used to assist with diagnosis. These should not, however, act as a substitute for a detailed clinical assessment because of the high risk of false positives and negatives and the possibility of bias in informant ratings (Sayal and Goodman, 2009). In the UK, two commonly used rating scales are the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997) and the Conners' Rating Scales – Revised (CRS-R) (Conners, 1997). The SDQ provides useful information regarding comorbid conduct and emotional symptoms as well as functional impairment in several domains including friendships, classroom learning, home life, and leisure activities. The short version of CRS-R has four scales relating to hyperactivity, cognitive problems/inattention, oppositional behaviour and a summary ADHD index with associated age- and gender-standardised *t*-scores. Many other rating scales are available, and a summary is given in Collett et al. (2003).

The NICE guidelines recommend that non-pharmacological interventions are tried first for children with moderate ADHD, for example parent training/education interventions or psychological interventions for the child such as cognitive behavioural or social skills approaches. If these are not effective, then medication should be tried. In contrast, for severe ADHD, medication is recommended as the first-line treatment. Where medication is used, it is important that this forms part of a comprehensive treatment approach that includes psychological, behavioural and educational interventions. For a summary of the consensus statement regarding treatment in children and adolescent, see Table 10.

Drug initiation and dosage

For immediate or modified-release preparations of methylphenidate, titration to the optimal dose should take place over a 4–6-week period. The dose can be increased up to the maximum 60 mg per day British National Formulary limit for children and adolescents. European guidelines support higher maximum doses (100 mg for immediate-release formulations and 108 mg for modified release) (Banaschewski et al., 2006). For dexamfetamine, the titration period is similar. The initiation dose recommended is 5–10 mg

Table 10. Consensus statements: treatment of ADHD in children.

1. All children with severe ADHD (conceptualised as hyperkinetic disorder) should be offered pharmacological treatment. In addition, consider pharmacological treatment for children with moderate symptoms of ADHD who have not responded to psychological interventions (A)
2. The treatment of choice for children with severe ADHD or moderate ADHD non-responsive to psychological treatments is psychostimulant medication (A)
3. Atomoxetine can be used instead when there is a risk of misuse of psychostimulants by children or the adults supporting the child (S)
4. Appropriate child and family-based psychological interventions should be available to all children with ADHD. These interventions should be tailored to the child's needs and not depend on the local availability of services (S)
5. Teachers should be given evidence-based information about ADHD (S)
6. Patient and parental preferences should be taken into account when designing a psychological intervention for ADHD (S)
7. Every effort should be made to facilitate the transition from adolescence to adulthood. This should include education of parents, children and professionals involved in the care of these children and the development of appropriate services and shared care protocols to enable this transition (S)
8. Systems and protocols need to be implemented to allow early re-access to services for young people who may have dropped out of treatment at an early age, but still have significant symptoms and impairment (S)

Research recommendations

1. New tools to assess ADHD-specific impairment and to detect inattention should be developed
2. More research is needed on psychological and non pharmacological interventions in children, particularly parent training/education groups, teacher-delivered interventions, individual cognitive behavioural therapy and dietary approaches
3. More research is needed on the specific problems posed by the transition period, usefulness of drug holidays and transitional services

per day up to 20 mg per day, depending on body weight. The maximum dosage for children and young people is 40 mg per day. Lisdexamfetamine can be initiated at 30 mg daily with increases of 20 mg at weekly intervals up to a maximum of 70 mg. For atomoxetine, the recommended titration approaches vary according to body weight. For children and young people whose weight is less than 70 kg, the recommendation is to commence 0.5 mg per kg per day for the first week and then increase according to response to 1.2 mg per kg per day. For those weighing over 70 kg, the recommended dose for the first week is 40 mg per day and then increased after a week to 80 mg per day. Response to treatment should be assessed over the first 12 weeks.

Non-response to treatment

If no response is obtained after a completed trial of pharmacological treatment, both the diagnosis and the possible comorbidity should be reviewed. Other circumstances surrounding treatment, such as adherence to medication schedule, side effects and motivation should be considered. Finally, in some areas it would be possible to refer to tertiary centres where either high doses of psychostimulants or alternative medications (clonidine, bupropion) can be attempted.

Combinations of psychostimulants and guanfacine have shown benefit in children resistant to stimulants alone (Ib) (Childress, 2012). Psychotherapeutic interventions can also be considered.

Duration of treatment

Pharmacological treatment in children and adolescents needs to be assessed and reviewed regularly. As a minimum, children should be assessed by a knowledgeable clinician before transitioning to adult services in order to establish if pharmacological treatment is still required. If possible, this assessment should include validated scales with parent and teachers ratings (S). Few

studies have addressed the impact of drug holidays, but it is accepted that stopping medication when the child is not attending school (such as during school holidays) can minimise the impact of possible adverse effects on appetite, allow catch-up growth, and enable assessment of persistence of symptoms and impairment (evidence level IV).

Psychological treatments in children

In moderate ADHD defined by DSM-IV criteria, NICE guidelines recommend group parent training and/or individual psychological treatments as first line. Family preferences for treatment should be considered when initiating a therapeutic plan for a child diagnosed with ADHD. Psychological treatment approaches can be effective if symptoms are mild and, compared with medication, the risk of adverse effects is relatively low. Commencing with psychological interventions is acceptable as long as progress is reviewed and there is access to pharmacological interventions if there is little improvement (IV).

Individual psychological interventions may include cognitive training or behavioural intervention approaches. Cognitive training interventions aim to improve neuropsychological deficits involving working memory or executive functioning. A recent rigorous meta-analysis of randomised controlled trials (Sonuga-Barke et al., 2013) confirmed the overall effectiveness of cognitive training for ADHD symptoms when ratings were completed by unblinded assessors, but found that positive effects were not demonstrable when more blinded assessments were used such as teacher ratings instead of parent's ratings (evidence level Ia). These studies mainly involved children under 13 years. Behavioural interventions are based either on operant learning principles that aim to improve ADHD symptoms or impairments, or on social learning principles that aim to improve social skills. Many of the studies assessing their effectiveness have used these as a combined intervention together with work with the parents or family. Studies assessing the effectiveness of behavioural and

social skills interventions reviewed for the NICE guidelines also mainly involved children under 13 years of age. There was evidence of their effectiveness for core ADHD symptoms as well as for conduct problem symptoms, social skills and self-efficacy. Given the ages of participants in most psychological intervention studies, these findings may not generalise to adolescents. However, for this age group, individual-level interventions might be more acceptable or effective than parent training/education interventions.

Parent training programmes may appeal to families as a good alternative to medication, particularly in relation to younger children or in the initial stages of treatment. The role of parent training/education programmes was assessed for the NICE guidelines. Most programmes available for parents of children with ADHD were developed for child behaviour problems in general, rather than specifically for ADHD. However, the 'New Forest Parenting Programme' (NFPP) has theoretical underpinnings related to ADHD and has evidence (level Ib) of efficacy for ADHD in preschool children (Sonuga-Barke et al., 2001).

There is also evidence (level Ib) of effectiveness of the 'Incredible Years' parent training programme for children with comorbid ADHD and oppositional/conduct problems (Jones et al., 2007). More recently, an intensive version with both parent and child components was found to have beneficial effects on ADHD symptoms in children with ADHD and combined ADHD and oppositional/conduct problems (Webster-Stratton et al., 2011). Similarly, there is some evidence of effectiveness for the 'Triple-P' programme on behavioural problems in children with ADHD (Sanders et al., 2002). However, local availability of these programmes varies considerably.

School-based interventions could be delivered at the level of the child (e.g. contingency management, self-control, or problem-solving approaches) or the teacher (e.g. changing teaching strategies or classroom environment). As part of the development of the NICE guidelines, a systematic review was carried out of randomised controlled trials that investigated the effectiveness of providing teachers with information or training about ADHD or teacher-led interventions in educational settings. Few rigorously conducted intervention studies were identified. Most studies were set in the USA, where service organisation within health and education is not readily generalisable to the UK. Collectively, these trials suggested limited evidence of effectiveness of teacher training interventions in improving child ADHD behaviours.

A large cluster randomised controlled trial in England investigated the impact of: a) feedback of screening information and b) the provision of an evidence-based educational booklet for teachers. At 2-year follow-up, the provision of the booklet was associated with improvements in child behaviour (Tymms and Merrell, 2006). However, findings from the 5-year follow-up suggested that just screening and providing teachers with the names of children who were high scorers at baseline was associated with worse behavioural outcomes (Sayal et al., 2010b). Collectively, these findings suggest that the development and delivery of interventions with teachers are feasible, but that simply naming children with difficulties without providing additional information for teachers might be unhelpful. RAPID, a cognitive behavioural therapy prosocial competence intervention, delivered in after-school clubs and including teachers as facilitators, has shown promising results in a small pilot (Young, 2013). For children with a clinical diagnosis of ADHD, sharing relevant information with the school may be helpful. There is a need for further

research to establish the effectiveness of school-based interventions for ADHD.

Dietary interventions

Several dietary interventions have been proposed for ADHD including elimination diets (exclusion of items associated with hypersensitivity), fatty acid supplementation (omega 3 and 6) and exclusion of food colouring. A recent meta-analysis (Sonuga-Barke et al., 2013) found small but statistically significant effects for fatty acid supplementation and exclusion of food colouring. The initial strong effect found in elimination diets dropped to non-significant levels when the analysis was restricted to blinded studies. Several caveats appear in dietary studies, first the inevitable pre-selection of the sample towards those parents more inclined to a dietary intervention, second the difficulty of blinding, and third the limitations of establishing comparable control interventions. However, the initial promising results of some of these studies (Pelsser et al., 2011) emphasise the need for further research on diet interventions and ADHD.

Transitional services

Adolescence poses many challenges for young adults with ADHD. The transition to adulthood includes changes in educational environment (school to college or work), in treatment (dosage and type of medication may require adjustment with age), social requirements and medical services available. Although the need for transitional services was recognised by the NICE guidelines in 2008, most health authorities have not established clear protocols for transition from child and adolescent to adult services. Underfunding of adult mental health services and lack of training of general adult psychiatrists in the field of ADHD makes this transition more challenging. Various ADHD clinics in Europe and Canada have approached this problem by establishing lifelong family clinics where children and parents can be effectively treated for long periods of time by the same team.

In terms of transition, although there is considerable cessation of treatment for ADHD between the ages of 15–21 years, (McCarthy et al., 2009) this is likely to reflect lack of availability of services as much as a desire to stop treatment or improvement in symptoms. There is a need for policy and service development and clinician education and training in order to improve the availability of services for young people with ADHD (Young et al., 2011a). This also applies for young people who may have dropped out of treatment during adolescence but remain impaired by symptoms. Young adults disengage from treatment easily if services are not able to liaise effectively. Local health authorities need to establish internal protocols to ensure follow-up and treatment of this group of patients (strength of recommendation S).

Treatment of ADHD in the adult

Prevalence of treatment in the adult

In the UK less than 10% of adults with ADHD requiring medication are thought to receive treatment. Based on primary care prescription records, the use of medication tails off rapidly once adolescents reach the age of 16–18, with a marked discrepancy between the numbers meeting full criteria for the disorder and the

numbers prescribed medication (McCarthy et al., 2009). The most recent UK published data, from 2008, show that primary care prescriptions drop from just under 0.8% of 13–17-year-olds, to under 0.1% in those over 18 years of age (McCarthy et al., 2012). Diagnostic and treatment rates are increasing rapidly, with new clinical services for adults with ADHD being commissioned in many regions of the UK, but are thought to remain far from sufficient to meet clinical need. This is surprising, since meta-analysis of ADHD drug treatments in adults show similar positive effects to those in children (level of evidence Ia) with only slightly smaller effect sizes.

Most efficacy studies for ADHD in adults have investigated various formulations of methylphenidate. Faraone and colleagues pooled data from six randomised controlled trials, finding an average effect size of 0.9 (measured as standardised mean difference), with a larger effect of 1.3 when studies optimised treatment including the use of higher doses (Faraone et al., 2004). A more recent meta-analysis using a larger set of studies found somewhat smaller effects, in the order of 0.42 when all studies are included, and 0.51 when studies that focused on alcohol and drug abuse populations were excluded (Koesters et al., 2009). This arises because overall, the studies of drug and alcohol abuse populations showed no significant effect. Effect sizes were higher for observer ratings than for self-ratings. Similar findings were reported in a further meta-analysis that estimated an average effect size in adult ADHD studies of 0.48, with a significant dose-response relationship indicating the need to titrate to higher doses in a subset of cases (Castells et al., 2011).

There have been fewer studies of dexamfetamine and no published studies in Europe, but the effects appear to be similar to that seen for methylphenidate (Faraone and Glatt, 2010; NICE, 2008). Methylphenidate is nevertheless recommended as the first-line treatment for ADHD in adults, because of the larger number of clinical studies and the availability in the UK of a wider range of short and extended-release formulations.

Lisdexamfetamine, an inactive prodrug for dexamfetamine with limited abuse potential that is licensed for use in adults in the USA and other countries, and in the UK in adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment showed higher effects sizes in one study (Wigal et al., 2010), but overall is likely to have similar average effect size to both short-acting dexamfetamine and methylphenidate (Faraone and Glatt, 2010).

Atomoxetine is the main non-stimulant drug recommended for the treatment of ADHD in adults. Recent unpublished meta-analyses indicate effect sizes in the region of 0.4 and are consistent with the earlier studies (Michelson et al., 2003). The data on clinical efficacy of stimulants and atomoxetine are therefore comparable, with relatively small differences in overall effect identified from the recent meta-analyses of clinical trials.

Although amphetamines, methylphenidate and atomoxetine are all effective in adults with ADHD, they cannot be considered equivalent because they have different mechanisms of actions and hazards.

In contrast to ADHD treatment in children, current UK guidelines recommend that pharmacological interventions are always first line in adults (NICE, 2008). This recommendation is in part based on the lack of evidence for the efficacy of non-drug interventions in the absence of medical treatment. Further research is

therefore required to evaluate the efficacy of non-pharmacological treatments, particularly in those with mild to moderate levels of symptoms and impairments.

Finally, treatment in adults may have to be administered on a daily basis, and drug holidays may not be possible since the pressures and demands of adult life are constant and not limited to the educational environment.

Choice of drug

Stimulant medications are the first-line drugs in adults with ADHD. In the UK, methylphenidate is usually tried first. This is mostly a consequence of the paucity of amphetamine formulations (extended-release formulations are not available) and of the restrictive licence of lisdexamfetamine. Response to medication should be assessed in the follow-up visits; some scales such as the ADHD checklist, the Snap IV and others can be used to obtain objective ratings of symptoms before and after medication. In general, the clinician should increase the dose until optimal management of symptoms is achieved. If the patient cannot tolerate higher doses of stimulants or no effect is seen after a trial of adequate duration, a switch to a non-stimulant drugs is recommended.

Drug titration and dosage

Treatment with psychostimulants requires careful titration due to marked individual differences in final dose. This is a relatively skilled process that requires a good understanding of the symptoms and impairments of ADHD and the expected response to medication. Titration to optimal dose usually takes around 6 weeks. For methylphenidate, a starting dose of 5 mg tds – or equivalent for extended-release preparations – is recommended, with daily or weekly increases depending on tolerance. The maximum recommended dose is 100 mg daily (bioavailability varies between formulations; these dosages correspond to instant-release preparations). However, the experienced clinician may choose to start at a higher dose and titrate more rapidly. The starting dose of dexamfetamine is 5 mg bd, and the maximum dose recommended by the NICE guidelines is 60 mg daily. Some patients may require higher doses to see a clinical effect (evidence level 1b); it is not possible to identify these patients a priori. Atomoxetine is relatively straightforward to prescribe starting on 40 mg (although lower doses can be used to improve tolerability) and increasing the dose weekly by 20mg/day up to 100 mg/daily. It is important to ensure that sufficient time (at least 12 weeks) on the therapeutic dose of atomoxetine has passed before drawing conclusions on the clinical response in individual cases. Atomoxetine is metabolised via the CYP2D6 pathway in the liver. About 7% of the population will have mutations or deletions in the genes codifying this enzymatic group, and as a consequence would be poor metabolisers of atomoxetine (Michelson et al., 2007). In this group of patients the half-life of atomoxetine will be prolonged, increasing the rate of side effects and reducing tolerance. It is difficult to identify these individuals, but a history of previous intolerance to other medications metabolised by this pathway should prompt slower titration of atomoxetine, in case the patient is a poor metaboliser.

Once methylphenidate, atomoxetine and amphetamines have all been given a fair trial, third-line medications can be considered. These include bupropion, modafinil, tricyclic

antidepressants, guanfacine and clonidine. Adults with ADHD often require medication daily. Stopping treatment at weekends and holidays is, in most cases, not possible. Adults may also learn to adjust their medication to the demands of the day, and some degree of 'flexible' dosing is common in clinical practice. There is a paucity of studies about flexible dosing, and more research is needed in this area.

Co-administration of drugs

Co-administration of psychostimulant and other drugs (mainly atomoxetine) is an option for patients showing a limited or lack of clinical response. There is, however, limited evidence supporting either the efficacy or safety of combination therapy (evidence level IV). Concomitant use of long and short-acting methylphenidate is also relatively common in clinical practice. In theory, instant-release formulations in small doses may act as a 'top up' when the extended release is wearing off. This titration allows the clinician to reduce the total quantity of long-acting methylphenidate administered, avoiding unwanted side effects such as insomnia. Combinations of stimulants with alpha 2 agonists (clonidine, guanfacine) have not been studied in adults despite the possible synergic effects and complementary side-effect profile. Alpha 2 agonists decrease blood pressure while both stimulants and atomoxetine can cause hypertension. Psychotherapy should be considered for those patients who are resistant to drug treatment and are well motivated for this approach. In this case, cognitive behavioural therapy is the preferred approach.

Duration of treatment

Drug treatment should be continued as long as clinically effective and reviewed at least annually (Consensus recommendation). Effects of missed doses, planned dose reductions, and periods of no treatment should be evaluated, and are particularly informative for stimulant medications. Drug holidays may be useful to ascertain the need of continuation of treatment (S).

Issues specific to stimulant prescribing in the UK

Methylphenidate and the amphetamines are controlled drugs in the UK. This means that prescriptions require the total quantity prescribed to be written in both letters and figures. In addition, any prescription is recommended to only cover 1 month of treatment (3 months is allowed if justified). This has led to difficulties in the interface between general practitioners and specialists. In many localities, family doctors are not allowed to prescribe off-licence controlled drugs to adults, adding a further layer of complexity to the transfer of care from specialist services to general practice.

Shared care protocols clearly establishing the role of general practitioners, psychiatrists and pharmacists are required to ensure a smooth transition. In the current climate of cost cutting, shared care agreements may be difficult to implement due to the inability of the different parties to agree on the source of funding for medication, despite these being quite low compared with the total service cost. Some localities take the view that medication should be funded by specialist services, while in others funding responsibility is assumed by primary care. For a summary of the components of a basic shared care agreement, see Table 11.

Table 11. Components of a shared care agreement.

Description of the role of specialist care:
Diagnosis
Initiation and stabilisation of treatment
Review of medication when required
Trigger points for primary care referral back to a specialist
Description of the role of primary care:
Continuation of treatment
Monitoring of common side effects
Referral back to secondary care when indicated
Description of the role of pharmacist:
Monitoring and audit of prescriptions
Ensuring the correct product is dispensed without treatment break
Description of situations that require referral to specialist services:
Rare or severe side effects, typically psychotic symptoms, cardiovascular problems or suicidal ideation
Description of characteristics of the stimulant drugs, including side effects and titration

ADHD in pregnancy and lactation

ADHD in pregnancy. There is no evidence to indicate that ADHD either worsens or improves during pregnancy. Young women with ADHD have a higher incidence of risky sexual behaviour (III) (Hosain et al., 2012) and adolescents with ADHD have been reported to be more promiscuous than their age peers (Brown et al., 2010). Amphetamine, lisdexamfetamine, methylphenidate, atomoxetine, bupropion, and modafinil are all category C by FDA classification (Bazire, 2012). This category includes drugs where animal studies have reported some harm without there being any robust evidence in humans. Most published research comes from mothers addicted to illicit drugs (Bolea-Alamañac et al., 2013), which may not be representative of the general population taking stimulant medication for ADHD.

Both continuing and stopping drug treatment carries risk. While discontinuation of drugs removes the risk of medication harming the child, there may be an increase in harmful behaviours related to the mother's mental state. These may include poor risk management, such as dangerous driving or the use of illicit drugs, alcohol or tobacco during the pregnancy; increased stress levels; and self-injurious behaviour.

Updated information about the teratogenic potential of psychotropic drugs can be obtained in the UK by contacting the National Teratology Information Service, and other European countries have similar bodies that provide advice to clinicians on demand.

It is advisable to coordinate prenatal care (S). With the patient's consent, the midwife and/or health visitor should be informed of the patient's condition. A short briefing about how to support a patient with ADHD may be necessary. Simple actions such as insisting that written as well as verbal information is given to the patient about prenatal care, or using text or phone reminders for the obstetrics appointments, are often useful. If there are comorbid conditions that may have an impact in pregnancy such as drug addiction, this should be addressed by referring the patient to the appropriate specialised health care professional as soon as this is feasible. It is also important to explore non-pharmacological treatment strategies such as psychosocial approaches, psychotherapy and counselling.

ADHD treatment and breastfeeding. The postnatal period is a stressful and challenging time for women with ADHD. A great deal of organisation and planning is required to meet the demands of a new child. Many women with ADHD will request to be restarted on medication after delivery. In this case, risks and benefits need to be carefully considered and a decision can only be reached by considering each case individually.

Little is known of the effects of ADHD medications reaching the child through breastfeeding; however, drugs that are licensed for use in children are in general less risky than those that have not been used in this population. A recent systematic review supports the idea that very little methylphenidate reaches the infant during breastfeeding (Bolea-Alamanac et al., 2013) (IV).

Some case reports have suggested that methylphenidate is relatively innocuous particularly if given after the morning feed, but there is very little evidence about its longer-term effects (IV). Caution should be exercised with atomoxetine and amphetamine; modafinil is contraindicated in breastfeeding. Bupropion accumulates in breastmilk and increases the risk of seizures in the newborn.

Ideally, the prescribed medication should be given in a once-a-day formulation and 1–2 hours before the child's longest period of sleep, to avoid a feed occurring during the peak secretion period. Finally, the effects of the drug on the child's development should be monitored and the child's paediatrician should be informed of any changes in medication dosage or formulation.

Psychological treatment of ADHD in the adult

The NICE guidelines recommend prescribing drug treatments for ADHD in the context of appropriate psychosocial treatments. In addition, psychological treatment may provide support during the transition from childhood to adulthood, and at other critical periods across the lifespan. Equally, psychological techniques can be used to improve acceptance of a diagnosis, and treat comorbidities and residual symptoms that do not require pharmacological treatment. Table 12 summarizes the BAP position regarding psychological treatments in adults with ADHD. A full analysis of psychotherapy for ADHD is beyond the scope of the BAP and this paper; however, we briefly summarise key elements below.

NICE guidelines recommend group or individual interventions employing a cognitive behavioural paradigm. Cognitive behavioural therapy strategies to improve core symptoms of ADHD include self-instructional training and memory aids to improve attention, 'stop and think' techniques to reduce impulsivity, diaries and time schedules to improve organisational

skills, and assertiveness and social skills training to improve communication abilities (Young and Amarasinghe, 2010). Traditional cognitive behavioural therapy may need to be adapted to the specific requirements of ADHD patients. Adaptations necessary include reward systems, frequent feedback and strategies to avoid procrastination. Cognitive remediation provides techniques that focus on retraining cognitive function, teaching internal and external compensatory strategies and restructuring the physical environment to maximise functioning. In dialectical behaviour therapy, cognitive behavioural therapy techniques are supplemented with 'acceptance strategies' that encourage the patient to balance acceptance with change.

In recent years, there has been an increase in the amount of published research of psychological therapies for the treatment of ADHD in the adult. However, methodological issues persist (mixed interventions, limitations of blinding, lack of a comparatively similar control intervention) which make these results only preliminary and subject to selection and reporting bias. Efficacy of psychotherapy in a trial performed by motivated and well-trained professionals at an expert centre does not guarantee that similar effect sizes are obtained when cascading the intervention to 'real-life' situations, where patients may not engage or not receive the same level of support (Nutt and Sharpe, 2008).

Despite these pitfalls, some commonalities emerge. Most studies follow a cognitive behavioural therapy paradigm, are highly structured and follow a skill-based programme including the practice of the techniques learnt in daily life. When effect sizes are reported these are generally large, even considering that methods of assessment vary between studies.

There has been an effort to continue studies for extended periods of time and assess maintenance of gains months after the intervention. This has reinforced the importance of psychological therapies as adjuvants to pharmacological treatments.

ADHD and comorbidity

Comorbidity in children with ADHD

Recent research based on parents' reports of ADHD children shows that 46% of children with ADHD had a learning disability versus 5% of those without ADHD, 27% with ADHD versus 2% non-ADHD had a conduct disorder, 18% with ADHD versus 2% non-ADHD had anxiety disorders and 14% with ADHD versus 1% non-ADHD had depression (Larson et al., 2011). Dyslexia was reported in 18–45% of children with ADHD (Germano et al., 2010) and up to 50% of children with ADHD will show motor impairment consistent with developmental coordination disorder (Fliers et al., 2011). Social circumstances were an important factor in comorbidity risk; children from poorer backgrounds had 3.8 times more risk of developing three or more comorbidities than affluent children (30% vs. 8%) (Larson et al., 2011).

From a developmental point of view, a hierarchy concerning the order of appearance of comorbidity can be established. Some conditions may be present before the appearance of the first ADHD symptoms ('pre-comorbidity'), such as sleep disturbance, autism spectrum disorders and atopic eczema. Other conditions may coincide with the development of clinically significant ADHD symptoms ('simultaneous comorbidity'): enuresis, encopresis, and developmental dyslexia. However, the majority of comorbidity occurs after the appearance of the full syndrome

Table 12. Consensus points.

- | | |
|----|---|
| 1. | Psychological treatments are a complement to pharmacological treatment (A) |
| 2. | Different approaches have been used but the majority the evidence is for structured treatments employing a cognitive behavioural paradigm (A) |
| 3. | The use of different methods of delivery (group and individual therapy), different criteria for control groups and different outcome measures limit the generalisation of results (S) |

(‘post-comorbidity’): tic disorders, depression, anxiety disorders, obsessive compulsive disorder, bipolar disorder, conduct and substance use disorders, obesity and personality disorders (Taurines et al., 2010). Most children with ADHD had at least one comorbid disorder (33%), 16% had two and 18% had three or more. Functioning declines with increasing numbers of comorbidities, and use of health and educational services and need for care coordination increases accordingly (Larson et al., 2011).

Transition of children with comorbidities

Transition of young adults from paediatric-orientated services to adult psychiatry currently remains challenging (Young, 2011). Of the many factors that account for this, the first is which specialist is responsible for requesting the transfer. Neurologists and paediatricians are more aware of epilepsy and allergic conditions while child psychiatrists are more sensitive to early symptoms of bipolarity, depression and personality disorders. Second, many services do not have any specific transition arrangements, leaving the young adult without a clear referral route. Third, many young adults will undergo changes in their lives in the transition period (e.g. distancing from parents, increased use of drugs or alcohol, etc), leading to disengagement with services. Fourth, in general adult psychiatry services are overstretched, leading to longer waiting times, and more time between appointments compared with child and adolescent services.

ADHD children with comorbidities should be transitioned to adult services with exceptional care, as comorbidity implies higher severity of symptoms. Clear pathways should be established to guide the young adult and their families into the new professional or group of professionals that are going to lead their care as an adult (S).

Comorbidity in the adult

Introduction. Comorbidity is frequent in adults with ADHD (I). A diagnosis of ADHD should always include assessment of comorbidity (S). Epidemiological data from the USA indicated five-fold increase in any mood disorder, four-fold in any anxiety disorder and seven-fold increase in drug or alcohol dependence (Kessler et al., 2006). The strength of the specific association with bipolar disorder is debated (Skirrow et al., 2012), but there is no doubt that mood dysregulation is a key component of ADHD (Barkley and Fischer, 2010; Rosler et al., 2010; Skirrow et al., 2009; Surman et al., 2011). The association of ADHD with neurodevelopmental disorders and traits (e.g. autism spectrum disorders, dyslexia, learning difficulties) is also seen in adults due to the lifelong nature of these impairments.

Significantly higher rates of personality disorders have been identified in clinical samples, especially antisocial (II) (Gudjonsson et al., 2013; Huntley and Young, 2014). Up to one-third of personality disordered offenders screen positive for ADHD. Up to 45% of young people with ADHD receive criminal convictions (Rosler et al., 2004; Young et al., 2011b). The association between ADHD and crime has received considerable attention in recent years; one-quarter of adult male prisoners are estimated to have ADHD, they are younger at first offence, receive multiple convictions, and their ADHD symptoms are strongly associated with institutional aggression (Young et al., 2011b). Analysis of data from the Swedish National Register

Table 13. Consensus recommendations.

- | | |
|----|---|
| 1. | Co-morbidity is common in both childhood and adulthood, and may determine outcomes (D). |
| 2. | Clinical assessment of ADHD needs to include careful evaluation for other disorders (S) |
| 3. | Expression of ADHD and co-morbidities is highly heterogeneous, thus management needs to be individualised (C) |

(reporting 37% males and 15.4% of females with ADHD were convicted of crime) found that the use of ADHD medication reduced the risk of criminality by 32% in men and 41% in women (Lichtenstein et al., 2012). Table 13 summarizes the consensus statements regarding comorbidity in ADHD.

Comorbidity with substance use disorder. ADHD is more prevalent in populations of substance misusers (I) (Arias et al., 2008; Wilens et al., 2011). About one-half of adolescents with substance misuse and one-quarter of adults will have ADHD (Wilens et al., 2011). A large epidemiological study has also found a six-fold increase in substance misuse by adolescent boys and girls reporting ADHD symptoms compared with their non-ADHD peers. In addition, poly-substance use was linearly and incrementally related to ADHD symptoms with a large effect size (Gudjonsson et al., 2012). A significantly greater history of drug dependence has also been reported by offenders with ADHD symptoms compared with non-ADHD offenders (Young and Thome, 2011). These latter studies were not clinical samples, suggesting that young people and adults who have undiagnosed ADHD may be attempting to self-medicate in the community. A study of clinically referred adults also reported significantly higher rates of substance misuse in ADHD, and indicated that these individuals placed higher demand on services. Importantly, significantly higher rates of substance use were found in those whose ADHD symptoms persisted over time; individuals in partial remission showed similar substance use to those with a full diagnosis. In contrast, those whose symptoms more fully remitted showed substance use rates similar to normal controls (Huntley and Young, 2014).

Treatment of ADHD in substance use disorder. Particular difficulties are faced on providing effective treatments for patients with ADHD and substance use disorder. Major stumbling blocks are poor engagement with clinical services and poor compliance. There is also a heightened potential for misuse of prescribed medications. Treatment of ADHD in childhood is likely to either be neutral, or reduce later substance use disorders (I). However, use of stimulants at high doses might lead to tolerance or sensitisation (II).

Currently available evidence (level Ib) from randomised clinical trials points towards a low efficacy of methylphenidate in the treatment of ADHD in substance abuse populations (Koesters et al., 2009). In contrast, atomoxetine is recommended as a first-choice treatment in adults with substance abuse disorders and ADHD because of the lack of abuse potential (S); however, evidence of efficacy is limited. One 3-month study of ADHD adults with comorbid alcohol abuse found significant effects on ADHD symptoms but inconsistent effects on drinking behaviour (Wilens et al., 2008). Another study of atomoxetine in 70 adolescents

with ADHD and substance abuse problems found improvements that were not statistically significant compared with placebo (Thurstone et al., 2010). Further studies are therefore required to provide an understanding on when and how to treat ADHD in patients with substance abuse problems.

Patients who use recreational drugs need to be advised of possible interactions with their medication, particularly concurrent stimulant-type drugs. Use of prescription psychostimulants and illegal amphetamines may increase the risk of cardiovascular events including cardiac infarction, angina and arrhythmias. Stimulants, especially short-acting preparations, are best avoided in this population (evidence level D). However, this recommendation is mainly based on the legal issues concerning prescription of drugs with abuse potential, and more research is needed to clarify first if substance abuse patients with ADHD will indeed abuse their prescription drugs, and second if treatments maintain their effectiveness in the presence of active substance abuse.

Current recommendations for the treatment of ADHD in the presence of active drug and alcohol abuse therefore meet criterion D. Based on expert opinion (S) these are as follows:

1. Refer and liaise with community drug and alcohol services for abstinence or substitution therapy.
2. Consider stabilisation of ADHD with atomoxetine as the first-line drug treatment.
3. If poor clinical response to atomoxetine, consider treatment with extended-release methylphenidate or lisdexamfetamine. If risk of stimulant abuse is high, consider bupropion.
4. Combine medication with psychoeducation, relapse prevention and cognitive behavioural therapy.
5. More research is needed into the treatment of ADHD and substance use disorder. Prevalence studies suggest that ADHD is common in this population, but lack of evidence is preventing the development of evidence-based protocols for the treatment of this group of patients.

ADHD and learning disabilities. ADHD is highly prevalent in adults and children with learning disability, with some studies (Mayes et al., 2000) finding that up to 30% of adults with learning disability fulfil criteria for ADHD. Adults with both diagnoses have increased severity of symptoms and higher risk of developing other comorbidities (Seager and O'Brien, 2003). Drug use and alcohol use during pregnancy, maternal infection, encephalitis and some genetic disorders (William's Syndrome, Turner's syndrome, Fragile X Syndrome and phenylketonuria) have been associated with ADHD in patients with learning disabilities (Dichter et al., 2012; Green et al., 2012). ADHD in the learning disabilities population is associated with increased incidence of challenging behaviour, stereotypies, self-harm, anxiety, oppositional defiant disorder, tic disorders and sleep problems (Simonoff et al., 2013).

Treatment of comorbid learning disability and ADHD. It is important to establish all possible aetiological factors before starting treatment; addressing these factors can improve symptoms of ADHD in this group of patients.

Methylphenidate, amphetamine and risperidone have shown efficacy (Ib) for the treatment of ADHD in children

Table 14. Table of evidence for pharmacological treatments in ADHD comorbid with learning disabilities.

-
- Stimulants (Ib)
 - Atypical antipsychotics¹
Risperidone (Ib)
Aripiprazole, olanzapine, quetiapine (III)
 - Atomoxetine (III)
 - Alpha-2 agonists
Clonidine (III)
 - SNRIs: clomipramine (IV), venlafaxine (IV)
 - Anticonvulsants: topiramate (IV), valproate (IV)
 - Others: donepezil (IV), galantamine (IV), carbamazepine (IV).
-

¹Use in this indication is not claimed by the manufacturer in its product labelling

with a learning disability (Table 14) (Aman et al., 2003, 2004). It is likely that this effect persists in adults, although specific studies are lacking. There is little evidence of worsening of tics or obsessive behaviours with stimulant treatment in this group of patients; however, some studies point to a decrease tolerance of stimulants in patients with comorbid learning disability (Simonoff et al., 2013). Atomoxetine has yielded good results in open-label studies, but the evidence is only level III (Mazzone et al., 2011), as it is the case with aripiprazole, olanzapine, quetiapine and clonidine. Serotonin–norepinephrine reuptake inhibitors, anticonvulsants and cognitive enhancers have little evidence supporting their use (IV). Side effects need to be monitored carefully, as patients with learning disabilities report higher rates of these. Cardiovascular risk in some types of learning disability is increased due to congenital malformations, and this risk needs to be assessed prior to treatment with stimulants (Young et al., 2012).

Psychological and alternative therapies should be considered as adjunct to pharmacological treatment, although the evidence is limited (level III). Approaches include family education, creative therapies, family therapy, sensory integration and Positive Behavioural Support.

Summary

In patients with learning disabilities it is important to assess all possible aetiological factors prior to treatment as these may exacerbate ADHD symptoms. Stimulants and risperidone are the drugs with more evidence in this group of patients. Atomoxetine is used as second-line drug, although there is less evidence for it. Psychological therapies can be added to pharmacological treatments but more research is required to clarify their role in the treatment of comorbid learning disability with ADHD.

Special comorbidities in children and adults

Autism. Studies conducted in children and young adults have established high prevalences of ADHD in patients with autistic spectrum disorders (Jahromi et al., 2009). Estimates of comorbidity of autism spectrum disorders with ADHD in the adult are limited; one multicentre study in adults reported that 43% of adult patients diagnosed with autism had ADHD symptoms

(Hofvander et al., 2009).

DSM-IV (and indeed ICD-10) prohibits a diagnosis of ADHD in the presence of autism; this has greatly impaired research in this area. DSM-V has acknowledged the possibility of comorbid ADHD in autism, opening the door to further developments in the study of both illnesses.

Regarding treatment, in children a small positive effect of methylphenidate (Jahromi et al., 2009; Posey et al., 2007) has been described (Ib). Second-line treatments include atomoxetine and risperidone, with carbamazepine and clonidine as third line (Iib). No increase in obsessive behaviours was found with methylphenidate or atomoxetine in comorbid children, but more side effects with stimulants have been described in comparison with only ADHD, the most common adverse effect being increased irritability (Stigler et al., 2004). Risperidone has been widely used in children with comorbid conduct disorder; its prescription in ADHD is considered 'off label'.

There are anecdotal reports of improvement in ADHD symptoms in autistic children with low doses of venlafaxine (Carminati et al., 2006), buspirone, tricyclics and lamotrigine (Aman and Langworthy, 2000) (IV). To our knowledge, there are no randomised placebo-controlled trials of stimulant medication in adults with comorbid autism and ADHD.

Tic disorders and ADHD. The prevalence of chronic tic disorders in children with ADHD is close to 20%, while about 50% of patients with chronic tic disorders will fulfil criteria for ADHD (Banaschewski et al., 2007). Despite existing literature indicating otherwise, recent research supports the idea that tics do not worsen with methylphenidate treatment in children with ADHD and chronic tic disorders (Dopfner and Rothenberger, 2007; Poncin et al., 2007).

Most of the information available on comorbid chronic tic disorders and ADHD comes from studies in children. Long-acting formulations of methylphenidate can be used as first-line medication in this group of patients (III). Clonidine and guanfacine have been used as monotherapy or in conjunction with stimulants with good results in comorbid Tourette's (IV). Atomoxetine (Poncin et al., 2007), can be useful in non-responders to methylphenidate (IV). Atomoxetine neither improves nor worsens tics.

Behavioural therapies can be a useful adjunct to pharmacological treatment in these children. Anger management interventions have been useful (Poncin et al., 2007), and habit reversal training can help to control tics when these are the main cause of impairment (IV). Data about the effectiveness of these interventions in adults are limited.

Foetal alcohol syndrome and ADHD. Up to 60% of children with foetal alcohol syndrome will also fulfil criteria for ADHD. The validity of an ADHD diagnosis in the presence of foetal alcohol syndrome has been questioned (Coles, 2001; Ostrander et al., 2008). Some authors argue that the pattern of attentional deficits is markedly different, and that many of the symptoms frequently labelled as ADHD are in fact secondary to alcohol-specific neural damage.

Studies in children report that half of these patients respond to methylphenidate (O'Malley and Nanson, 2002) (IIa). In animal models a higher response rate to dexamfetamine has been described, but there are no data available in humans (Randall and Hannigan, 1999). Literature on other treatments (atomoxetine, fluoxetine, guanfacine, clonidine) is limited (IV). Data in the

adult are scarce and do not provide enough evidence to produce recommendations.

Children with foetal alcohol syndrome have a higher rate of congenital heart malformations, therefore stimulants should be used with caution.

Summary of special comorbidity in children and adults

ADHD is highly prevalent in children with autism, chronic tic disorders and foetal alcohol syndrome, despite methodological controversies in the diagnosis of these conditions.

Medication remains the first-line treatment for children with comorbid ADHD, autism and chronic tic disorders (I). Data about treatment of these comorbidities in the adult are very limited, and no recommendations can be extrapolated.

Service provision

Impact of previous guidelines and services in the UK

The NICE guidelines published in 2008 promoted the development of psychiatric services in England for children and adults with ADHD. Most health authorities considered these guidelines a formal sanctioning of the validity of ADHD as a diagnostic entity. Many healthcare providers have developed shared care protocols for stimulant treatment, created specialised services for adults with ADHD, or integrated ADHD care in their portfolio of community psychiatric care.

Specialist vs. generalist services in the treatment of ADHD in adulthood

Referral pathways for ADHD in the UK vary greatly. In some areas a general practitioner can refer after the patient has expressed symptoms suggestive of inattention. In other areas the patient needs to be screened first by a general psychiatrist for other conditions. It is essential that referral pathways are homogenised across the country in order to provide equal care to all patients with a suspicion of ADHD. In addition, patients with ADHD reaching adulthood should be transitioned smoothly and efficiently to adult care, but at present this usually requires primary care involvement.

The diagnosis of ADHD is a clinical one. Professionals need to be trained in the assessment, diagnosis and treatment of ADHD using a combination of diagnostic tools and clinical experience.

In the UK, there are three main types of ADHD clinics: research-based, specialist and integrated care clinics. Research clinics were the first to be established. These services started as recruiting facilities for specific studies on ADHD and then developed into care centres. Although some research-orientated clinics still exist, in general the high prevalence of ADHD has led to the development of more complex services following the specialised or the integrated care model.

Specialist services. In many areas it is not possible to integrate ADHD care into community psychiatry services. Local psychiatrists often do not have adequate training, may lack experience managing stimulants, or ADHD may not be included in the

budget for the range of services agreed with the local primary care provider. This leads to the separation of ADHD services from community psychiatric care. However, this approach has several advantages; first it provides a single point of reference (usually one medical professional or one dedicated team) for patients with ADHD, second it permits the development of local expertise by concentrating all the patients in one service, third it facilitates training for psychiatric trainees who can include the service in their rotations, and fourth it allows a flexibility of care that may not be possible in community psychiatric services.

The ideal specialised adult ADHD clinic would include at least a consultant psychiatrist and a specialised mental health nurse. It would work in close liaison with social services, transition teams, psychology departments and general practitioners.

Integrated services. In some localities ADHD has been included in the range of services provided by community psychiatric teams. This approach requires good liaison with general practitioners and the establishment of detailed shared care protocols between general practitioners, psychiatrists and pharmacists. The advantages of this model include first the normalisation of ADHD as a mental health condition, second the accessibility of general psychiatric resources (social support, psychotherapy) to ADHD patients on the same grounds as any other patients with mental illness, third its relative inexpensiveness as no new infrastructure is needed, and fourth, the fact that comorbidities can be treated inside the team without further referral.

Both models have disadvantages. A highly specialised model can be expensive, as resources are only dedicated to treat one pathology. ADHD-only specialised care may encounter difficulties when treating patients with comorbid illness. The referral process to a dedicated unit may be complicated and difficult to navigate for patients. What is more, it is not uncommon for referral pathways to change according to resource availability instead of following clinical need.

An integrated model requires good communication between primary and tertiary care, which can sometimes be challenging. Shared care agreements may be difficult to negotiate. General services may be overwhelmed by extensive caseloads and may enforce entry criteria relating to 'psychosis or suicidality only', which precludes ADHD patients being seen. Patients with ADHD may not engage in a rigid environment where there is no flexibility about appointments, and where they are seen and followed by a team of professionals and not only by one specialised psychiatrist.

Finally, it is important to consider costs when developing any type of new service. Clinics for ADHD will reflect the reality of the economic situation of the area where they are being developed, and the model of service chosen needs to adjust to these realities. Regardless of model preference, it is important to audit ADHD services to ensure quality and accessibility of care for patients.

Summary of guidelines

The present guidelines summarise current literature, generating expert consensus recommendations for the treatment of ADHD in children and adults. Since the publication of the previous BAP guidelines, new neuroimaging studies have highlighted the role of brain connectivity in the pathophysiology of ADHD. Research into the neuropsychology of hyperactivity has produced new physiological hypotheses. Genome-wide association studies are

under way to detect genetic variants. As was the case in 2007, ADHD is still considered a neurodevelopmental disease, with the hypothesis of a delay in brain maturation gaining support in the scientific community. New drugs have been licensed and novel compounds are being investigated. The publication of randomised controlled trials having one or more treatment arms that involve psychological interventions (cognitive behavioural therapy, *dialectical behaviour therapy* and computerised therapy) has increased the evidence for their use in ADHD. The importance of comorbid conditions in ADHD and how these impact treatment has been widely recognised in recent years.

Updates on the treatment of ADHD comorbid with learning disabilities, autism, tic disorders and foetal alcohol syndrome are included in these guidelines. A summary of evidence-based treatment of ADHD in pregnancy and lactation has been added. As more services have been developed for the treatment of ADHD in adults, various models of care have appeared, with distinct advantages and disadvantages.

ADHD is a common condition with a high societal burden which may be reduced as we gain a better understanding of the disorder through well-targeted research programmes. Research is needed into its aetiology (e.g. the role of gene-environment interactions, nutrition, and the importance of genetic variants), its pathophysiology (e.g. validity of the dopamine hypothesis and connectivity) and its treatment (e.g. use of stimulants in substance use disorder and autism, novel compounds and new psychological treatments).

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Conflict of interest

Blanca Bolea has received speaker fees and travelling expenses on one occasion from Janssen Pharmaceuticals and from the UK Adult ADHD Network (UKAAN) for talks at scientific and educational meetings.

David Nutt has received honoraria from Janssen and Lilly and consulting fees from Shire.

Marios Adamou does not have any conflict of interest to declare.

Phillip Asherson on behalf of Kings College London, received funds for consultancy from Shire, Janssen-Cilag, Eli-Lilly and Novartis and has been a speaker at events sponsored by these companies. He received educational and/or research grants from Janssen-Cilag, Shire, Vifor and QbTech. He was a member of the NICE Guideline Development Group for ADHD.

Stephen Bazire has been a paid member of advisory boards for Roche, Sunovion and AstraZeneca and has received speaker honoraria for non-promotional talks for Lundbeck, Janssen, Pfizer, Servier, Otsuka and Shire.

David Coghill has received research grants from Vifor Pharma and Shire, consultancy fees from Shire and Lundbeck, and speaker fees from Flynn, Janssen-Cilag, Lilly, Medice, Novartis, Shire and Vifor Pharma.

David Heal is director of RenaSci Ltd, he has received consultancy fees from Shire Pharmaceuticals and Eli Lilly.

Ulrich Muller has been invited to advisory boards and received educational funding from Janssen Cilag and Eli-Lilly, UK; he has received travel expenses and honoraria from the British Association for Psychopharmacology (BAP), Janssen Cilag, Eli-Lilly, Shire, UCB Pharma and the UK Adult ADHD Network (UKAAN) for talks at scientific and educational meetings.

John Nash has no conflicts of interest to declare. Paramalah Santosh does not have any conflicts of interest to declare.

Kapil Sayal was a member of the NICE Guideline Development Group for ADHD.

Edmund Sonuga-Barke has received speaker, consultancy fees, travel funds and research support from Shire pharmaceuticals, he has also been a member of this company's advisory board. He has received speaker fees from Janssen Cilag. He has received grants from MRC, ESRC, Wellcome Trust, Solent NHS Trust, European Union, Child Health Research Foundation New Zealand, NIHR, Nuffield Foundation, Fonds Wetenschappelijk Onderzoek - Vlaanderen (FWO).

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