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A guide to ADHD in children and adolescents

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A guide to ADHD in children and adolescents

Attention-deficit hyperactivity disorder (ADHD) is a common childhood disorder that can persist into adulthood, and often has other comorbidities. Treatment recommendations aim to address the suboptimal response to treatment seen in clinical practice, to ensure that children with ADHD receive optimal care.

Attention-deficit hyperactivity disorder (ADHD) is a common, heterogeneous neurodevelopmental disorder, characterised by developmentally inappropriate levels of hyperactivity, impulsivity or attention deficit. Impulsivity refers to premature acting without thinking, hyperactivity signifies a restless and shifting excess of movement, and inattention is a disorganized style preventing sustained effort to complete tasks (Kendall et al, 2008). The core symptoms of ADHD and coexisting conditions are associated with a range of impairments in social, academic and family functioning and have the potential to alter the developmental trajectory of the affected child (Mirza and Buckstein, 2010). Low self-esteem, accidents and injuries, academic underachievement, difficulties in relationship with parents and siblings, difficulties in peer relationships, conduct disorder, antisocial behaviour and substance misuse are just a few of the many complications or associated features of children and young people with ADHD (Klassen et al, 2004).

Symptoms of ADHD persist into adulthood in about two thirds of children with ADHD, and adolescents and adults with ADHD are at higher risk of developing other psychiatric disorders, substance misuse and antisocial behaviour (Taylor, 1986). ADHD is also associated with a range of physical health problems, such as asthma (Fasmer et al, 2011), and there is emerging evidence of a significant association between ADHD and obesity (Cortese et al, 2016a). Perhaps the most striking and serious repercussion of ADHD is a marked increase in mortality. A national cohort study from Denmark has shown that rates of mortality are over twice as high in those with ADHD *vs* those without (Dalsgaard et al, 2015). The excess mortality in ADHD was mainly driven by deaths from unnatural causes, especially accidents. In view of the increased risk of morbidity and mortality, ADHD is currently seen as a major public health problem.

Because of the broad impact of ADHD across different domains of the individual's life, the disorder is likely to have significant economic implications for society through direct (assessment and treatment costs) and indirect costs (increased social care costs, increased cost to the criminal justice system and costs associated with work loss among parents of children suffering from ADHD) (Sayal et al, 2003; Swensen et al, 2003). Providing optimal treatment will improve the quality of life of children with ADHD and their families, and at the same time will reduce the financial implications and psychological burden of ADHD to society.

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Prevalence and aetiology

The clustering of hyperactivity, impulsivity and inattention appears to be stable across different countries and continents (Taylor et al, 1991; Ho et al, 1996). However, the prevalence of ADHD across the world varies significantly, depending on the diagnostic practices and whether the impairment criteria are applied rigorously or not. Prevalence figures range from 6.8–15.8% for ADHD as per the criteria described by the *Diagnostic and Statistical Manual of Mental Disorders IV* classification (American Psychiatric Association; 1994; Faraone et al, 2003) while the British Child and Mental Health Survey reported a prevalence of 3.6% in male children and less than 1% in females (Ford et al, 2003). Polanczyk and colleagues (2007) undertook a systematic review of prevalence studies across the world and suggested a summary of rates of ADHD around 5.3%.

ADHD is more common in boys than girls, with a ratio of 4:1. However, in adults the gender ratio is almost equal and women with ADHD are as impaired as men (Cortese et al, 2016b). It is distributed across all social classes. ADHD is an aetiologically complex and highly heritable condition for which there is evidence of both genetic and environmental influences. The complex interplay between genes and environment is not well understood and current evidence indicates that ADHD is not caused by a single genetic change, but is likely caused by a number of genetic changes interacting with a child's environment (*Table 1*).

Symptoms and signs

Symptoms of ADHD appear to be on a continuum in the general population. The distinction between ADHD and normal variation in the general population requires the association of a characteristic cluster of symptoms and significant levels of impairment. In this regard, ADHD is similar to other common medical and psychiatric conditions that represent the extreme of dimensional traits, such as hypertension, obesity, anxiety and depression; the distinction from normality being made by the presence of high levels of ADHD symptoms when they are accompanied by significant impairments, which are enduring across different settings. The clinical diagnosis of ADHD is based on developmentally inappropriate behaviour within two symptom domains: inattention and impulsivity or hyperactivity (American Psychiatric Association, 2015) (*Table 2*).

The presence of a certain number of symptoms as the cut-off for diagnosis was established on the basis that there was an associated level of clinical impairment and thus need for treatment. On the Clinical Global Assessment Scale, describing global psychosocial function, level 60 represents such a cut-off point.

Variations of symptoms across age

The symptoms of ADHD start early in life, usually before the age of 12 years, and persist through adolescence in to adulthood. There are developmental variations in the symptoms of ADHD across different ages, as the individual matures and as the environmental requirements for sustained self-control increase (Taylor and Sonuga-Barke, 2008). Hyperactivity in a pre-school child may involve incessant and demanding extremes of activity; during the school years an affected child may make excess movements during situations where calm is expected rather than on every occasion; during adolescence hyperactivity may present as excessive fidgetiness, or inner sense of restlessness rather than whole body movement. Attention deficit in adolescents and adults manifests as disorganization in personal life and difficulties in planning, time management and managing academic, vocational and household duties; impulsivity may present as engaging in reckless driving, antisocial acts, emotional dysregulation or abrupt ending of relationships.

Coexisting conditions

ADHD is associated with a range of psychiatric and developmental disorders. Comorbidity is the rule rather than the exception, with 87% of children with ADHD having at least one coexisting condition. The most common coexisting conditions include oppositional defiant/conduct disorder, specific learning disorders (such as dyslexia), anxiety disorder and developmental coordination disorder. Less frequent comorbid conditions include tic disorder, depressive disorder, autism spectrum disorder and general learning disability.

Table 1. Attention-deficit hyperactivity disorder (ADHD): causes and associations

Genetic factors	Twin, family and adoption studies suggest a significant genetic basis for ADHD	
	Mean heritability has been estimated at 0.77 (60–90%)	
	Molecular genetics	Two candidate dopamine genes have been investigated and reported to be associated with ADHD: the dopamine transporter (DAT1) gene and the dopamine receptor 4 gene (DRD4)
		Genetic variants consistently associated with small increases in the risk for ADHD have been identified within and close to the dopamine receptor 5 gene (DRD5)
	Whole genome association studies	Novel genes such as CDH13 (a cadherin gene) have been identified as potential risk factors
	Inherited or de novo chromosomal deletions and/or local duplications	Children with ADHD have a significantly higher rate of missing or duplicated DNA segments (copy number variants) compared to control children
Acquired biological factors	Intrauterine exposure to alcohol or nicotine	
	Extreme prematurity, fetal hypoxia, low birth weight	
	Brain disorders (e.g. encephalitis, brain trauma)	
	Exposure to toxins such as lead	
	Food allergies (in some selected cases)	
Other environmental factors associated with ADHD	Prenatal maternal stress	
	Early deprivation	
	Maltreatment, sexual abuse	
	Severe marital discord	
	Low social class	
	Large family size	
	Maternal mental disorder	
	Foster care placement	

From Li et al (2006), Martin et al (2015)

Diagnosis, referral pathways and role of primary care

In the UK diagnosis of ADHD is made in specialist services by child psychiatrists or paediatricians. There is no single definitive psychological or biological test for ADHD. A comprehensive assessment of ADHD involves diligent integration of detailed information from parents, children, schools and other sources, and clinical assessment and observation in various settings. Thus diagnosis of ADHD is a painstaking clinical process and the standardized rating scales and psychological tests are only meant to support the clinical diagnostic process, not to replace them. However, standardized questionnaires such as SDQ (strengths and difficulties questionnaire), SNAP-IV (Swanson, Nolan and

Table 2. Core features of attention-deficit hyperactivity disorder (ADHD) (Diagnostic and Statistical Manual of Mental Disorders V)*

Inattention – six or more symptoms should be present for at least 6 months

- Often fails to give close attention to details or makes careless mistakes in schoolwork, or other activities
- Often has difficulty sustaining attention in tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions; fails to finish schoolwork and other chores
- Often has difficulty organizing tasks and activities
- Often avoids, dislikes or is reluctant to do tasks requiring sustained mental effort
- Often loses things necessary for tasks or activities, e.g. losing pens, books, school uniforms
- Is often easily distracted by extraneous stimuli
- Is often forgetful in daily activities

Hyperactivity-impulsivity – six or more symptoms persisting for at least 6 months

Hyperactivity

- Often fidgets with hands or feet or squirms in seat
- Often leaves seat in classroom or in other situations where remaining seated is expected
- Often runs or climbs excessively where inappropriate (feelings of restlessness in young people)
- Often has difficulty playing or engaging in leisure activities quietly
- Is often 'on the go' or often acts as if 'driven by a motor'
- Often talks excessively

Impulsivity

- Often blurts out answers before questions have been completed
- Often has difficulty awaiting turn
- Often interrupts or intrudes on others (e.g. butts into conversations or games)

** Symptoms should be present before the age of 12 years, should be pervasive across two or more settings and cause significant impairment in social, school or vocational functioning (American Psychiatric Association, 2015).*

Pelham) and Conners questionnaires are useful as screening tools and can help in monitoring response to treatment.

Role of GPs in assessment and management

GPs play a key role in the early identification and referral of children suspected to have ADHD and support secondary care in the ongoing management of children with ADHD under shared care protocols. When a child or young person presents to primary care with behavioural and/or attention problems suggestive of ADHD, GPs should determine the severity of the problems, how these affect the child or young person and the family and the extent to which they pervade different domains and settings. It is worth emphasizing that direct observation of a child for a short time in a primary care setting may not demonstrate any of the core features of ADHD and is not necessarily a helpful diagnostic approach.

Treatment of ADHD: basic principles

Treatment of ADHD is more about care than cure. The key treatment objectives are:

- Educate the patient, family and others in the environment about the disorder and its impact
- Reduce core symptoms of ADHD
- Reduce coexisting conditions and difficulties
- Reduce risk of further complications
- Adapt the environment to the patient's needs
- Change maladaptive views and prejudices
- Empower the child and the family by celebrating their strengths and resources and help them to enhance their coping skills.

Every child with ADHD is unique in his/her symptom manifestations and psychosocial contexts. An individually tailored ADHD treatment must take into account not only the variability of the core symptom presentation but also the coexisting disorders such as conduct or learning disorder and impaired social and academic functioning.

Treatment of ADHD does not and should not be confined to medication alone, as most children and young people with ADHD have coexisting problems that require a whole range of psychological and social interventions. About 20% of children with ADHD have parents who may also have a diagnosis of ADHD, and parental ADHD can significantly impact on treatment. ADHD should be recognized as a chronic condition that needs to be treated and monitored over time.

National Institute for Health and Care Excellence guidelines for treatment

National Institute for Health and Care Excellence (NICE) (2008) guidelines have extensively reviewed the evidence for both pharmacological and psychological treatments for children and adolescents (*Table 3*). Since the NICE review of psychosocial treatments in ADHD, Young and Amarasinghe (2010) have published a review of non-pharmacological treatments and carefully presented the evidence for different non-pharmacological treatment methods across ages. There appears to be quite good quality evidence for psychological interventions such as parent training and social skills training classroom-based behaviour interventions in younger children. However, the evidence base for adolescents appears limited and Young and Amarasinghe (2010) noted that none of the studies that have shown effectiveness involved significant numbers of young people (>13 years of age).

Although intuitively one would expect parent training, classroom interventions and academic interventions to be beneficial for the treatment of ADHD, current research does not allow a conclusive decision to be made with regards to the efficacy of these interventions. In fact, a meta-analysis and systematic review showed that psychosocial treatments are unlikely to have significant impact on core symptoms of ADHD (Sonuga-Barke et al, 2013). However, ADHD often co-exists with other problems and non-pharmacological interventions such as behaviour interventions are effective in addressing oppositional behaviour, and cognitive training for working memory (Daley et al, 2014; Cortese et al, 2015).

Table 3. Treatment options in attention-deficit hyperactivity disorder (ADHD)

Treatment options across the age groups	For pre-school children: behaviour interventions and parent training	
	For school-age children 5–12 years with moderate levels of impairment, a group parent-training programme for parent plus group cognitive behavioural therapy and/or social skills training for the child	
	For school-age children with severe ADHD: medication as first line	
	For older adolescents with mild level of impairment: individual cognitive behavioural therapy or social skills training may be considered	
	For older adolescent with moderate to severe impairment: medication as first line	
Medications for ADHD: recommendations	Methylphenidate should usually be tried first in patients with ADHD	
	Atomoxetine should be considered when methylphenidate is ineffective or not tolerated	
	If patients do not respond to methylphenidate or atomoxetine, further treatment options include	Higher doses of methylphenidate or atomoxetine
		Switching to dexamphetamine
		Further or alternative psychological treatments
		Referral to a regional specialist for an alternative drug treatment

From National Institute for Health and Care Excellence (2008)

A more recent systematic appraisal of the evidence of psychosocial interventions in ADHD concluded that pharmacological treatment along with psychosocial interventions seems to better address the multifaceted needs of children with ADHD (Watson et al, 2015). Döpfner et al (2004) recommended the use of a multimodal treatment, which is incorporating a number of psychosocial interventions such as behavioural parent training, social skills, cognitive behavioural therapy and other interventions. In view of our current lack of knowledge about which components of the multimodal treatment actually makes a difference, a step by step approach may be an alternative to combining all the different interventions together in one go (Taylor et al, 2004; Doepfner, 2015).

Medications

NICE guidelines (2008) recommended that medications should be used for moderate to severe ADHD in school-age children and adolescents as part of a comprehensive treatment programme that includes psychosocial interventions to address coexisting conditions (*Table 3*).

At the time of the publication of NICE guidelines in 2008, atomoxetine, dexamfetamine (immediate release preparation) and methylphenidate (immediate release and long-acting preparations) were the only medications licensed in the UK for the treatment of ADHD in children and young people. The NICE (2006) technology appraisal concluded that these medications are effective in controlling the symptoms of ADHD relative to no treatment. Numerous clinical trials have shown that pharmacological treatment improves outcomes across a number of domains including control of core symptoms of ADHD, improves academic productivity, improves classroom behaviour and improves mother–child interactions, at least in the short term. NICE (2008) guidelines recommended that methylphenidate should be used as the first-line drug followed by atomoxetine. Short-acting dexamfetamine is unlikely to be used as a first-line treatment for the majority of children or young people with ADHD because it has a greater potential for diversion and misuse than other medications (NICE, 2006).

Initiation and monitoring of treatment

Medications should only be initiated by a child psychiatrist or paediatrician with expertise in ADHD. The MTA study showed that careful titration and monitoring of pharmacological treatment led to higher efficacy (The MTA Cooperative Group, 1999). Since both effects and side effects are dose related, careful and gradual individual titration is needed for optimal treatment (Vitiello et al, 2001). Once the patient is stabilized on an optimal dosage of medication, continued prescribing and monitoring of medications may be performed by GPs under shared care arrangements (NICE, 2006).

Establishing whether symptoms and impairments have resolved is largely a matter of clinical judgment and careful monitoring. The ADHD management cycle (*Figure 1*) provides a useful structure to ensure optimal management of ADHD and includes identification and prioritization of treatment needs, identification and prioritization of treatment goals, agreeing a treatment approach and regular measurement of treatment outcomes.

Target symptoms and behaviours should be evaluated through a range of validated rating scales such as SNAP-IV, SKAMP (Swanson, 1992; Wigal et al, 1998) and individually tailored 5-point visual analogue scales to evaluate patient- and family-driven targets and outcomes. The SNAP-IV 18-item questionnaire is a succinct clinical

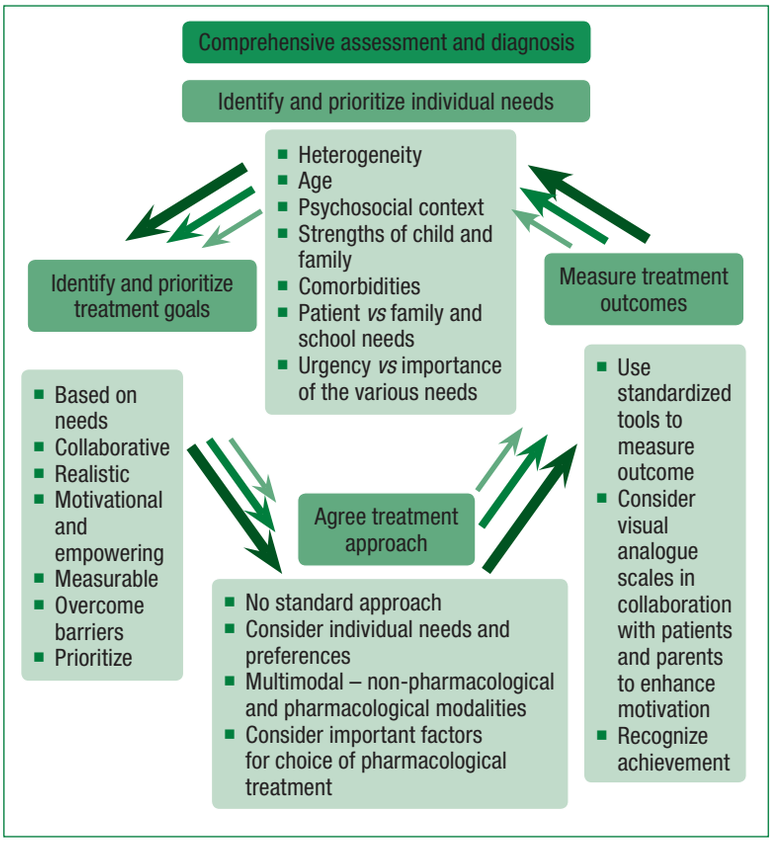

Figure 1. Attention-deficit hyperactivity disorder (ADHD) management cycle.

tool that gives repeatable measurements of core symptoms which can be used to define remission of ADHD. Eighteen items are rated on a scale of 0–3 giving a maximum of 54, with remission defined as a score <18. In many clinical trials sufficient response to treatment is often defined as a significant decrease in symptoms (e.g. >50% reduction in symptoms). However, in clinical practice one should aim for even better response to treatment, ideally an absolute reduction in symptoms to close to normal (<18 on SNAP-IV). Functional remission (full recovery) requires that the patient has less than one third of the symptoms on a standardised rating scale such as SNAP-IV and no impairment (i.e. a score >60 on the Clinical Global Assessment Scale).

Beyond NICE guidelines

Since the NICE guidelines were published in 2008, there have been a number of advances in the field of ADHD including introduction of new medications, publication of head-to-head trials and meta-analysis of the comparative efficacy of the medications used to treat ADHD in children and adolescents (Faraone, 2009; Faraone and Buitelaar, 2010; Schwartz and Correll, 2014). A revision of the NICE guidelines is currently underway, with publication due in 2017, and clinicians should be aware of the recent advances while awaiting the revised guidelines. *Table 4* gives more information about the medications that are currently licensed for ADHD in children and adolescents.

Newer medications and formulations

Lisdexamfetamine dimesylate

Lisdexamfetamine dimesylate▼ was licensed in the UK in 2013 for treatment of ADHD in children aged ≥6 years when response to previous methylphenidate treatment is considered clinically inadequate. Lisdexamfetamine dimesylate is the first long-acting prodrug stimulant consisting of a molecule of lysine, an essential amino acid, bound to a molecule of dexamfetamine. This confers a number of pharmacokinetic and pharmacodynamics advantages. Lisdexamfetamine dimesylate is inert in its capsular form, remains inert in the gastrointestinal tract and does not undergo first pass metabolism in the liver. Lisdexamfetamine dimesylate is rapidly absorbed into the bloodstream independent of whether it has been taken with or without food or any gastric pH-altering medications. Lisdexamfetamine dimesylate is enzymatically hydrolyzed by peptidases within red blood cells to release the therapeutically active moiety dexamfetamine. Hydrolysis of the prodrug molecule in red blood cells is the rate-limiting step and explains the long duration of action and low potential for misuse or diversion. Pharmacokinetic studies in humans have shown that exposure to d-amfetamine following oral administration of lisdexamfetamine dimesylate is monophasic, sustained and dose proportional, with low intra- and inter-patient variability. Thus in clinical practice, lisdexamfetamine is not affected by gender, ethnic background and other factors that could potentially affect the metabolism of other medications in the liver. The prodrug molecule itself is highly soluble so the capsule can be opened and the contents mixed with a small amount of water, orange juice or soft food such as yoghurt. Systematic reviews have attested to the good tolerability and efficacy of lisdexamfetamine dimesylate in children and adolescents in short-term clinical trials. Adverse effects in children and adolescents were typical of those reported for stimulant medications, with decreased appetite and insomnia most frequently reported (Coghill et al, 2012).

Guanfacine

Guanfacine▼ prolonged release is a recent non-stimulant medication that has been licensed in the UK since 2015 for treatment of children and adolescents for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. A number of randomized controlled trials have shown that guanfacine prolonged release is effective for the treatment of ADHD in children and adolescents aged 6–17 years as monotherapy or when administered as adjunctive therapy with stimulants (Biederman et al, 2008; Sallee et al, 2009a,b; Wilens et al, 2012; Newcorn et al, 2013; Hervas et al, 2014). The improvement was observed within 3 weeks of starting treatment. Guanfacine prolonged release has a license for monotherapy in the UK. The selective mode of action of guanfacine may provide particular benefit for children or adolescents who have specific comorbidities such as chronic tic disorders, or oppositional defiant disorder (or oppositional symptoms) that have failed to respond to first-line treatment options (Connor et al, 2010). Children

Table 4. Medications currently licensed for attention-deficit hyperactivity disorder (ADHD) in children and adolescents

Medication	Class of drug	Proposed neurobiological effect	Duration of action	Dosage	Common side effects
Methyl-phenidate	CNS stimulant schedule 2 controlled drug	Increases dopamine by blocking the dopamine transporter. Increase noradrenaline by blocking the noradrenaline transporter, to a lesser extent	Immediate release= 4 hours	Start with 10 mg, up to 60 mg/day	Insomnia, nervousness, headache, decreased appetite, abdominal pain, tachycardia, palpitations and minor increases in blood pressure. Growth can be affected, at least in the short term
			Concerta XL= 12 hours	Start with 18 mg, up to 54 mg/day	
			Equasym XL= 8 hours	Start with 10 mg, up to 60 mg/day	
			Medikinet XL= 8 hours	Start with 10 mg, up to 60 mg/day	
Amphetamine	CNS stimulant schedule 2 controlled drug	Increases dopamine and noradrenaline through blocking the dopamine and noradrenaline transporter. Promotes vesicular release of dopamine from the presynaptic neurone into the synapse	Dexamfetamine= 4 hours	Start with 10 mg, up to maximum of 40 mg /day	Insomnia, nervousness, headache, decreased appetite, abdominal pain, tachycardia, palpitations and minor increases in blood pressure. Growth can be affected, at least in the short term
			Lisdexamfetamine = 13 hours	Up to 70 mg day – start with 20 or 30 mg/day)	
Atomoxetine	Non-stimulant, not a controlled drug	Selective noradrenaline reuptake inhibitor, blocks the noradrenaline transporter, leading to moderate increase in noradrenaline and dopamine	Atomoxetine= up to 24 hours as a result of the metabolites	1.2–1.6 mg/kg body weight – usual maximum dose 80 mg in younger children, 100 mg in adolescents	Abdominal pain, decreased appetite, increased heart rate and small increases in blood pressure. Cases of hepatic disorders reported, and a possible risk of self-harm
Guanfacine	Non-stimulant, not a controlled drug	Selective alpha2a agonist, acts directly on α2A-adrenergic receptors to enhance noradrenaline neurotransmission Possible influences on dendritic spine plasticity in the prefrontal cortex	Guanfacine – prolonged release – up to 24 hours	0.05–0.12 mg/kg once daily, usual maximum dose is 4 mg for 6–12 year olds and 7 mg* for 12–17 year olds	Somnolence, headache, upper respiratory tract infection, fatigue, upper abdominal pain and sedation. Small changes in blood pressure

**Adolescents weighing 58.5 kg and above may be titrated to a 7 mg/day dose after the subject has completed a minimum of 1 week of therapy on a 6 mg/day dose and the physician has performed a thorough review of the subject's tolerability and efficacy.*

with comorbid anxiety symptoms and substance misuse are potential likely candidates for the use of guanfacine, although there is little evidence from controlled trials at present to guide clinical practice.

Meta-analyses of comparative efficacy and head-to-head trials

Meta-analyses have shown that effect sizes were significantly greater for stimulants than for non-stimulants and that effect sizes compared with placebo were modestly but statistically significantly greater for amphetamine-based stimulants than for methylphenidate (Faraone, 2009; Faraone and Buitelaar, 2010) (*Table 5*). Although not a perfect measure, variability of drug–placebo effect sizes provides some guidance in the choice of medications. Despite efforts such as the above to generate comparative data on efficacy, it should be pointed out that the field lacks an up to date and comprehensive evidence base on how ADHD medications compare with each other and rank in terms of their efficacy and tolerability. In the absence of confirmatory head-to-head studies, caution is warranted when comparing the effects of different medications across studies.

A review of stimulant treatment in the US by Hodgkins et al (2012) has shown that up to 70% of patients respond to the first stimulant (methylphenidate or dexamfetamine preparations); if two stimulants are used consecutively, the response rate is >87%. However, there is at present no method to predict which stimulant will produce the best response in a given patient. The current UK licence for use of lisdexamfetamine dimesylate in children is somewhat

Table 5. Effect sizes of medications in attention-deficit, hyperactivity disorder (ADHD) in children and adolescents

Medication	Effect size
Amfetamine/lisdexamfetamine	1.2–1.8
Methylphenidate	0.8–1.2
Atomoxetine	0.59–0.67
Guanfacine	0.43–0.86

In the absence of confirmatory head-to-head studies, caution is warranted when comparing the effects of different medications across studies

KEY POINTS

- Attention-deficit hyperactivity disorder (ADHD) is a common, heterogeneous, childhood disorder that can persist in to adulthood and alter the developmental trajectory of the affected individual.
- The core symptoms of ADHD often co-exist with other mental health problems, developmental disorders and learning difficulties.
- ADHD is associated with a range of health related adverse outcomes as well as adverse family, social and vocational functioning throughout the lifespan.
- Treatments for ADHD include education and training, non-pharmacological treatments and medication. Pharmacotherapy should be 'fine-tuned' and closely monitored at regular intervals to optimize the outcomes for affected children and adolescents.
- There have been significant advances in our understanding of the treatment options in ADHD since the National Institute for Health and Care Excellence guidelines were published in 2008 including the availability of new medications, enhanced awareness of the comparative efficacy of medications used and the role of non-pharmacological treatments in ADHD.

restrictive in this regard as it can be used only after an inadequate response to methylphenidate.

A head-to-head trial of lisdexamfetamine dimesylate *vs* atomoxetine in patients who had had an inadequate response to treatment with methylphenidate found that lisdexamfetamine dimesylate was superior to atomoxetine both in terms of efficacy and faster onset of response (Dittmann et al, 2013).

Inadequate response to treatment

Despite the advances in pharmacological treatments, 25–30% of patients with ADHD do not respond adequately to initial treatment with stimulants (Arnold, 2000). Inadequate response to treatment is common in clinical practice and a European study found that only 30% of children treated with ADHD achieve full symptom control (Mitra et al, 2012). Suboptimal response could manifest in clinical practice as failure to control the core symptoms of ADHD despite optimal dosing, inadequate duration of action and daily variation in symptom control. A number of factors could contribute to an inadequate response to treatment, including poor concordance with medication, severity and/or complexity of ADHD, inadequate stimulant dosing and/or dose-limiting adverse effects.

Current treatment recommendations

Pharmacological treatment of ADHD is highly rewarding but getting adequate response from medications requires careful consideration of the whole portfolio of medications and patient characteristics (*Table 4*). Suboptimal response to medication is common and every effort should be made to get the best out of medication by carefully crafted psychopharmacotherapy. The recent advances in the field of ADHD including the availability of new molecules, and comparative efficacy of various medications should be taken into account when deciding about the initial choice of medication or about switching to another medication when the response to treatment is deemed inadequate. *Table 6* provides valuable recommendations based on consensus from European clinicians and researchers regarding the choice of medications for ADHD (Coghill and Danckaerts, 2015).

Conclusions

ADHD is a common neurodevelopmental disorder of childhood that persists into adult life and exacts a pernicious toll on a number of domains in the affected individual's life across the whole lifespan. Undiagnosed or poorly treated ADHD can contribute to problems in social, academic and vocational settings throughout life, cause distress to family and friends, and impair the quality of life of the affected individual. Most patients with ADHD have complex needs and would benefit from a combination of medication and psychosocial treatments. Clinicians' judgement and

Table 6. Recommendation for use of medications in attention-deficit hyperactivity disorder (ADHD) in children and adolescents

Current treatment	Suggested interventions
Mild to moderate ADHD, unable to adhere to or fail to respond to behaviour treatment	Initiate a trial of methylphenidate
Suboptimal response to methylphenidate	Optimization of dose and compliance issues. Switch to lisdexamfetamine or dexamfetamine
Methylphenidate not tolerated as first line	Switch to lisdexamfetamine, dexamfetamine or atomoxetine
Suboptimal response to atomoxetine as first line	Optimization of dose and duration. Switch to methylphenidate, lisdexamfetamine or dexamfetamine
Suboptimal response to guanfacine as first line	Switch to methylphenidate or lisdexamfetamine or consider using combinations of guanfacine with methylphenidate or lisdexamfetamine*
Atomoxetine or guanfacine not tolerated as first line	Switch to methylphenidate, lisdexamfetamine or dexamfetamine
Failure to respond to or not able to tolerate methylphenidate, lisdexamfetamine, atomoxetine, dexamfetamine and guanfacine	Advice from regional or national specialist. Options include modafinil, bupropion, clonidine, nicotine patch

*Adapted from Coghill and Danckaerts (2015) *not licensed*

patient and family choice are key components in choosing treatments. Methylphenidate, amphetamine preparations, atomoxetine and guanfacine are effective treatments via distinct neurochemical mechanisms. Recent advances in understanding of the neurobiology of ADHD and current range of treatment options will help clinicians make informed decisions to optimize the care of children with ADHD. Clinicians should pay particular attention to the issue of managing inadequate response to medications and use of psychological therapies to address coexisting problems. Flexibility, innovation and a systemic framework will never go amiss. **BJHM**

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ELVANSE®▼ (lisdexamfetamine dimesylate) 20MG, 30MG, 40MG, 50MG, 60MG AND 70MG CAPSULES, HARD. PRESCRIBING INFORMATION

(Please refer to full Summary of Product Characteristics (SmPC) before prescribing.)

Active Ingredient: Lisdexamfetamine dimesylate 20mg, 30mg, 40mg, 50mg, 60mg and 70mg. Uses: ELVANSE is indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate. ELVANSE is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and potential for abuse, misuse or diversion. **Dosage and Administration:** Children (aged 6 years and over) and adolescents: For all patients the starting dose is 30mg taken once daily in the morning. Patients may begin treatment with 20mg daily if the clinician judges a lower dose to be appropriate. The dose may be increased by 10 or 20mg increments, at approximately weekly intervals. ELVANSE should be administered orally at the lowest effective dosage. The maximum recommended dose is 70mg/day; higher doses have not been studied. Patients with severe renal insufficiency should not exceed 50mg/day. Further dose reduction should be considered in patients on dialysis. Administration: ELVANSE may be taken with or without food and swallowed whole, or the capsule opened and the entire contents emptied and mixed with soft food such as yoghurt or in a glass of water or orange juice and taken immediately. If the contents include any compacted powder, a spoon may be used to break apart the powder. The contents should be stirred until completely dispersed. **Long-term Use:** Pharmacological treatment of ADHD may be needed for extended periods. The physician who elects to use ELVANSE for extended periods (over 12 months) should re-evaluate the usefulness of ELVANSE at least yearly, and consider trial periods off medication to assess the patient's functioning without pharmacotherapy, preferably during times of school holidays. **Contraindications:** Hypersensitivity to sympathomimetic amines or any of the excipients; concomitant use of monoamine oxidase inhibitors or within 14 days after MAOI treatment, hyperthyroidism or thyrotoxicosis, agitated states, symptomatic cardiovascular disease, advanced arteriosclerosis, moderate to severe hypertension, glaucoma. **Warnings:** Stimulants including ELVANSE have a potential for abuse, misuse, dependence or diversion for non-therapeutic uses that physicians should consider when prescribing these products. Stimulants should be prescribed cautiously to patients with a history of substance abuse. Monitor cardiovascular status carefully as sudden cardiac or unexplained death has been reported. Monitor psychiatric status as treatment may exacerbate symptoms of behaviour disturbance and thought disorder in patients with pre existing psychotic disorders. Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of mixed/manic

episode. ELVANSE is associated with worsening or emergence of aggressive behaviour, onset or exacerbation of tics, worsening of Tourette's syndrome, worsening of pre-existing anxiety, agitation or tension. Use with caution in those with epilepsy as may increase frequency of seizures. **Precautions:** Monitor weight, growth, blood pressure. Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. ELVANSE should be used with caution in patients who use other sympathomimetic drugs. The least amount of ELVANSE feasible should be prescribed or dispensed in order to minimise the risk of possible overdose by the patient. **Interactions:** Extended-release guanfacine, extended-release venlafaxine, ascorbic acid and other agents that acidify urine, sodium bicarbonate and other agents that alkalinise urine, monoamine oxidase inhibitors, serotonergic drugs, antihypertensives, narcotic analgesics, chlorpromazine, haloperidol, lithium carbonate. **Pregnancy and Lactation:** Not recommended. **Driving:** Caution is advised. **Adverse Effects:** *Very common*: Decreased appetite, insomnia, headache, upper abdominal pain, weight decreased. *Common*: Anxiety, depression, tic, affect lability, aggression, dizziness, restlessness, somnolence, dry mouth, diarrhoea, constipation, nausea, vomiting, rash, irritability, fatigue, feeling jittery, pyrexia, tremor, tachycardia, palpitation, dyspnoea. Consult SmPC in relation to less common side effects. **Pharmaceutical Precautions:** Store below 25°C. **Legal Category:** Prescription Only Medicine. **Product Licence Numbers:** 20mg: PL 08081/0062, 30mg: PL 08081/0050, 40mg: PL 08081/0063, 50mg: PL 08081/0051, 60mg: PL 08081/0064, 70mg: PL 08081/0052. **NHS Cost** (for 28 capsules) 20mg: £54.62, 30mg: £58.24, 40mg: £62.82, 50mg: £68.60, 60mg: £75.18, 70mg: £83.16. **Date of Revision:** September 2016. **Name and Address of MA Holder:** Shire Pharmaceutical Contracts Limited, Hampshire International Business Park, Chineham, Basingstoke, Hampshire RG24 8EP, UK. Tel: 0800 055 6614. Email: medinfoeuceemea@shire.com. Further information is available on request. ELVANSE is a registered trade name.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Shire Pharmaceuticals Ltd on 01256 894000.

EQUASYM XL (methylphenidate hydrochloride) Prescribing Information

Consult the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: 10mg, 20mg and 30mg modified-release capsules, hard, for oral administration. **Indication:** Attention-deficit hyperactivity disorder (ADHD) in children aged 6 years and over as part of a comprehensive treatment programme under the supervision of a specialist in childhood behavioural disorders where remedial measures alone prove insufficient. **Dosage and Administration:** *Children (aged 6 years and over) and adolescents:* Prior to prescribing, it is necessary to conduct an evaluation of cardiovascular status, psychiatric status and height and weight. *New patients:* The starting dose is 10mg taken before breakfast. Careful dose titration is necessary. The maximum daily dose is 60mg. *Patients currently using methylphenidate:* A 20mg dose of Equasym XL is intended to replace 10mg of immediate release methylphenidate taken at breakfast and lunchtime. *Administration:* The capsules may be swallowed whole with liquid, or the contents may be sprinkled onto soft food and swallowed immediately, followed by a drink. The capsules and their contents must not be crushed or chewed. *Adults:* Not applicable. **Long-term Use:** Long-term use has not been evaluated in controlled trials. Patients on long-term therapy (i.e. over 12 months) must be monitored for cardiovascular status, growth, appetite, and the development of de novo or worsening of pre-existing psychiatric disorders. The continued usefulness of the drug should be re-evaluated at least yearly by trial periods off medication to assess the patient's functioning without pharmacotherapy. **Contraindications:** Hypersensitivity to methylphenidate or excipients; glaucoma, phaeochromocytoma, hyperthyroidism, thyrotoxicosis, treatment with non-selective irreversible monoamine oxydase inhibitors (or within 14 days of their discontinuation), diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder, diagnosis or history of severe and episodic (Type I) bipolar (affective) disorder, pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies, pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke. **Warnings and Precautions:** Monitor cardiovascular status carefully as sudden cardiac or unexplained death has been reported. Monitor psychiatric status as treatment may exacerbate symptoms in psychotic children, or may precipitate mixed/manic episodes. Equasym XL is associated with worsening or emergence of aggressive behaviour, emergent suicidal ideation or behaviour, onset or exacerbation of tics, worsening of Tourette's syndrome, worsening of pre-existing anxiety, agitation or tension. Use with caution in those with epilepsy as may increase frequency of seizures. Monitor abuse potential as chronic abuse may lead to tolerance and dependency with abnormal behaviour. Monitor weight, growth, blood pressure. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Equasym XL. Supervise drug withdrawal. Should not be used for treatment or prevention of normal fatigue states. **Interactions:** Drugs that elevate blood pressure, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), tricyclics and SSRIs, coumarin anticoagulants, clonidine and other alpha-2 agonists, anti-hypertensives, halogenated anaesthetics, alcohol, dopamine agonists or antagonists including antipsychotics. **Pregnancy and Lactation:** Not recommended. **Driving:** Caution is advised. **Adverse Effects:** *Very common:* Nervousness, insomnia, headache. *Common:* Arrhythmia, palpitations, tachycardia, hypertension, abdominal pain, nausea, diarrhoea, stomach discomfort and vomiting, dry mouth, changes in blood pressure and heart rate, decreased appetite and reduced weight and height gain during prolonged use, pyrexia, arthralgia, dizziness, dyskinesia, abnormal behaviour, bruxism, aggression, agitation, anorexia, anxiety, depression, irritability, alopecia, rash, pruritus, urticaria, nasopharyngitis, affect lability, psychomotor hyperactivity, somnolence, cough, pharyngolaryngeal pain. Consult SmPC in relation to other adverse reactions. **Pharmaceutical Precautions:** Store below 25°C. **Legal Category:** CD (Sch 2) POM. **Marketing authorisation number and holder:** *PL 27303/0004-0006*, Shire Pharmaceuticals Ireland Limited, 5 Riverwalk, Citywest Business Campus, Dublin 24, Ireland. Tel: 0800 055 6614. Email: medinfoeuceemea@shire.com **NHS Cost** (for 30 capsules) 10mg: £25.00, 20mg: £30.00, 30mg: £35.00. **Date of Revision**: September 2015. *Further information is available on request.*

EQUASYM XL is a registered trade name.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.
UK: Adverse events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard
Ireland: Adverse events should be reported to the Pharmacovigilance Unit at the Health Products Regulatory Authority (HPRA) at: http://hpra.ie
UK and Ireland: Adverse events should also be reported to Shire Pharmaceuticals Ltd. on +44 (0)1256 894000 or faxed on +44 (0) 1256 894715 or emailed to: globalpharmacovigilance@shire.com

Intuniv®▼ (guanfacine hydrochloride) Prescribing Information
Consult the Summary of Product Characteristics (SmPC) before prescribing.
Presentation: Prolonged-release tablets, 1 mg, 2 mg, 3 mg and 4 mg; each tablet contains guanfacine hydrochloride equivalent to 1 mg, 2 mg, 3 mg and 4 mg respectively. **Indication:** Treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 - 17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Use as a part of a comprehensive ADHD treatment programme. **Dosage and administration:** Oral, take once daily morning or evening, with or without food, but not with high fat meals. Do not crush, chew or break before swallowing. Do not take with grapefruit juice. Initiate treatment under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders. *Pre-treatment screening:* Baseline evaluation to identify patients at increased risk of somnolence and sedation, hypotension and bradycardia, QT-prolongation arrhythmia and weight increase/risk of obesity. *Posology:* Careful dose titration and monitoring is necessary at the start of treatment since clinical improvement and risks for several clinically significant adverse reactions are dose and exposure related. Recommended starting dose is 1 mg of guanfacine which may be adjusted in increments of not more than 1 mg per week. Dose should be individualised according to the patient's response and tolerability. Recommended maintenance dose range is 0.05-0.12 mg/kg/day. When stopping Intuniv, the dose must be tapered with decrements of no more than 1mg every 3 to 7 days and blood pressure and pulse monitored in order to minimise potential withdrawal effects, in particular increases in blood pressure and heart rate. For further information on dose adjustments, dose titration and discontinuation plus monitoring requirements, refer to the Intuniv SmPC. *Renal and hepatic impairment:* Dose reduction may be required in patients with different degrees of hepatic impairment, and in patients with severe renal impairment (GFR 29-15 ml/min) and end stage renal disease (GFR<15 ml/min or requiring dialysis). *Children under 6 years:* Intuniv should not be used because efficacy and safety in this patient population has not been studied. *Patients treated with CYP3A4/5 inhibitors/inducers:* Patients on moderate/strong CYP3A4/5 inhibitors: a dose reduction is recommended. Patients on strong CYP3A4 inducers: a dose increase within the recommended range is recommended. See SmPC for further details. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Warnings and precautions:** Intuniv can cause syncope, hypotension and bradycardia. Caution is advised when treating patients with a history of hypotension, heart block, bradycardia, or cardiovascular disease, who have a history of syncope or a condition that may predispose them to syncope. Caution also advised with patients treated concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. Patients should be advised to drink plenty of fluid. Prescribe with caution in patients with a known history of QT prolongation, risk factors for torsade de pointes or patients taking medicinal products that prolong the QT interval. These patients should receive further cardiac evaluation based on clinical judgement. Intuniv may cause somnolence and sedation predominantly at the start of treatment and could typically last for 2-3 weeks and longer in some cases, therefore it is recommended that patients are monitored weekly during dose titration and stabilisation. Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Children and adolescents treated with Intuniv may show an increase in their BMI, therefore, monitoring of height, weight and BMI should be done prior to initiation of therapy and then every 3 months for the first year. Six monthly monitoring should follow thereafter with more frequent monitoring following any dose adjustment. Intuniv contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Intuniv. **Interaction with other medicinal products and other forms of interaction:** All drug-drug interaction studies have been performed in adults. However, the outcome is expected to be similar in the indicated paediatric age range. *QT-Prolonging medicinal products:* Intuniv causes a decrease in heart rate, therefore the concomitant use of Intuniv with QT prolonging medicinal products is generally not recommended. *CYP3A4, MATE1, OCT1 and CYP3A5 inhibitors:* See SmPC for further details. *Valproic acid:* Co-administration can result in increased concentrations of valproic acid. Adjustments in the dose of valproic acid and Intuniv may be indicated when co-administered. *Antihypertensive medicinal products:* Caution when administered concomitantly due to the potential for hypotension and syncope. *CNS depressant medicinal products:* Caution when administered concomitantly due to the potential for sedation and somnolence. *Effects on ability to drive and use machines:* May cause drowsiness and somnolence. **Side effects:** *Very common* (≥1/10 patients): somnolence, headache, abdominal pain, fatigue; *Common* (≥1/100, <1/10 patients): decreased appetite, depression, anxiety, affect lability, insomnia, middle insomnia, nightmare, sedation, dizziness, lethargy, bradycardia, hypotension, orthostatic hypotension, vomiting, diarrhoea, nausea, constipation, abdominal/stomach discomfort, dry mouth, rash, enuresis, irritability, blood pressure decreased, weight increased. *Serious adverse events:* hypotension, weight increase, bradycardia, syncope, hypertension, asthma, hypertensive encephalopathy, sedation, hypersomnia, convulsion, orthostatic hypotension, tachycardia. See the Intuniv Summary of Product Characteristics for full details of Undesirable Effects. **Package quantity and price for the UK:** 28 tablet pack: 1 mg: £56.00; 2 mg: £58.52; 3 mg: £65.52; 4 mg: £76.16. **Pharmaceutical precautions:** None. **Legal category:** POM. **Date of preparation:** December 2016. **Marketing authorisation number and holder:** EU/1/15/1040/001-009. Shire Pharmaceuticals Ireland Limited, 5 Riverwalk, Citywest Business Campus, Dublin 24, IRELAND. Email: medinfoeuceemea@shire.com. Further information is available on request.
INTUNIV is a registered trade name.