# ADHD and Hyperkinetic Disorder

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SECOND EDITION · SECOND EDITION · 2

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# O  P  L

# ADHD and Hyperkinetic Disorder

**Second Edition**

by

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# Symbols and abbreviations

| | |
|---|---|
| AAQOL | Adult ADHD Quality of Life Scale |
| ADHD | Attention-deficit/hyperactivity disorder |
| ADL | activities of daily life |
| AERS | adverse event reporting system |
| ASRS | Adult ADHD Self Report Scale |
| ATX | Atomoxetine |
| AUC | area under the plasma-concentration time curve |
| BASC | Behavioural Assessment System for Children |
| BPT | behavioural parent training |
| BPVS | British Picture Vocabulary Scale |
| BRIEF | Behaviour Rating Inventory of Executive Function |
| CAADID | Conners Adult ADHD Diagnostic Interview for DSM-IV |
| CAI | computer-assisted instruction |
| CAMH | Child and Adolescent Mental Health |
| CBCL | Child Behaviour Checklist |
| CBF | cerebral blood flow |
| CBT | cognitive–behavioural therapy |
| CD | Conduct disorder |
| CDI | Child Depression Inventory |
| CGAS | Children's Global Assessment Scale |
| CGI-I | Clinical Global Impressions Improvement scale |
| CGI-S | Clinical Global Impressions Severity scale |
| CNV | copy number variants |
| CPRS | Conners Parent Rating Scale |
| CPRS-R | Conners Parent Rating Scale, Revised |
| CTRS-R | Conners Teacher Rating Scale, Revised |
| CSBQ | Children's Social Behaviour Questionnaire |
| CSHQ | Children's Sleep Habits Questionnaire |
| CWPT | class-wide peer tutoring |
| DA | dopamine agonists |
| DAT | dopamine transporter |
| DAWBA | Development and Well-being Assessment |
| DCD-Q'07 | Developmental Coordination Disorder Questionnaire 2007 |
| DHA | docosahexaenoic acid |
| DHPG | dihydroxyphenylethylene glycol |

| | |
|---|---|
| DISC | Diagnostic Interview Schedule for Children |
| DIVA | Diagnostic Interview for ADHD in Adults |
| DMRD | Disruptive mood dysregulation disorder |
| DSM | Diagnostic and Statistic Manual |
| EAGG | European ADHD Guidelines Group |
| EEG | electroencephalogram |
| EF | executive function |
| EPA | eicosapentaenoic acid |
| FDA | Food and Drug Administration |
| GPT | group psychotherapy |
| GXR | guanfacine extended release |
| HKD | Hyperkinetic Disorder |
| ICD | International Classification of Diseases |
| LDX | lisdexamfetamine |
| MBD | minimal brain dysfunction |
| MOA | monoamine oxidase |
| MPH | methylphenidate |
| NE | norepinephrine |
| NET | norepinephrine transporter |
| NICE | National Institute for Health and Care Excellence |
| NNT | needed to treat |
| ODD | Oppositional defiant disorder |
| PACS | Parental Account of Children's Symptoms |
| PD | pharmacodynamics |
| PDD | Pervasive developmental disorder |
| PET | positron emission tomography |
| PK | pharmacokinetics |
| P-YMRS | Parent version of the Young Mania Rating Scale |
| R-CMAS | Revised Children's Manifest Anxiety Scale |
| RCT | randomized controlled trial |
| RS | rating scale |
| SADS | Schedule for Affective Disorder and Schizophrenia |
| SCQ | Social Communication Questionnaire |
| SDQ | Strengths and Difficulties Questionnaire |
| SERT | serotonin transporter |
| SKAMP | Swanson, Kotkin, Atkins, McFlynn, and Pelham |
| SNAP | Swanson, Nolan, and Pelham |
| SNAP-IV | Swanson, Nolan, and Pelham (DSM-IV version) |
| SNRI | serotonin-norepinephrine re-uptake inhibitor |
| SPECT | single photon emission tomography |

| | |
|---|---|
| SSRI | serotonin re-uptake inhibitor |
| SWAN | Strengths and Weaknesses of ADHD—Symptoms and Normal Behaviour |
| TOWRE | Test of Word Reading Efficiency |
| TRF | Teacher Rating Form |
| VMAT | vesicular monoamine transporter |
| WAIC | Weschler Intelligence Scale for Children |
| WAIS | Weschler Adult Intelligence Scale |
| WASI | Wechsler Abbreviated Scale of Intelligence |
| WCST | Wisconsin Card Setting Test |
| WHO | World Health Organization |
| Y–BOCS | Yale–Brown Obsessive Compulsive Scale |

## Chapter 1

# Introduction

Eric Taylor

## 1.1 Introduction

The second edition of this book takes account of growing knowledge in neuroscience, the recent changes in classification of psychiatric disorders, and an increasing range of treatment opportunities. It comes at a time when the diagnosis in most countries is made more frequently than ever before—with a corresponding public anxiety that the diagnosis is made too often. Developmental science has found that ADHD often persists into adult life and this has led to an increasing clinical recognition of the problem in adults.

## 1.2 Past

The concepts of ADHD originally developed from the long-standing recognition that some children and young people are hard to control and are unable to control themselves. From the early nineteenth century, Benjamin Rush in the USA, Alexander Crichton in Scotland, Désiré-Magloire Bourneville in France, and George Frederick Still in England were among those who wrote in clinical terms about failures of self-control as problems for development (Taylor 2011). The language used became more refined, and new concepts appeared—for example, 'hyperkinetic syndrome' from Kramer and Pollnow, and 'minimal brain dysfunction' from authors such as Tredgold. These new concepts tied together the ideas of motor dyscontrol and behavioural dysregulation.

The discovery of the therapeutic actions of the amphetamines made it clearer that they affected a triad of restless overactivity, impulsiveness, and inattentiveness (Taylor 2011). The need to measure the effects of treatment led to systematized rating scales, and statistical analysis of the questionnaires confirmed that the triad of behaviours did indeed occur together. Longitudinal studies showed that they tended to persist and to be impairing, and clinical research showed that they predicted consistently to cognitive changes and were susceptible to treatment (Taylor and Sonuga-Barke 2008). In all these respects, the behaviours make up a valid psychiatric condition. It exists as 'attention deficit/hyperactivity disorder' in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM5) and 'hyperkinetic disorder' in the WHO's International Classification of Disease (ICD 10). A major systematic review of the scientific evidence concluded that it is indeed a valid way of describing a common and impairing mental health condition in children, adolescents, and adults (NICE 2009).

## 1.3 Present

We now have the benefits of standardized rating scales to help in assessment and in monitoring of progress (see Chapter 4), an extensive literature of experiments that demonstrate and analyse cognitive changes (see Chapter 3), a range of effective medicines, both stimulants and

non-stimulants (see Chapter 5), knowledge of psychological methods to reduce the behavioural problems that often accompany ADHD (see Chapter 6), guidelines based on systematic reviews about how to use the various treatments in practice (see Chapter 7), and understanding how the problems affect adults (see Chapter 8). Readers of this book will find that they are equipped to make a real and helpful difference to the lives of affected children.

Nevertheless, and in spite of those advances, ADHD remains a controversial topic. Many educators, journalists, and politicians in Europe have expressed a suspicion that the definition is too vague and subjective, and allows a medical concept to be applied to children who are, in fact, developing normally; that medication is being used too much; and that the fifth revision of the Diagnostic and Statistical Manual of the American Psychiatric Association is exacerbating all these trends. Diagnosis and medication are increasing in frequency, especially in the USA (Visser *et al.* 2014). Serious journalism[1] has raised important questions, including the following:

- Why do rates of diagnosis and treatment vary so much from place to place and at different times?
- How frequently should ADHD be diagnosed and treated?
- Why are there no objective tests, and does this invalidate the diagnosis?
- Why is there no satisfactory cut-off to demarcate those with and those without ADHD?

These are issues, not only for ADHD and hyperkinetic disorder, but for psychiatric diagnosis generally. We do not yet have a full understanding of the underlying physiological processes (though progress is being made; see Chapter 3). Accordingly, the diagnosis depends entirely on the clinical presentation and we have nothing like a blood test to give a reassuringly 'objective' answer. This means that the clinical presentation has to be deeply understood—Chapter 2 gives a clear account.

The questions above also arise from a common background. The behaviours constituting ADHD are continuously distributed in the population. They seem to constitute a dimension (or set of dimensions) rather than a categorically distinct condition. The borderlines between normal development, atypical development, and overt disorder are not absolute but reflect the extent to which the behaviours interfere with normal life. This situation is in no way unique: the same applies to conditions such as autism, oppositional behaviour problems, and anxiety states. Indeed, it is a common situation in physical medicine. A raised blood pressure, for instance, is on a continuum with normal levels. The clinical decision about the level at which it should be regarded as a disorder is taken in the context of the individual's age, and the level of risk that it imposes for later health. Psychiatric judgement, too, needs to be based on clinical experience and knowledge. Chapter 2 explains the issues involved. The consensus of experts becomes embodied in classification systems, in evidence-based treatment recommendations, and in the kind of authoritative field accounts that readers will find in the succeeding chapters.

Cultural factors also play a part. The rates of diagnosis and medication in the USA are much higher than in Europe, and to a worrying extent (Rapoport 2013). European countries differ but in most, the rates are about one-tenth of those in the USA. By contrast, the epidemiological data suggest that the actual problems occur at much the same rate on both sides of the Atlantic (Polanczyk *et al.* 2007).

There are some good reasons for the European clinicians' caution. A specialist assessment is usually provided in Europe, and if this finds an underlying cause (such as a hearing difficulty or chronic sleeplessness or a learning problem) then that can be treated (see Chapter 4). Many European countries value psychological interventions above pharmacological ones, and

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[1]E.g. by Alan Schwartz; New York Times, 14 December 2013.

in publicly funded systems there are often few obstacles (other than shortage of professionals) to accessing psychotherapies (see Chapter 7 for organizing services and Chapter 6 for how psychotherapies work and can be delivered). Unfortunately, there are bad reasons too for a low use of medication in parts of Europe. Recognition of ADHD is patchy and services are sometimes limited by a lack of professional time. Lazy journalism can spread the idea that the USA style of overtreatment occurs in European countries too, and may generalize even to arguing against the existence of ADHD problems. Accurate information presented to the public is therefore needed, and this book seeks to be a resource for those who are seeking to inform health education.

The major diagnostic schemes are being revised. The American DSM is the most influential and its fifth revision has recently been published (APA 2013). The World Health Organization's ICD10 is in the process of revision. The basic idea, of a triad of inattentiveness, impulsiveness, and restless overactivity, has not been changed; it has worked well in scientific and clinical study. DSM5, however, does relocate it from being considered as a childhood disorder to a neurodevelopmental disorder that can cause problems across the lifespan. This reflects increased knowledge about the existence and impact of ADHD in adult life (see Chapters 2 and 8). The criteria for recognition in adult life have been relaxed a little, and it has been recognized that the childhood antecedents of ADHD can in fact be the symptoms rather than any impairment arising from them. It has also become clearer that ADHD can still be recognized and treated when other conditions are present as well, and autism spectrum disorder is no longer considered to exclude the diagnosis of ADHD, but to be a comorbidity with it.

Priorities in therapy have also needed re-evaluation. The high priority given to behavioural parent training by existing guidelines (e.g. NICE 2009) may need reconsideration in the light of meta-analysis. The value of nutritional approaches—previously discounted—may need to be upgraded in the light of recent reviews. New drugs are appearing in Europe: the pro-drug lisdexamfetamine and guanfacine have received substantial trials, and lisdexamfetamine has achieved a marketing licence for children and for adults who were treated when they were children. Chapter 5 has been correspondingly updated. Considerations of cost-effectiveness have become particularly important for publicly funded services in a period of economic recession and austerity.

Increasing numbers of affected adults are presenting themselves to psychiatry for the first time in adult life. They sometimes meet services that are unprepared, a situation in which no medicines for their needs are yet licensed in Europe, and a sceptical approach by many professionals. They combine with an increasing number of diagnosed young people who are reaching an age at which adult services should be involved. Clinical guidance for this adult age group would therefore be helpful, even in the absence of the strong evidence from longitudinal studies and treatment trials that has been developed for children and adolescents. A new section (Chapter 8) has been written for this edition to propose recommendations for management in adult life.

## 1.4 **Future**

The last word has not, of course, been written. There are still areas of real uncertainty. One of the largest is how we should think about children who show no hyperactivity at all, but are nevertheless handicapped by serious problems of inattention. In DSM-IV they were considered as a subtype of ADHD, but later research found very little difference between the different 'subtypes'. This is probably because the definition of 'inattentive subtype' allowed for a considerable amount of overactivity and impulsiveness to be present (up to five out of nine possible symptoms). This means that a new generation of study is needed to find

a better account of those people who are not overactive at all, yet still cannot concentrate appropriately.

Other uncertainties that research should clarify include the establishment of 'objective' bio-markers, measures of severity that describe impairment in the real world, validated cut-offs to demarcate those who have a disorder from those who do not, and a better understanding of emotional (as well as behavioural and cognitive) dysregulation. DSM5 has created a new dis-order, 'disruptive mood dysregulation disorder', which is defined by emotional dysregulation, severe irritability, and dysphoria. It is nearly always 'comorbid' with ADHD but predicts mood disorder later. Research can be expected to cast light on it, and therefore on how to help young people with ADHD who have this extra problem. We can also expect progress in learning to use neuroimaging, cognitive testing—and eventually genetic analysis—to identify different types of ADHD. Longitudinal research will help clinicians understand what environmental influ-ences are involved in development over time, and which are susceptible to modification. We shall probably come to learn how to use neuroscience methods to predict and monitor the effects of treatment. All these advances in knowledge would lead to the improvement of our ability to help people to understand and overcome their disability. Nevertheless, many affected people are already having their lives transformed by the work already done and described in the succeeding chapters.

The authors of this book have been at the forefront of clinical science. They are unified by membership of a European network, EUNETHYDIS, led by Professor Sergeant. The network has enabled them to meet together, to make systematic and critical reviews of the international literature, to develop published guidelines, and to join basic scientists in multicentre genetic and neuropsychological research.

This book provides a concise and authoritative account of modern knowledge about hyper-kinetic disorder and ADHD. It is recommended to all those who need to know about them.

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## Chapter 2

# Phenomenology

Tobias Banaschewski and Luis Augusto Rohde

### Key points

- ADHD is a clinical diagnosis; the core symptoms are inattention, hyperactivity, and impulsivity.
- As the presentation and challenges of ADHD change over time, clinicians must take a lifespan approach and follow patients closely, modifying their care and treatment according to the individual's current needs.
- Comorbid conditions are the rule in clinical samples.
- ADHD is associated with seriously impairment for patient, family, and society.

## 2.1 Definitions

5

Attention-deficit/hyperactivity disorder (ADHD) and hyperkinetic disorder (HKD) are defined as psychiatric disorders characterized by a developmentally inappropriate, pervasive (across different situations such as home and school) and persistent pattern of severe inattention, hyperactivity, and/or impulsivity with an onset in childhood that is associated with substantial impairment in social, academic, and/or occupational functioning (Box 2.1).

Both diagnoses, ADHD (DSM-5, American Psychiatric Association, 2013) and HKD (ICD-10, WHO, 1992), are based upon the almost identical sets of 18 symptoms (Table 2.1). However, there are major differences in the decision rules, determining that HKD represents a subset of ADHD in ICD-10 and can be used to identify a more restricted and refined phenotype, which is accompanied by more impairment and inhibitory control deficits and which does imply a slightly different treatment algorithm (Swanson *et al.*, 1998; Taylor *et al.*, 2004; Schachar *et al.*, 2007; see also chapters 5–7).

DSM-5, as the old DSM-IV, lists 18 symptoms covering two dimensions: inattention, hyperactivity/impulsivity. It distinguishes three presentations of ADHD: a predominantly inattentive presentation, which displays at least six (or more) symptoms of inattention, and less than six of hyperactivity/impulsivity, a predominantly hyperactive/impulsive presentation suffering from

### Box 2.1 ADHD/HKD—core symptoms

The core symptoms are:
- Inattention
- Impulsivity
- Hyperactivity

These symptoms are required to be:
- Present from an early age (before the age of 6 (ICD-10) or 12 years (DSM-5)),
- Pervasive across at least two situations (e.g. home, school, and social life), and
- The cause of significant interference in functioning.

| Table 2.1 Symptom domains for ADHD/HKD in DSM-5 and ICD-10 |
| --- |
| **Inattention** <br> Often… <br> • fails to give close attention to details or makes careless mistakes in schoolwork, work, or during other activities (e.g. overlooks or misses details, work is inaccurate) <br> • has difficulty sustaining attention in tasks or play activities (e.g. has difficulty remaining focused during lectures, conversations, or lengthy reading) <br> • does not seem to listen when spoken to directly (e.g. mind seems elsewhere, even in the absence of any obvious distraction) <br> • does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions; e.g. starts tasks but quickly loses focus and is easily sidetracked) <br> • has difficulty organizing tasks and activities (e.g. difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines) <br> • avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework) (e.g. schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers) <br> • loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, tools, school materials, pencils, books, tools, wallets, keys, paperwork, spectacles, mobile telephones) <br> • easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts) <br> • forgetful in daily activities (e.g. doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments) |
| **Hyperactivity** <br> Often… <br> • fidgets with or taps hands or feet or squirms in seat <br> • leaves seat in situations in which remaining seated is expected (e. g. leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place) <br> • runs about or climbs in situations where it is inappropriate (in adolescents or adults, may be limited to feeling restless) <br> • unable to play or engage in leisure activities quietly <br> • 'on the go' or acting as if 'driven by a motor' (e.g. is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with (DSM-5); exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands (ICD-10)) <br> • talks excessively (DSM-5) |
| **Impulsivity** <br> Often… <br> • talks excessively without appropriate response to social constraints (ICD-10) <br> • blurts out answers before questions have been completed (e.g. completes people's sentences; cannot wait for turn in conversation) <br> • has difficulty waiting his or her turn (e.g. while waiting in line) <br> • interrupts or intrudes on others (e.g. butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing) |

six (or more) symptoms of hyperactivity/impulsivity, and less than six of inattention, and a combined presentation, which meets both sets of criteria. Clinicians are required to describe the current presentation of the patient.

The symptoms must have persisted for at least six months, must occur pervasive across at least two situations (e.g. home, school, and social life), and several of them must have been present before 12 years of age. Furthermore, these symptoms are required to not occur exclusively during

## Table 2.2 DSM-5 diagnostic criteria for ADHD

A. Either 1 or 2[#]
   1. Six (or more) of symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level[*]
   2. Six (or more) of symptoms of hyperactivity/impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level[*]

B. Several hyperactive/impulsive or inattentive symptoms were present before 12 years of age

C. Several inattentive or hyperactive/impulsive symptoms are present in two or more settings (e.g. at school/work or at home)

D. There must be clear evidence of clinically significant interference in social, academic, or occupational functioning

E. The symptoms do not occur exclusively during the course of schizophrenia or other psychotic disorder, and are not better accounted for by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, or personality disorder)

[#] The symptoms are not only a manifestation of oppositional behaviour, defiance, hostility, or inability to understand task or instructions.

[*] For older adolescents and adults (age 17 and older) at least five symptoms are required.

## Table 2.3 Differences between DSM-5 and ICD-10 criteria of ADHD or HKD

|  | DSM-5 ADHD | ICD-10 HKD |
|---|---|---|
| Symptoms | Either or both of following:<br>• At least six of nine inattentive symptoms<br>• At least six of nine hyperactive or impulsive symptoms[*] | All of following:<br>• At least six of nine inattentive symptoms<br>• At least three of five hyperactive symptoms<br>• At least one of four impulsive symptoms |
| Cross-situational pervasiveness | Several symptoms are present in more than one setting such as home and school | Criteria are met for more than one setting such as home and school |
| Age of onset | Several symptoms are present before age 12 years | Symptoms should be present before age six years |
| Comorbid diagnoses | Comorbid diagnosis with conduct, anxiety, and mood disorders recommended if inclusion criteria of multiple disorders are met | Diagnosis of HKD if there are anxiety and mood disorders is not recommended |
| Diagnostic presentations | Combined and partial presentations based on symptomatology<br>• Combined: six or more from the IN domain and six or more from the HI domain<br>• Inattentive: six or more from the IN domain and less than six from hyperactive/impulsive domain<br>• Hyperactive/Impulsive: six or more from HI domain and less than six from the IN domain | Subtypes based on comorbid disorder diagnosis<br>• Disturbance of activity and attention (without conduct disorder)<br>• Hyperkinetic conduct disorder (with conduct disorder) |

[*] In individuals 17 years of age or older, five symptoms of inattention and/or five symptoms of hyperactivity/impulsivity are enough!

the course of schizophrenia or other psychotic disorder, and not to be better accounted for by another mental disorder (Box 2.1). DSM-5 diagnostic criteria for ADHD are outlined in Table 2.2.

Although the ICD-10 criteria for hyperkinetic disorder describe similar symptoms to DSM-5, ICD-10 criteria are more restrictive in that they require (Table 2.3) hyperactivity, impulsivity, and inattention all to be present (in addition to at least six inattention symptoms, the presence of at least three hyperactive symptoms and at least one impulsive symptom), all symptoms to be impairing across two or more settings, an earlier age at onset, an exclusion of the diagnosis if mania, depression, and/or anxiety disorders are also present, whereas DSM-5 allows these diagnoses to be made as comorbid conditions.

The application of these more restrictive criteria defines the subgroup of those patients with combined ADHD presentation with the most severely impairing symptomatology, as hyperkinetic disorder. The main subdivision is between HKD and hyperkinetic conduct disorder, the latter defining a category of HKD plus conduct disorder.

Both classification systems include a criterion for the age of onset of symptoms (before the age of six (ICD-10), respectively 12 years (DSM-5)). It is recommended that clinicians do not rule out the possibility of a diagnosis of ADHD in patients who have not had symptoms causing impairment before the age of six years.

## 2.2 **Epidemiology**

The differences between countries in the prevalence of ADHD and HKD have generated considerable controversy. However, when operational definitions of ADHD/HKD are used, differences between countries are small. A recent systematic review on ADHD prevalence during childhood and adolescence based on 102 studies from across all world regions calculated an overall prevalence of ADHD of 5.3%. The prevalence for children was 6.5% and for adolescents 2.7% (Polanczyk *et al.* 2007). Differences between studies were mainly accounted for by:

- the use of differing diagnostic criteria (DSM-III, DSM-III-R, DSM-IV, or ICD-10),
- the source of information used to gather diagnostic information (best-estimate procedure, parents, 'and rule', 'or rule', teachers, or subjects),
- the requirement, or not, for impairment to be present in order for the diagnosis to be made.

After adjustments were made to account for these methodological issues, the estimates from North America and Europe were not significantly different from each other.

The prevalence of the more restrictive ICD-10 hyperkinetic disorder diagnosis has been estimated to be around 1.5% in school-age children. In clinical practice, the rate of recognition of a disorder—the administrative prevalence—often differs from the epidemiological prevalence. Administrative prevalence depends on factors that affect referral and access to service, and cultural factors that influence tolerance of the symptoms, as well as on the actual presence of symptoms.

Despite concerns that the prevalence of ADHD might be increasing worldwide in the last years, a recent meta-analysis showed that there is no evidence for an increase in the number of children in the community who meet criteria for ADHD in the past three decades when standardized diagnostic procedures are followed (Polanczyk *et al.* 2014).

Estimates of the prevalence of adult ADHD vary significantly. A meta-analysis of available studies in adults suggests a prevalence rate of 2.5% (95% CI 2.1–3.1) (Simon *et al.* 2009). The only populational study found in the literature assessing ADHD in young adults using the most recent DSM-5 criteria showed a prevalence of 3.6% (95% CI 2.9–4.1) (Matte *et al.* 2014).

Although a higher proportion of males than females is found in both community and clinical samples of children with ADHD (Polanczyk *et al.* 2007), a more balanced ratio is found in samples of adults (Simon *et al.* 2009).

The impact of ethnic and socio-economic issues on the prevalence rates of ADHD has been less investigated. However, in general it appears that ADHD is a worldwide disorder and that as long as similar methodologies are used, the prevalence rates are similar in most ethnic communities (Coghill *et al.* 2008). Regarding socio-economic status, recent data suggest that low family income in early childhood is associated with increased likelihood of ADHD (Larsson *et al.* 2013).

## 2.3 **Clinical presentation**

Clinical presentation of ADHD is highly variable. Some patients have only very minor symptoms, while others may have severe impairments. Diagnosis requires that there should be clear evidence of clinically significant impairment in social, academic, or occupational functioning. Impairment implies not only a higher severity or frequency of symptoms but also interference with functioning in the major life domains of the child (e.g. at home, at school, with friends, or elsewhere).

The predominantly inattentive presentation is relatively more common in females and, together with the combined presentation, seems to have a higher impact on academic performance. Children with the predominantly hyperactive/impulsive presentation are more aggressive and impulsive than those with the predominantly inattentive type of ADHD, and tend to be unpopular and highly rejected by their peers. The combined presentation causes more impairment to global functioning, compared with the other two types.

Clinical presentation may also vary according to age and stage of development (see below). In addition, there are cultural differences in the level of activity and inattention that are regarded as a problem (Taylor *et al.* 2004).

## 2.4 **Differential diagnoses**

It is important to note that ADHD/HKD symptoms are not specific to the disorder. As isolated symptoms, inattention, hyperactivity, and impulsivity may be the final path for many problems such as conflicts with parents and/or peers, inappropriate educational systems, or may even be associated with other disorders that are commonly observed in childhood and adolescence (Box 2.2). Therefore, a careful assessment of each symptom in the child's history and

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**Box 2.2 Potential differential (or comorbid) diagnoses**

- Oppositional defiant disorder or conduct disorders (may sometimes impose difficulties in the differential diagnosis)
- Autistic spectrum disorders, anxiety and mood disorders
- Acute adjustment disorders
- Attachment disorders
- Learning disorders (differential diagnosis to inattention)
- Intellectual disability (does not exclude the diagnosis of ADHD)
- Disruptive mood dysregulation disorder (DMDD)
- Family conflict, bullying, child abuse can also present with ADHD-like symptoms (alternative explanations or co-occurring problems)
- Chromosomal, metabolic, neurological or somatic disorders (e.g. fragile X syndrome, 22q11 deletion syndrome, petit mal epilepsy, migraine, hyperthyreosis) can masquerade as ADHD
- Use of medication, especially anticonvulsants, antihistamines, sympathomimetics, steroids

consideration of a range of differential diagnoses and co-existing conditions are always necessary for the diagnosis of ADHD (see Chapter 4, sections 4.2.1, 4.2.2). For instance, a child may show difficulty following instructions due to an oppositional defiant behaviour towards parents or teachers, which characterizes a symptom of an oppositional defiant disorder instead of ADHD. In most cases differential diagnoses can be addressed by a careful initial assessment, however in some situations observation over time is required (Taylor *et al.* 2004).

## 2.5 **Comorbid disorders**

The co-existence of several other types of psychopathology along with ADHD is very common in clinical and community samples (up to 80% in clinical samples) (Biederman and Faraone 2005; Yoshimasu *et al.* 2012). Clinicians should therefore be prepared to encounter a wide range of psychiatric symptoms in the course of managing patients with ADHD.

In Figure 2.1, the ADHD comorbid profiles in three different clinical samples from Brazil (Souza *et al.* 2004), the US (MTA Cooperative Group, 1999), and Europe (Steinhausen *et al.* 2006) are depicted suggesting a worldwide consistent profile of high comorbidity in ADHD samples.

### 2.5.1 **Oppositional defiant disorder and conduct disorder**

Both clinical and epidemiological studies show a high prevalence of comorbidity between ADHD and disruptive behavioural disorders (conduct disorder and oppositional defiant disorder), which ranges from 30% to 80% (median odds ratio of 10; conduct disorder in about 25% of cases). Conduct disorder and oppositional defiant disorder should often be seen not necessarily as a differential diagnosis or a comorbid condition, but as a complication. Both comorbidities predict the persistence of ADHD into adulthood and mediate the risk for the development of other problems, such as substance use, antisocial personality disorder, and
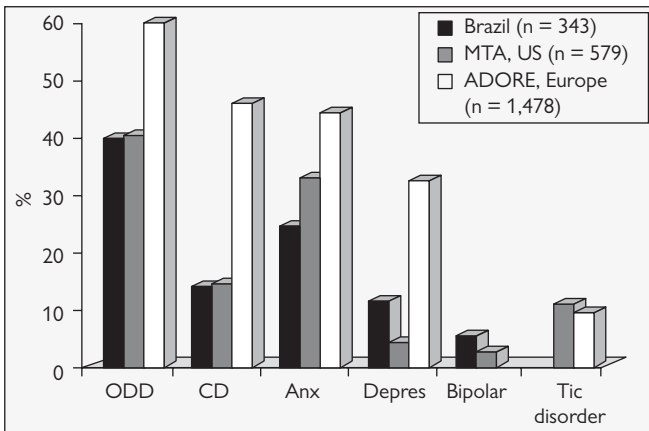


**Figure 2.1** ADHD comorbid profile in three studies: the MTA (MTA Cooperative Group, 1999), the ADORE (Steinhausen *et al.* 2006), and Souza *et al.* (2004; Brazil). Data are presented as percentages. In the Brazilian study, the comorbid profile is described only for one site (Porto Alegre) and no information is reported for tic disorders. In the MTA, only ADHD-combined type is included and several restrictions were applied to enroll patients with severe mood disorders. No information is available for bipolar disorder in the ADORE study. ODD—oppositional defiant disorder; CD—conduct disorder; Anx—anxiety; Depres—depression.

Reproduced from Coghill *et al.* (2008), with kind permission from Karger, Basel.

major depression, and index a higher severity (Hamshere *et al.* 2013). Hyperactive behaviour is a high risk factor for developing conduct disorder, even in children who showed a pure pattern of hyperactivity without conduct disorder at the beginning of their problems. Conduct disorder does not give rise to ADHD in the same way (Angold *et al.* 1999; Biederman and Faraone 2005).

### 2.5.2 **Emotional disorders**

There is also a significant comorbidity with anxiety disorders (up to 25%; median odds ratio of 3.0) and depression (15–20%; median odds ratio of 5.5). The reasons for the frequent co-existence of hyperactivity and problems of anxiety and depression are not well understood. Some children may develop low self-esteem and insecurity as a result of failures at school and interpersonal relationships. Emotional disorders are often overlooked (Angold *et al.* 1999; Biederman and Faraone, 2005; Willcutt *et al.* 2012).

### 2.5.3 **Bipolar disorder and disruptive mood dysregulation disorder**

Many children with ADHD have extreme and uncontrolled mood changes and a specialist referral is advised because the problems are often complex (Sobanski *et al.* 2010). Comorbidity with bipolar disorder needs to be considered, but the relationship between ADHD and paediatric bipolar disorder remains controversial (the two main areas of controversy are the role of cardinal symptoms—grandiosity and euphoria versus irritability and the relevance of episodicity for the diagnosis). Bipolar disorder is rare in pre-adolescents, even when severe irritability and anger are prominent, whereas ADHD is common among children and adolescents who display excessive anger and irritability.

Current evidence suggests that severe, non-episodic irritability may rather be a variant of depression, and children and adolescents with severe, non-episodic irritability seem to differ from those with bipolar disorder in longitudinal course, family history, and pathophysiological mechanisms. Thus a new diagnosis, disruptive mood dysregulation disorder, has been included in DSM-5 for children up to age 18 years who exhibit persistent irritability, intolerance of frustration, and frequent episodes of extreme behavioural dyscontrol. Most children and adolescents with the disorder have symptoms that also meet criteria for ADHD, which is diagnosed separately.

It is recommended that the diagnoses of bipolar disorder or bipolar disorder not otherwise specified should only be made in the presence of identifiable manic or hypomanic episodes, including a distinct change from baseline mood with concurrent alterations in behaviour (Baroni *et al.* 2009).

### 2.5.4 **Pervasive developmental disorders**

While ICD-10 and DSM-IV preclude the diagnosis of ADHD, if problems are better explained by autism or other pervasive developmental disorders, ADHD and symptoms of autistic spectrum disorders can often co-exist. Several studies have shown social deficits, peer relationship and empathy problems to be common in ADHD; both disorders share a substantial proportion of the genetic variance (Lichtenstein *et al.* 2010). DSM-5 does now allow a comorbid diagnosis of ADHD and autism spectrum disorder. Clinically, children with ADHD and autistic symptoms may respond to stimulants (though caution is needed in view of possible adverse effects). It is therefore desirable to recognize both types of symptoms when they are present (Taylor *et al.* 2004).

### 2.5.5 **Tic disorders**

Children with ADHD have an increased risk to develop comorbid tic disorders during their early school years. Similarly, about half of the cases with chronic tics or Tourette syndrome

also meet criteria for ADHD (Freeman *et al.* 2006). In these cases, the degree of psychoso-cial impairment is usually determined by ADHD. Usually, ADHD starts about two to three years before the tics, while in a smaller proportion of cases ADHD can be seen only after tic onset.

### 2.5.6 **Substance abuse**

Several studies have found evidence for earlier and increased use of alcohol, tobacco, and substance abuse in adolescents with ADHD compared to controls; a high prevalence of drug abuse or dependency is reported in adulthood (9–40%). Whilst controlling for comorbid dis-orders (particularly conduct disorder) substantially weakens this association, there is some evidence that non-comorbid ADHD in adolescents and adults does act as an independent risk factor for substance-use disorders (Szobot *et al.* 2007; Wilens *et al.* 2011).

### 2.5.7 **Language delays, learning disorders, and neuropsychological deficits**

In addition, children with ADHD may experience a wide range of other problems. Population studies suggest that mental retardation may be more common (up to 5–10 times) in ADHD than in children without ADHD (Simonoff *et al.* 2007).

Patients with ADHD are at risk for co-existing language disorders. Some studies have sug-gested that girls with ADHD may be particularly at risk of language development delay and current co-existing language disorders.

A variety of learning problems are associated with ADHD that need to be separately addressed both as regards assessment and interventions. About 25–40% of all patients with ADHD have major reading and writing difficulties. The overlap of ADHD and reading disor-ders seems to be largely accounted for by genetic overlap. Similarly, there is a considerable overlap between ADHD and specific disorder of arithmetical skills.

Furthermore, ADHD is associated with weaknesses in multiple neuropsychological domains, that is, global intellectual functioning, executive functions (motor response inhibi-tion, working memory, vigilance, and planning), processing speed, response variability, and a motivational style that is characterized by a significant aversion to delay (see also Chapter 3), even when comorbid disorders are excluded or controlled. Executive function weaknesses are associated with inattention symptoms more specifically and may be more severe in those individuals with ADHD and comorbid reading disorder. However, individual differ-ences in executive functions do not explain a high amount of variance in ADHD symptoms (Willcutt *et al.* 2008).

### 2.5.8 **Developmental coordination disorder**

ADHD is often accompanied by problems in sensory motor coordination, especially seen as poor handwriting, clumsiness, poor performance in sports, and marked delays in achieving motor milestones. Many children with ADHD fulfil criteria of a developmental coordination disorder. Interestingly, the rate is equally high in those with severe and moderate variants of ADHD, and also in those with subclinical variants of the disorder (Reiersen *et al*. 2008).

### 2.5.9 **Sleep problems and other comorbidities**

Children with ADHD are more likely to have sleep problems. These problems include dif-ficulties in falling asleep and more disruptions during the course of the night (Cortese *et al.* 2006). Recent studies suggest that there may be also a slightly increased prevalence of allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and urticarial (Chen *et al.* 2013), as well as of obesity (Cortese *et al.* 2013).

Treatment considerations of several specific groups are described in Chapters 5 and 6.

## 2.6 **Gender aspects**

ADHD is more common in males than in females in the general population. In the systematic review mentioned above including 102 epidemiological studies, the pooled ADHD prevalence for boys was 2.45 times higher than the one detected for girls (Polanczyk *et al.* 2007). In clinic-referred samples, ratios between 6:1 and 9:1 might be found but this may decrease with age.

The increased prevalence among girls found in epidemiological samples compared to clinical samples suggests that there may be greater barriers to recognition, referral, and diagnosis of ADHD in girls than in boys, or that the clinical severity may differ between both genders (Gaub and Carlson 1997).

The latter explanation seems more likely; among children with ADHD identified from epidemiological samples, girls with ADHD appear to be less impaired in a number of domains, such as hyperactivity, inattention, impulsivity, and externalizing problems, than non-referred boys with ADHD; however, girls and boys with ADHD identified from clinic-referred samples are more similar than different, except for a trend for greater severity of inattention, greater intellectual impairments, and more internalizing problems among girls. Thus, they are more often diagnosed as predominantly inattentive than boys with ADHD. Developmental patterns may differ. With age, girls with ADHD seem to be increasingly rejected by peers while the social status of boys with ADHD remains stable (Gaub and Carlson *et al.* 1997; Rucklidge 2008).

## 2.7 **Prognosis, course, and outcome**

In each developmental stage, ADHD is associated with various negative outcomes, which may be exacerbated by the presence of comorbid disorders. Children and adolescents with ADHD may face problems in many different domains, including school problems and academic underachievement, low self-esteem, difficulties in parent–child interactions, sibling interactions, and peer relationships, and poorer psychosocial adjustment. Children with ADHD are often rejected by peers even after only brief interactions and have fewer friends, they tend to choose other ADHD youths as playmates, and have difficulty regulating their emotions. Furthermore, they are at increased risk for all types of accidents from early childhood. Social difficulties may be more extensive if the child also has ODD or CD. However, ADHD as such is a strong risk factor for later psychiatric diagnosis, antisocial behaviour, and social and peer problems, even after allowing for a co-existent conduct disorder. Poor self-esteem is thought to be a mediating factor of future adverse outcomes, such as depression, deviant peer choices, and substance abuse in children with ADHD.

Academic deficits, school-related problems, and peer neglect tend to be most associated with symptoms of inattention, whereas peer rejection is more strongly linked to hyperactivity or impulsivity (Willcutt *et al.* 2012).

Outcomes over the life span differ widely. Changes in symptoms across childhood and adolescence may be a consequence of natural developmental processes seen in all children, but symptoms may also diminish due to learned skills, coping strategies, and environmental restructuring.

The majority of children diagnosed with ADHD while in elementary school continue to have significant manifestations of the disorder throughout adolescence. Adolescents with ADHD are often emotionally immature and tend to feel more comfortable interacting with younger children.

### 2.7.1 **Preschoolers**

Although ADHD is most frequently identified during elementary school years, epidemiologic data suggest that core symptoms are frequently present from early childhood and may be noticed as early as three years of age. Difficult early temperament features may even be precursors. Of the core symptoms, hyperactivity is likely more noticeable than symptoms of

inattention which may not become apparent until the child enters elementary school. While current data suggest that once age adjustments have been made, there is some equivalence between pre-school and school-based ADHD in terms of symptom structure and impairment (Döpfner *et al.* 2004), the diagnosis of ADHD should be made with caution before the age of six years, because more intense activity and a short attention span may occur more frequently in normal pre-school children than in school-aged children, and the developmental course and its persistence may still be more variable. Mild delays in language, motor, or social development are not specific to ADHD but often co-occur. Associated features may include low frustration tolerance, irritability, or mood lability.

### 2.7.2 **Adults**

While ADHD symptoms, as a whole, decline with age and hyperactivity/impulsivity symptoms tend to diminish after puberty or present differently with age, symptoms of inattention do not, and symptoms of other disorders, such as conduct and anxiety disorders, increase with age (Faraone *et al.* 2006). A very large majority (60–85%) of children with ADHD will continue to meet criteria for the disorder during the teenage years. Longitudinal studies have documented that ADHD/HKD persists through childhood into adolescence and adulthood in many cases. The extent to which ADHD persists into adulthood depends heavily on how it is defined. About 65% of children with ADHD experience partial remission in adulthood (with significant clinical impairments), and the full ADHD diagnosis is met in approximately 15% at age 25, when full diagnostic criteria were required (Faraone *et al.* 2006).

The risk factors determining the persistence of ADHD diagnosis in adults remain unclear. However, some studies suggested that higher persistence is associated with (Lara *et al.* 2009; Biederman *et al.* 2011):

- family history of ADHD
- adversities during childhood, including family adversity
- increased severity of ADHD symptoms
- presence of comorbidities (e.g. major depressive disorder, high comorbidity, paternal (but not maternal) anxiety mood disorder, and parental antisocial personality disorder)

Evidence from population studies points to substantially elevated rates of comorbid psychiatric disorders in adults with ADHD (Kessler *et al.* 2006). Adults with ADHD have a particularly high risk for antisocial personality disorder (up to ten times that of controls, i.e. about 20% of the cases) and comorbid substance abuse disorder (four to eight times that of controls). Compared to control populations, adults with ADHD have also elevated rates of mood disorder (twice to six times), anxiety disorders (twice to four times), relationship dysfunction (twice) and learning disorder. Additional psychopathology may include disorganized behaviour related to executive function deficits in attention, behavioural inhibition, problems with verbal long-term memory, problem-solving ability, and planning and emotional dysregulation is common in adulthood (Hervey *et al.*, 2004). Impulsive emotions, including impatience, low frustration tolerance, hot-temperedness, quickness to anger or volatility, irritability, are frequently present.

While many children with ADHD will grow up without persistent problems, patients with ADHD are at increased risk of a worse outcome across the life span (Kessler *et al.* 2006; Barkley and Fischer 2010). Thus, adult ADHD is associated with:

- higher rates of several psychiatric comorbidities, such as disruptive behaviour disorders, anxiety, mood disorders, and substance-use disorders. However, although substance-use disorders and antisocial personality disorder are relatively more frequent among adults with ADHD in the general population, the disorders are present in only a minority of adults with ADHD. Low self-concept and low self-esteem.

- significant deficits in work performance and greater levels of unemployment, sub-employment, and job changes compared to control groups. Workplace safety is also an issue, with ADHD associated with increased risk of workplace accidents and injuries.

- family dysfunction such as divorce and poor quality of family relations; difficulties in peer relationship and family functioning that often affect children and adolescents with ADHD frequently extend into adulthood. Thus, adults with ADHD also report higher rates of separation and divorce. Parents with ADHD may face problems in parenting effectively due to their symptomatology.

- accidents and driving impairments; adults with ADHD are at greater risk of adverse driving outcomes such as greater numbers of motor vehicle accidents and traffic violations.

- increased sexual risk-taking behaviours; adolescents and adults with ADHD may take greater sexual risks—for example, more teen pregnancies.

- Social and legal problems; although the vast majority of individuals with ADHD will never become involved with crime, research indicates a consistent association between ADHD and delinquency, antisocial and criminal behaviour, and recidivism; it appears that the symptoms of hyperactivity/impulsivity, but not inattention, contribute to the risk for criminal involvement over and above the risk associated with early conduct problems alone.

- by early adulthood, ADHD is associated with an increased risk of suicide attempt, primarily when comorbid with mood, conduct, or substance-use disorders (Agosti *et al.* 2011).

Overall, burdens for families as well as the economic costs for society caused by ADHD are substantial.

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## Chapter 3

# ADHD pathogenesis

Edmund Sonuga-Barke

| Key points |
| --- |
| • ADHD has a complex etiology. Multiple genetic common and rare variants and early operating environmental risk factors of small effect act and interact to create a spectrum of neurobiological liability. |
| • Brain structure and function is disrupted in subtle ways across multiple systems that regulate both intrinsic spontaneous and extrinsic task elicited cognition and action. |
| • ADHD performance can be normalized in certain contexts, highlighting the importance of motivational and energetic processes. |
| • ADHD is not a single pathophysiological entity, there is growing evidence for different subgroups of individual patients with different pathogenic and cognitive deficit profiles. |

ADHD has a complex pathogenesis. A growing body of evidence supports a model in which multiple genetic and environmental factors interact during pre-natal and early post-natal development to increase an individual's neurobiological liability to ADHD. This in turn leads to subtle alterations within multiple brain systems producing diverse deficits across multiple neuropsychological domains. Such a model acknowledges the high degree of pathogenic heterogeneity in the ADHD population, with marked individual differences with regard to the extent to which particular genetic, environmental, and neuro-pathophysiological processes are implicated in the disorder. The possibility that the pathways between early-established risk and disorder can be moderated by later socio-environmental factors is also being taken increasingly seriously.

## 3.1 Etiology

### 3.1.1 Genetics

Genetic factors are implicated in ADHD—although the mechanisms of effect are not understood at present, they are without doubt complicated: ADHD is not a genetic disorder in any simple sense. ADHD is familial and highly heritable. Twin studies suggesting heritability estimates of 60–90% (Thapar *et al.* 2000) raised initial expectations that it would be relatively easy to identify the gene or patterns of genes responsible for the condition. This has not been the case. Candidate gene studies focusing in particular on genes regulating neurotransmitter systems thought to be implicated in ADHD identified a number of replicable associations with common variants in dopamine genes with putative functional significance for ADHD (D4 and D5 receptors and the dopamine transporter; Faraone *et al.* 2005) with suggestive evidence for a role of genes in other neurotransmitter systems (e.g. norepinephrine and

serotonin systems). Effect sizes for individual variants are extremely small, accounting even when aggregated, for a limited fraction of variation in the ADHD within the population. This picture is reinforced by non-hypothesis-driven quantitative searches for genes. Linkage studies have been largely unsuccessful in identifying common disease susceptibility loci for ADHD (e.g. Hebebrand *et al.* 2006). Genome-wide association scans, including many hundreds of thousands of genetic markers, although confirming an overall genetic contribution to ADHD (Stergiakouli *et al.* 2012) have so far failed to find good evidence for effects significant at the level of the whole genome (Neale *et al.* 2010). Evidence is emerging from cross-disorder analyses that functional risk variants coding for activity within nerve cells may be shared by ADHD and other major psychiatric disorders (Smoller *et al.* 2013). The recent shift in focus from common to rare variants has provided evidence for increased rate of *de novo* and inherited chromosomal deletions and/or local duplications (so-called copy number variants, CNVs) in ADHD (Williams *et al.* 2012).

Although definitive answers are still lacking, a number of inferences can be drawn consistent with the current genetic evidence. First, there are almost certainly no major genes accounting on their own for a substantial proportion (e.g. >5%) of ADHD variation in the population. Second, common variants of multiple genes with very small effect are likely to be implicated in many cases of ADHD, individually and in combination with each other. Third, rare genetic variants may have much larger effects for specific, affected individuals but very small effects at group level. Fourth, the diagnostic specificity for some genes may be lower than initially anticipated, with effects shared across different disorders. Fifth, the mismatch between the high heritability of ADHD revealed by twin studies and the relatively small amount of variance captured even when effects are pooled suggests that environmental factors play a more important role in the etiology of ADHD than previously thought and that genetic and environmental variants are likely to interact in creating the risk for ADHD. Finally, etiological heterogeneity is high in ADHD with individual patients being affected by different combinations of genetic risk factors in different ways. This means that although the effect of a gene when assessed across the whole ADHD population may be small and of limited importance, it may be especially important for a subgroup of patients. A major challenge for future ADHD research involves attempts to partition this heterogeneity to produce more etiologically homogeneous groupings in which the role specific genes and environments play may be more powerful. This could be achieved be exploring gene x environmental effects (as described above and reviewed below) as genes may only be implicated in individuals exposed to a specific environment (and vice versa). This could also be achieved by using alternative phenotypes within the broader ADHD category that might define a more etiologically homogeneous subtype. This can be done at the clinical or (exo-)

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### Box 3.1  The genetic basis of ADHD

- Twin studies have demonstrated that ADHD is highly heritable.
- Pooled measured genetic effects are small at the group level – ADHD appears genetically heterogeneous and has a complex genetic architecture.
- Genome-wide approaches, although supporting the genetic basis of ADHD in general, have not been sufficiently powered to definitively identify individual common genetic risk variants.
- ADHD samples are enriched for rare genetic variants. Current data are consistent with the idea that effects arise from the action and interaction of a combination of multiple common (e.g. polymorphisms) and rare (e.g. deletions, duplications) functional genetic variants known to affect activity across multiple brain systems.

phenotypic level where the genetic factors implicated in patients with different clinical profiles (more severe vs less severe or inattentive vs hyperactive impulsive) can be investigated (see Box 3.1). It can also be done at the endo-phenotypic level where the genetic profile of patients with different neurobiological or neuropsychological characteristics can be explored (Doyle *et al.* 2005).

### 3.1.2 **Environment**

The strategy of studying genes in isolation from environments was never likely to be optimal in the case of a complex and heterogeneous disorder such as ADHD. Indeed, evidence from many different sources suggests that pre-, peri- and post-natal environmental factors play a role in the pathogenesis of ADHD (Taylor and Rogers 2005). The situation with regard to the role of environmental factors is in some ways similar to that found for genetics. There are multiple environmental influences of small effect implicated in the pathogenesis of the ADHD. *Pre-natal factors* associated with maternal lifestyle during pregnancy, have been implicated in ADHD etiology. The association with maternal smoking during pregnancy has been replicated in a number of studies. Maternal alcohol consumption may also be important but these effects are less marked if foetal alcohol syndrome is taken into account (Linnet *et al.* 2003). The effects of pre-natal exposure to both prescribed therapeutic and non-prescribed drugs of abuse (i.e. cocaine) have been investigated, although evidence is inconclusive and their effects hard to disentangle from maternal mental state during pregnancy. Evidence that maternal mental health might be important also comes from replicated findings that maternal stress during pregnancy may play a role, possibly via its effects on cortisol secretion (O'Connor *et al.* 2003). *Peri-natal factors* have also been implicated with a twofold increase in ADHD in very low birthweight children and an increased rate of pregnancy and birth complications in ADHD individuals (Taylor and Rogers 2005). Factors within the *post-natal environment* seem also to play a role. The child's physical environment seems important. For instance, diet may play a small but significant role. Recent randomized controlled trials (RCTs) support the idea that diet involves general effects that extend both beyond clinically diagnosed cases and those who seem to be influenced by idiosyncratic allergic reactions (McCann *et al.* 2007). A role for malnutrition and dietary deficiency in ADHD has been proposed. Social, and more specifically family adversity, appears to be implicated in the course and persistence of the condition rather than in its onset. ADHD is associated with social disadvantage (Russell *et al.* 2013). It is also higher in samples of foster children who have experienced abuse (McMillan *et al.* 2005). ADHD is associated with negative, intrusive, and harsh parenting, but typically these are viewed as a response to the child's challenging behaviour rather than a cause of the disorder. However, the relationship is likely to be complex and the possibility that inappropriate parenting can exacerbate the ADHD presentation, especially with regard to the emergence of significant impairment, should not be ruled out (Seipp and Johnston 2005). However, it seems clear that inappropriate parenting is associated with the onset of comorbidity (Ostrander and Herman 2006) in ADHD children.

### 3.1.2.1 *The challenge of inter-correlated genetic and environmental risks*

Teasing apart the influence of these individual risks for ADHD is extremely challenging because of the inevitable interrelations between individual environmental risks and other risks relating to lifestyle, social class/economic adversity, and maternal personality. Furthermore, this mix of adversity and risk is also likely to be correlated with genetic risk, and it may be that the reported effects are simply the product of correlations between environments and genes, and that patterns of environmental adversity are simply marking an increase in genetic risk. These correlations can take two forms, examples of which have already been mentioned. First, risk environments experienced by the child may be correlated with genes shared with parents as

| Box 3.2 The environmental basis of ADHD |
| --- |

- The environment is also important in ADHD pathogenesis.
- Exposures to prenatal adverse environments (e.g., maternal smoking) and negative perinatal experiences is associated with increased risk of ADHD.
- Post-natal dietary (exposure to artificial additives or dietary deficiencies) and social factors (e.g. social deprivation, maltreatment, parental mental illness) are also associated with increased ADHD risk.
- Environmental effects may in part be driven by correlated genetic risk operating within families.
- Initial evidence supports a role for the moderating effects of environmental factors on genetic risk through gene-environment interactions and the regulation of gene expression.

in the case where maternal smoking during pregnancy may be correlated with genetic risk for ADHD shared by parent and child (passive gene–environment correlation; Thapar *et al.* 2009). Equivalent mechanisms could plausibly operate in relation to many other risks linked to parental likestyle, mental health, and socio-economic status. Second, risk environments may be evoked by genetically based characteristics in the child as when ADHD symptoms elicit maternal hostility (active gene–environment correlations), as appears to be the case in adoptive parents of children at risk for ADHD (Harold *et al.* 2013). However, even in designs that allow genetic factors to be controlled, environmental main effects sometimes persist. For instance, children exposed to extremely depriving institutional environments from very early on in their formative years appear to be at marked risk for ADHD independent of the operation of either passive of evocative gene–environment correlational processes (Rutter *et al.* 2007).

#### 3.1.2.2 *Gene by environment interplay*

Given the limited explanatory power of simple main effects of genetic and environmental risks, more complex models of the etiology of ADHD incorporating gene–environment interplay need to be considered. Emerging evidence does support gene x environment interactions in ADHD (Nigg *et al.* 2010). In gene x environment interactions the effect of a gene is moderated by exposure to a particular environmental risk (or vice versa) so that its effects are larger following risk exposure than where no exposure occurs. Most studies so far have focused on the dopamine genes DAT1 and DRD4, providing evidence that exposure to pre-natal risks such as *in-utero* exposure to smoking and alcohol during pregnancy moderates the effect of these genes (e.g. Becker *et al.* 2008). Serotonin genes (e.g. 5-HTT-LPR) interact with social adversity to increase risk for externalizing problems including (Retz *et al.* 2008) but have not been specifically implicated in ADHD as yet. How might these effects operate? There are a number of hypotheses. First, environmental exposures may moderate gene expression—that is, they may 'switch on' or 'switch off' a particular ADHD-susceptibility gene. Alternatively a gene may alter the degree of exposure to an environment and the way it is experienced, or may increase resilience to its negative effects. Understanding epigenetic mechanisms in ADHD also represents an important research priority (see Box 3.2).

Our current knowledge of ADHD etiology provides some pointers for clinicians which will help them to advise patients and their parents on cases of ADHD. Some of these are outlined in Table 3.1.

| Table 3.1 Clinical implications of current understanding of the etiology of ADHD |
| --- |
| Environmental influences to include in the clinical history |
| *Pregnancy* <ul><li>alcohol</li><li>smoking</li><li>prescribed drugs (especially psychotropics and anticonvulsants)</li><li>illegal drugs</li><li>toxaemia, haemorrhage</li><li>rashes and fever</li><li>psychological stress</li><li>foetal distress</li></ul> *Peri-natal* <ul><li>gestational age and birth weight</li><li>Apgar below 5</li><li>hypoglycaemia</li><li>respiratory distress</li><li>encephalopathy (e.g. fits)</li></ul> *Post-natal* <ul><li>neurological illness or injury</li><li>severe deprivation</li><li>abuse and neglect</li><li>parental mental health</li><li>sub-nutrition/diet</li></ul> |
| Genetic counselling |
| *When counselling is requested, always* <ul><li>clarify what parents wish to know</li><li>ask about affected relatives (and if there are many test as for low IQ below)</li><li>physical examination for specific genetic disorders</li></ul> *In the presence of ordinary IQ* <ul><li>no case for molecular genetic screening</li><li>recurrence risk substantially raised for siblings</li><li>exact prediction not possible</li></ul> *In the presence of intellectual disability* <ul><li>routine chromosome examination</li><li>fragile-X</li><li>other specific tests (e.g. 22q11) if condition suspected clinically</li><li>consider FISH* for telomeric rearrangements</li></ul> |
| *FISH: fluorescence in-situ hybridization. |

## 3.2 **Pathophysiology**

The brain of individuals with ADHD are disrupted in subtle but important ways across a wide range of regions and systems—both structurally and functionally. The high levels of pathogenic heterogeneity seen in ADHD populations affecting etiological processes are also observed in individual differences in brain structure and function.

### 3.2.1 **Brain structure**

Meta-analyses of MRI structural findings support subtle alterations in the size, structure, and integrity of a broad range of brain regions and networks in patients with ADHD. Children

with ADHD have significantly smaller brains in general, with the largest reduction in specific structures being found for cerebellum, corpus callosum, cerebrum (especially the right lobe), right caudate, and specific frontal regions (Valera *et al.* 2007). Grey matter differences have also been shown in the putamen/globus pallidus (Ellison-Wright *et al.* 2008), and regions associated with emotion and motivation such as the amygdala/insula and ventral striatum have been identified (Plessen *et al.* 2006). There is also evidence of cortical thinning in the region of the dorso-lateral prefrontal cortex (Batty *et al.* 2010). Studies of white matter integrity using diffusion tensor imaging have found abnormalities in the frontal fibre pathways (van Ewijk *et al.* 2012). Stimulant medication used to treat ADHD may normalize certain aspects of brain structure and function (Schweren *et al.* 2013).

### 3.2.2 **Neurochemistry**

Genetic, imaging, and pharmacological studies implicate catecholamine (especially dopamine) dysregulation in ADHD (Oades *et al.* 2005). Single photon emission tomography (SPECT) and positron emission tomography (PET) data relating to transporter occupancy are consistent with the notion of dopamine depletion in ADHD (Spencer *et al.* 2005, although the effects of prior stimulant use complicates the picture; Fusar-Poli *et al.* 2012). This is also consistent with evidence that dopamine (DA) and norepinephrine (NE) agonists (e.g. methylphenidate and atomoxetine) reduce ADHD symptoms by increasing extracellular DA and NE. Brain networks implicated in ADHD deficits are heavily innervated by DA and NE branches and medication targeting these systems improves functioning across neuropsychological domains deficient in ADHD (Boonstra *et al.* 2005) and normalize patterns of brain activity in key regions (e.g. Bush *et al.* 2008). The catecholamine hypothesis is also consistent with data implicating polymorphisms in genes affecting catecholamine function, especially dopamine (Faraone 2005). Furthermore, ADHD can be mimicked in animal models with pharmacological lesions and gene knockout of catecholamine systems (Madras *et al.* 2005). However, when interpreting this evidence one needs to be aware that catecholaminergic drugs can have effects in the absence of ADHD, and that neural systems are complex and plastic: altered neurochemical responses could be directly linked to causes of ADHD or could be a consequence of the condition or a marker of some more fundamental neurobiological process (see Box 3.3). Finally, it is extremely difficult to isolate the role of any one neurotransmitter given the complex patterns of interaction between DA and NE and other systems such as serotonin and acetylcholine.

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**Box 3.3  The neurobiology of ADHD**

- Structural imaging studies show that ADHD children's brains are significantly smaller than unaffected controls.
- A diverse range of brain networks regulating key cognitive, motivational, and emotional processes are subject to subtle but important disruptions in structure and function.
- Evidence exists for reduced functional and structural connectivity within affected networks.
- Functional effects are task specific with effects most consistent in the prefrontal cortex and the neo-striatum on tests of inhibitory control, while alternations within ventral networks (orbito-frontal cortex–ventral stratum) have been observed on reward-processing tasks.
- Brain functioning is disrupted even when the brain is not actively processing externally present information (i.e. at rest).
- Genetic, pharmacological, imaging, and animal models highlight the key role of dopamine dysregulation in the neurobiological basis of ADHD.
- The high degree of pathophysiological heterogeneity in the ADHD population raises the possibility of neurobiological sub-types.

### 3.2.3 **Brain function and neuropsychology**

As is the case with brain structure, meta-analyses of functional imaging studies highlight the role of multiple brain systems in ADHD pathophysiology (Cortese *et al.* 2012).

Executive function is altered in a number of ways (Willcutt *et al.* 2008) linked to hypo-activation in brain circuits anchored in the prefrontal cortex and the dorsal striatum (Hart *et al.* 2013). The reward network is a second brain network implicated with the ventral striatum/nucleus accumbens and the orbito-frontal cortex displaying deficient responses to cues of anticipated rewards (e.g. Plichta *et al.* 2009). ADHD individuals seem especially sensitive to delayed reward (e.g. Marco *et al.* 2009), perhaps because of increased discounting of the value of delayed rewards (Sagvolden *et al.* 2005) or delay aversion (a negative affective state induced by delay cues and imposition; Sonuga-Barke *et al.* 2008). Timing functions underpinned by cortico–thalamo–cerebellar circuits are also disrupted (Smith *et al.* 2012). The highly context-dependent nature of ADHD performance is consistent with the notion that ADHD children have particular difficulties adapting their state while preparing to respond to meet the changing demands of their environments. This is thought to be particularly obvious during periods of under- or overactivation where children with ADHD may be unable to apply effort to regulate sub-optimal states (Sergeant 2005). Consistent with this view is the finding that ADHD children perform poorly on tasks with very fast or very slow stimulus presentation (Metin *et al.* 2012).

Recently, the research focus has shifted from deficits in brain networks responding to extrinsically presented information to examinations of spontaneous brain activity in so-called resting networks. One such network is the default mode network. It is centered on the mid-line structures—the medial prefrontal cortex and the posterior cingulate cortex/precuneus—which in optimal conditions are active during rest when they are associated with a range of introspective or reflective mental states and deactivate during the transition to task performance (Raichle and Snyder 2007). Activity within this network during task performance is associated with intra-individual variability and intermittent errors thought to reflect attentional lapses In ADHD there is reduced connectivity between the key nodes of the default mode network (Fair *et al.* 2010), and between that network and other resting state networks (Tomasi *et al.* 2012), and reduced attenuation during rest-to-task transitions (e.g. Liddle *et al.* 2011).

#### 3.2.3.1 *Are there pathophysiological subtypes?*

Given the heterogeneous nature of the pathogenesis of ADHD, understanding the relationship between cognitive energetic, motivational, and executive processes in ADHD is a major research goal (Sonuga-Barke *et al.* 2010). It now seems highly unlikely that there is just one core deficit that explains the condition suggesting a single pathophysiological entity. It is more likely that the disorder in different subgroups of the ADHD population is mediated by deficits in different and distinctive pathophysiological processes. Indeed, deficits in executive and non-executive processes and motivational and energetic processes are relatively modest when seen at the level of diagnostic group as a whole, and each type of deficit therefore may affect only a minority of cases. In one relevant study, Solanto and colleagues (2001) found that delay aversion and executive dysfunction were unrelated constructs each implicated in the disorder, but each affecting a different subsection of ADHD individuals. Following on from this, a number of multiple pathway or process models have been proposed to account for these sort of data. The question of how other deficits associated with ADHD, such as timing and state regulation, map onto this dichotomy is currently unknown and needs to be investigated.
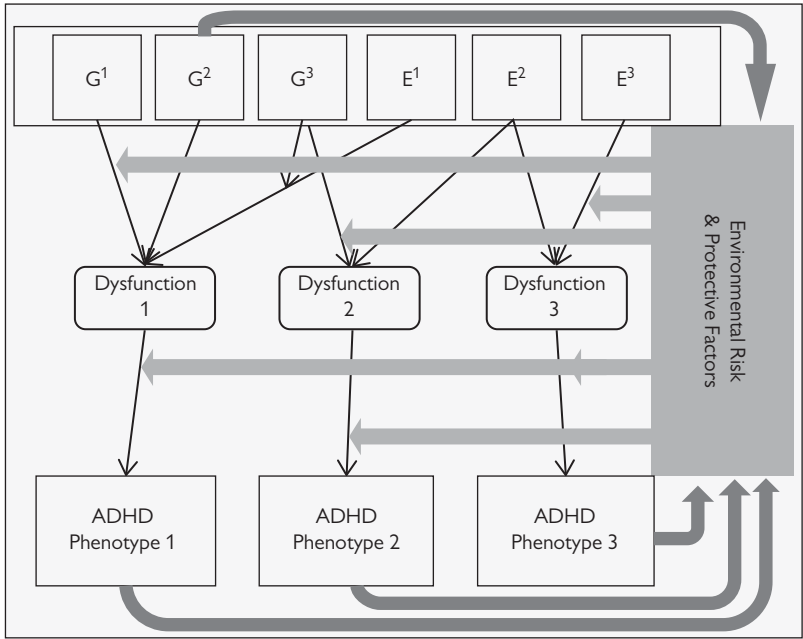
**Figure 3.1** The interaction between genetic (G) and environmental (E) causal factors mediated by different forms of dysfunction in different patients leading to different clinical outcomes with reciprocal effects between causal factors, the social environment and the clinical outcome.

## 3.3 **Conclusion**

ADHD has a complex and heterogeneous pathogenesis. A reasonable working hypothesis is that multiple genes and environments interact to create a spectrum of biological risk, the effects of which are mediated by a range of underlying neurobiological deficits and moderated by significant environmental and genetic factors. The disorder is heterogeneous, with different children displaying different psychopathological and pathophysiological profiles. While a developmental framework offers a way of understanding this complexity and partitioning this heterogeneity, the longitudinal data do not yet exist to disentangle the complex, dynamic, and reciprocal patterns of interactions between factors and levels of analysis required. Figure 3.1 provides an illustration of a framework for understanding the complex pathogenesis of ADHD.

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# Assessment

David Coghill

> ### Key points
>
> - The diagnosis of ADHD is based on clinical judgement of integrated data gathered from multiple sources.
> - ADHD is best assessed by clinical interviews.
> - These can be augmented by:
>   - questionnaires
>   - direct observations
>   - neuropsychological measures.
> - Education of staff at a primary care level, and education about ADHD is essential to ensure that children with ADHD are promptly identified and referred.
> - A comprehensive assessment for ADHD is complex and often time consuming. Those conducting these assessments need to be well trained.
> - The purpose of an 'ADHD' assessment is not only to confirm or exclude the presence of ADHD but also to identify whether there are any other problems or disorders that are causing impairment.
> - At the end of the assessment process the clinician should have developed a comprehensive formulation that comprehensively describe the patient's problems.

## 4.1 Introduction

As indicated in Chapter 2, ADHD is a complex disorder wherein the core problems of impairing inattention, hyperactivity, and impulsivity frequently occur alongside other disorders and difficulties (see Box 2.2, Chapter 2). As a consequence, the assessment of ADHD cannot occur in a vacuum and must be considered as part of a comprehensive assessment process. A further complication to the assessment process arises due to the fact that, notwithstanding the availability of various tools that can assist the assessment, ADHD cannot be diagnosed by using a simple biological test. Rather, it involves the integration of information from different sources and a clinical decision-making process able to resolve conflicting observations and information. The diagnosis is, however, supported by a strong evidence base and there are a range of validated questionnaires and interview schedules available to support the assessment process. It is sometimes, but not always, helpful to supplement the information gathered from the child/young person, parents, carers, other family members, teachers and others, with direct observation. A (neuro) psychological assessment can also sometimes be helpful to assess cognitive strengths and difficulties. At the end of the process the clinician will need to determine a principal and differential diagnosis, a judgement about the presence of any comorbid disorders, and develop a formulation that places these diagnoses in context.

First we present a brief overview of a series of clinical toolkits that can assist in the evidence-based approach to the assessment of ADHD. We will then discuss the various approaches to psychological assessment of ADHD. Following this we present schematically an approach to the assessment process designed to help clinicians organize their assessments in a structured manner that facilitates good clinical practice and the ongoing evaluation and audit of clinical pathways and processes.

## 4.2  **Clinical assessment tool kit**

Since ADHD manifests itself behaviourally, three general (complementary) clinical proce-dures are used to assess the child empirically: interviews, questionnaires, and observa-tions. In this chapter we present primarily instruments currently used in English-speaking countries. Fortunately many of the instruments discussed have been translated into various European and Asian languages. We do however recommend that clinicians wishing to use these international versions check the data concerning validity and reliability of local ver-sions before use.

### 4.2.1  **Interview schedules**

Although many clinical assessments will be conducted via a standard clinical history and exami-nation, there are occasions where a more structured assessment is useful. In particular, clini-cians who have not had a full psychiatric or clinical psychology training may find it useful to use a

formal interview schedule to guide this part of the assessment process. Two types of interview schedule are available: the structured interview where the questions are fixed and there is an algorithm converting answers into a diagnosis, and the semi-structured clinical interview where the clinician is given a degree of flexibility with respect to the questions asked and then evalu-ates the answers and reaches a decision as to whether the symptom is present or not. Examples of these two types of interviews are the structured Diagnostic Interview Schedule for Children (DISC-IV; Shaffer *et al.* 2000), which is based on DSM-IV, and the semi-structured Parental Account of Children's Symptoms (PACS; Taylor *et al*. 1986) and Kiddie-SADS (Kaufman *et al*. 1997). In some settings the Development and Well-being Assessment (DAWBA; Goodman 2000), another structured interview, may be of particular interest, as it is possible for parents to complete the interview online and for it to be scored prior to attendance at the clinic for a face-to-face assessment. A list of commonly used interviews is given in Table 4.1. While most interviews are still based on DSM-IV rather than the newer DSM-5 this is not really a problem due to there being only minimal changes in the diagnostic criteria between the two versions

| Table 4.1  Clinical interviews for the assessment of ADHD | | |
|---|---|---|
| Interview | Full title | Reference |
| CAPA | Child and Adolescent Psychiatric Assessment | Angold and Costello 2000 |
| DAWBA | Development and Well-being Assessment | Goodman 2000 |
| DICA | Diagnostic Interview for Children and Adolescents | Reich 2000 |
| DISC | Diagnostic Interview Schedule for Children | Schaffer *et al.* 2000 |
| K-SADS-PL | Schedule for Affective Disorders and Schizophrenia for School-age Children | Kaufman *et al.* 1997 |
| PACS | Parental Account of Children's Symptoms | Taylor *et al.* 1986 |

and, most importantly, that the symptoms, whilst better described in the new version, are essentially the same in both. A need to be able to assess to both the DSM-5 and ICD-10 diagnostic criteria, to be able to extrapolate diagnoses under both sets of rules has led to the development of computer algorithms for easy comparison. The Hypescheme is a good example.

### 4.2.2 **Questionnaires**

Questionnaires also fall into two classes: broadband questionnaires, which assess for a wide range of psychopathology and allow the clinician to screen for several disorders, and narrowband, which are specific instruments designed to screen for a particular condition (Table 4.2). An example of the former is the Child Behaviour Checklist (CBCL; Achenbach 1991), and of the latter, the Conners Rating Scales (Conners 1978). Some instruments are multisource (teacher and parent and self-respondent) and multidimensional (various types of psychopathology measured) such as the Behavioural Assessment System for Children (BASC; Reynolds and Kamphaus 1992). Questionnaires vary in length, test retest reliability, and the age range originally used to generate normative data. Careful evaluation of the psychometric properties should be undertaken prior to their use. An overview of several common instruments is presented in Table 4.2.

In clinical practice, it is useful to have a standardized teacher telephone interview to ensure standardized practice. Several tools specifically designed for this purpose are available; (e.g. Holmes *et al.* 2004; Mota and Schachar 2000). Alternatively, it is possible to use the ADHD-RS or SNAP-IV as a semi-structured interview (as is frequently done when measuring outcome in clinical trials).

Since children referred for ADHD often present with a considerable variety of associated disorders and deficits it is important to routinely screen for these. Table 4.3 provides a set of instruments that can be used to screen and assist the initial evaluation of these difficulties. These do not all need to be included as routine but should be considered when the information

| Table 4.2  Questionnaires used in the assessment of ADHD | | |
|---|---|---|
| Abbreviated title | Full title | Reference |
| Broadband questionnaires (general psychopathology) | | |
| CBCL | Child Behaviour Checklist | Achenbach 1991a |
| TRF | Teacher Rating Form | Achenbach 1991b |
| BASC | Behavioural Assessment System for Children | Reynolds and Kamphaus 1992 |
| SDQ | Strengths and Difficulties Questionnaire | Goodman 1997 |
| Narrowband questionnaires (ADHD) | | |
| CPRS-R CTRS-R | Conners Parent and Teacher Rating Scales, Revised | Conners 1998a and 1998b; Goyette *et al.*1978 |
| ADHD-RS | ADHD Rating Scale, IV | DuPaul *et al.* 1998 |
| SNAP and SNAP-IV | Swanson, Nolan, and Pelham (DSM-IV version) | Swanson *et al.* 1998 |
| SWAN | Strengths and Weaknesses of ADHD—Symptoms and Normal Behaviour | Swanson *et al.* 2005; Hay *et al.* 2007 |
| SKAMP | Swanson, Kotkin, Atkins, McFlynn, and Pelham Scale | Wigal *et al.* 1998 |

| Table 4.3  Questionnaires used to assess for disorders commonly associated with ADHD | | |
|---|---|---|
| Purpose | Title | Reference |
| Pervasive developmental disorder (PDD) | Children's Social Behaviour Questionnaire (CSBQ) | Hartman *et al.* (2006) |
| Pervasive developmental disorder (PDD) | Social Communication Questionnaire (SCQ) | Rutter, Bailey, and Lord (2003) |
| Anxiety | Revised Children's Manifest Anxiety Scale (R-CMAS) | Reynolds and Richmond (1979) |
| Depression | Child Depression Inventory (CDI) | Kovacks (1985) |
| Mania | Parent version of the Young Mania Rating Scale (P-YMRS) | Gracious *et al.* (2002) |
| Sleep | Children's Sleep Habits Questionnaire (CSHQ) | Owens *et al.* (2000) |
| Tics/Tourette's | Tourette's Disorder Scales—Clinician Rated | Storch *et al.* (2007) |
| Tics/Tourette's | Yale Global Tic Severity Scale | Leckman *et al.* (1989) |
| Obsessive Compulsive Disorder | Yale–Brown Obsessive Compulsive Scale (Y–BOCS) | Goodman *et al.* (1989) |
| Coordination disorders/ Dyspraxia | Developmental Coordination Disorder Questionnaire 2007 (DCD-Q'07) | Wilson *et al.* (2009) |
| Language, pragmatics | Children's Communication Checklist | Bishop (1998) |
| Learning Difficulties Dyslexia Dyscalculia | Woodcock-Johnson III | Woodcock-Johnson (1989) |
| Dyslexia | Test of Word Reading Efficiency (TOWRE) | Torgesen, Wagner, and Rashotte (1999) |

gathered as a part of clinical observation, history taking, and/or evaluation of input from parents, teachers, and the child, is suggestive of other difficulties. It is, however, our clinical experience that since certain common co-existing disorders such as the pervasive developmental disorders, developmental coordination disorders, and dyslexia are often missed by the busy clinician, screens for these should be considered to be a part of routine assessment process. Furthermore, as children with ADHD are assessed both by paediatricians, who may not have received specialist training in general child psychiatry, and mental health practitioners, who may not have been specifically trained in general developmental assessments, each clinician should think about his or her own strengths and weaknesses and include the appropriate tools in the routine assessment package.

### 4.2.3 **Observation**

Whilst there are few validated observational measures for ADHD it is our clinical experience that a structured approach to recording observations is often very helpful. In fact, although not explicitly an observational measure, the SKAMP, designed specifically to measure the classroom manifestations of ADHD, has been used to rate observed behaviour in the laboratory school study setting (Wigal 1998). Within our own clinical team we have developed a tool

to help structure and record school observations (Box 4.1). As this same tool is also used for making observations of children being assessed for pervasive developmental disorders, it contains extra information than would not necessarily be required for an ADHD assessment. However, we find it helpful to consider both sets of observations for each child even if only to exclude the diagnosis of one or other disorder.

### 4.2.4 **Neuropsychological assessment**

Neuropsychological assessments cannot prove or disprove the presence of ADHD. They can however support the clinical assessment and add valuable information about an individual's cognitive specific strengths and weaknesses which can help shape management plans and strategies.

### 4.2.5 **Neuropsychological discrimination between ADHD and typically developing children**

At a time where the providers of health services have to justify any additional examinations that are used, it is helpful to consider the extent to which the main dimensions of neuropsychological functioning are able to discriminate between ADHD and normally developing children. For this purpose, Figure 4.1 details the effect sizes associated the executive function (EF) measures and compare these with non-EF measures and findings derived from standardized IQ assessment as in the Weschler Intelligence Scale for Children III (WISC III) or Weschler Adult

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#### Box 4.1  Potential domains of interest in a school observation

**General information**
- Time of day
- Age of child
- Setting
- Number of children
- Number of adults
- Activity (e.g. maths class, quiet time, group or individual working)
- Room type and set up (e.g. traditional classroom, open-plan, individual or group desks, etc.)

**Observed behaviours**
- Overactivity (e.g. out of seat, climbing, fidgeting, etc.)
- Impulsivity (e.g. answering questions directed at others, butting in, shouting out, unable to wait, etc.)
- Inattention (e.g. needs reminding to stay on task, difficulty getting started, poor task completion, etc.)
- Oppositional behaviours (argues with teacher or peers, aggressive to others, etc.)
- Evidence of mood lability
- Level of communication and interaction with others
- Ability to use comprehend and use language
- Ability to socially interact with others
- Reciprocal social interactions
- Repetitive behaviours
- Ability to imitate others
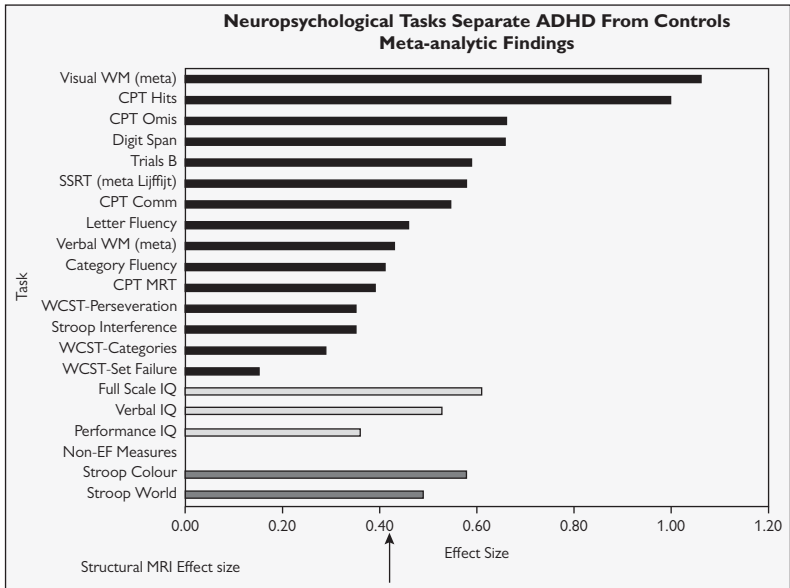- Ability to play appropriately
- Evidence of anxiety

**Figure 4.1** Summary of current meta-analytic evaluations of commonly employed neuropsychological tests and tasks for ADHD—normally developing children comparison.

Intelligence Scale (WAIS). An arrow indicates the comparative strength of structural magnetic resonance imaging to perform the same discrimination (Valera *et al*. 2007). This suggests that both working memory and vigilance give the strongest discrimination. This figure also indicates that a non-executive function, colour naming in the Stroop, has more power than some of the EF measures (e.g. Wisconsin Card Setting Test (WCST) set failure), suggesting that both executive and non-executive functions need to be considered as important determinants of ADHD. Several important measures are not included in this figure; measures of delay aversion, have been found to have an effect size of 0.66 (Willcutt *et al*. 2008) and of non-executive visuospatial memory effect size 0.89–0.92 (Rhodes *et al*. 2005). It is, however, very important to point out that due to the heterogeneity inherent to ADHD many children with ADHD will still perform well on any one of these tasks and not everybody with poor performance on them will have ADHD. As a consequence their sensitivity and specificity with respect diagnosing ADHD in individual cases is relatively low, and we would currently not recommend that diagnostic considerations should **not** be based on neuropsychological task performance.

### 4.2.6  **Neuropsychological assessment as an adjunct to clinical assessment**

There are several situations where it may be considered helpful to conduct more extensive neuropsychological examination alongside the clinical assessment. These include where there are suspicions of significant intellectual impairment, and where there are concerns about specific deficits in neurocognitive functioning. In such situations there are a wide range of potential tasks that can be considered. Table 4.4 provides an overview of cognitive domains that the clinician and neuropsychologist are most likely to wish to evaluate. Table 4.4 also presents

| Table 4.4 Neuropsychological domains and tests/tasks | |
|---|---|
| Domain | Neuropsychological test/task |
| Attention | Stroop task |
| | Freedom from distractibility (WAIS-R) |
| | Letter cancellation task |
| Vigilance/Sustained attention | Continuous performance task (time on task) |
| Inhibition | Stop signal reaction time task |
| | Opposite Worlds (TEACH) |
| Planning | Tower of London/Hanoi, Stockings of Cambridge |
| Fluency | F-A-S Fluency test |
| Flexibility | Trails B |
| | WCST |
| Working memory | Self-ordered pointing task, CANTAB spatial working memory |
| | Digit span forwards and backwards |
| | Corsi block pointing, CANTAB spatial span |
| | CANTAB delayed matching to sample |

examples of some (but not all) of the readily available tests/tasks that have been found to be helpful assessing these domains in clinical practice. Performance on these tasks can help inform clinicians and teachers about potential obstacles to learning and suggest strategies for managing them. In particular the identification of short-term memory problems and slow processing speed can be of particular help to both parents and teachers. For example, a child with memory problems will do better with written rather than verbal instructions and when instructions are given in small chunks rather than combined.

## 4.3 **The assessment process**

Having a clearly thought through and comprehensive assessment protocol that covers all the right territory is as, if not more, important as having the appropriate tools (see Box 4.2).

### Box 4.2 Process diagrams

We have designed a series of process diagrams, based on the recommendations made in the European Guidelines for the Assessment and Treatment of ADHD (Taylor *et al.* 2004). These will be used here to illustrate an approach to developing a comprehensive care pathway for the recognition and assessment of ADHD. Each diagram describes; a trigger, the clinicians involved, the aims, European Guidelines recommendations, and the expected outcomes. This approach will be continued in chapter 7.

These process diagrams should not be seen as prescriptive, and we suggest that they are used to stimulate discussion within teams and services and to help to develop an evidence-based care pathway that works for their particular circumstances and problem solve any barriers to practice that are identified.

### 4.3.1 **Recognition**

The assessment process actually starts before a referral to specialist services is made with the identification in the family, school, and/or community that a child is having difficulties and that these difficulties may be due to ADHD. Whilst this may sound simple, it is the case that across much of the world, with the possible exception of the USA and certain European countries such as the Netherlands and Germany, only a very small minority of those children with ADHD are currently receiving a diagnosis. For example, a recent audit of ADHD care in Scotland identified that only 0.6% of school-age children are currently diagnosed as suffering from ADHD compared to epidemiological projections of between 3% and 5% (i.e. between 80% and 90% of children are currently not diagnosed). Further research from the UK suggests that the major stumbling block to recognition is a failure by primary care doctors to recognize that the problems presented to them by parents are an indication of possible ADHD.

At this stage in the process it is essential that the primary care physician listens to and believes the parents' descriptions of behavioural difficulties, and recognizes the importance of the core ADHD symptoms of inattention, hyperactivity, and impulsivity (see Figure 4.2), and associated impairments. It is also important for them to be able to distinguish these symptoms from other disorders such as oppositional defiant disorder, autism spectrum disorder, intellectual impairment, hearing impairment, or restless legs syndrome. Population screening for ADHD is not currently recommended due to the high rates of false positives identified and the

Figure 4.2  Recognition of ADHD.

subsequent risks of misdiagnosis as well as the burden this would place on child and adolescent mental health (CAMH) and paediatric services. It is, however, appropriate for the primary care and education staff to be trained in the use and interpretation of common questionnaires such as the broadband SDQ and narrowband Conners questionnaires. There is emerging evidence that training teachers to use tools like the SNAP-IV as a semi-structured interview can improve the accuracy of screening and reduce false positives to acceptable levels. Good communication between health and education staff is very helpful but is often difficult to achieve at the primary care level. However, school reports are a valuable source of collateral information about a child's difficulties and their use should be encouraged. A physical examination is also essential to exclude physical causes for the child's difficulties.

Primary care staff will generally have had very little education about ADHD and it is therefore important that specialist services consider how they can facilitate learning both here and in educational settings to ensure increased recognition of ADHD and appropriate referral to specialist services for a fuller assessment.

### 4.3.2 **Assessment**

As with any other mental health assessment the primary aim of the 'ADHD' assessment is to develop a formulation that fully explains the child/young person's difficulties (Figure 4.3). If the assessment is to meet this aim successfully several key points need to be borne in mind. In order to meet criteria for ADHD it is not enough that the patient is assessed as having the requisite number of symptoms. It is also necessary that these symptoms are developmentally inappropriate, pervasive across more than one setting, are associated with a significant degree of impairment, and cannot be accounted for by an alternative explanation. It is also necessary to consider, and assess for a wide range of possible comorbid or co-existing disorders including both psychiatric and non-psychiatric disorders (e.g. dyslexia, developmental coordination disorder, and hearing problems).

As a consequence, a full assessment for ADHD is never a simple task and requires skill, specialist training, and experience with a broad range of mental health and developmental disorders. It is therefore often best conducted jointly by members of a multidisciplinary team. Ideally such a team will include (or at least have good access to) mental health, paediatric, clinical psychology and neuropsychological and occupational therapy skills, and have access to speech and language therapy, family/systemic therapy, physiotherapy and educational skills. A good-quality full assessment takes time and cannot normally be completed in a single meeting. *Whilst the full assessment should be seen as a whole, it can also be broken down into several key 'tasks'.*

The basis for assessment consists of patient's history, observation of the patient's current behaviour, and the account of parents and teachers about the child's functioning in his/her settings. It is not uncommon for there to be differences between informants (children, parents, and teachers) about their perceptions of a child's mental health. Children often do not reliably inform about their own behavioural symptoms and have low test–retest agreement for ADHD symptoms. They can, however, make invaluable comments about other aspects of their life and their inner worlds. Parents seem to be good informants with respect to ADHD symptoms, but often are less accurate at describing emotional difficulties.

Teachers sometimes have a tendency to overestimate the presence of ADHD symptoms, especially when another disruptive behavioural disorder is also present. At other times, some teachers can minimize a child's difficulties as they want to avoid them being labelled as having ADHD. With adolescents, the value of the information given by teachers may be less consistent. Teens have several teachers, each of whom spends little time with each class, which can prevent them from knowing each student well enough to comment accurately. However, the process of diagnostic evaluation necessarily involves collection of data from each of these sources as each can provide complementary information.

| Trigger | • Child/young person is referred with possible ADHD |
| --- | --- |
| **Clinicians involved** | • Child and adolescent mental health services (CAMHS)<br>• Developmental/behavioural paediatrics |
| **Aims** | • To assess whether or not patient meets diagnostic criteria for ADHD<br>• To distinguish ADHD from other disorders and exclude other explanations for behaviours<br>• To assess whether patient is suffering from any comorbid disorders |
| **European Guidelines recommendations** | • A full assessment should be conducted. This will require more than one meeting and should include:<br>  • clinical interview with the parents<br>  • a separate interview with the child<br>  • pre-school, kindergarten, and school information<br>  • school observation if required<br>  • physical evaluation and investigations<br>  • intelligence/cognitive tests if there is a specific indication |
| **Outcomes** | • Confirmation or exclusion of an ADHD diagnosis<br>• In cases where ADHD is confirm there should also be confirmation or exclusion of any comorbid disorders<br>• In case where a diagnosis of ADHD is excluded there should be a formulation of an alternative explanation for the presentation |

Figure 4.3 Assessment of ADHD.

4.3.2.1 *Clinical interview with the parents*

This forms the core of the clinical assessment (Box 4.3). Tasks can be divided into a general evaluation of the child, their problems and the context within which they are occurring, and specific questioning about ADHD and its common comorbidities.

Whilst these lists make the distinction between the two tasks seem very clear and orderly it is important to remember that parents will often have waited a long time to tell their story 'to someone who understands', and at the same time may be quite anxious about the assessment process. It is therefore very important that they are allowed space and time to describe the difficulties from their perspective and to vent their frustrations. The assessment can be seen as the start of a relationship between the clinical services and the family, and as those with a diagnosis of ADHD will often require a prolonged period of treatment it is important to get off on the right foot and start to cultivate a strong therapeutic alliance from the beginning. This will often pay dividends further down the line where continued concordance and compliance with treatment is likely to be central to success.

An assessment of possible parental ADHD is also an important facet of the assessment process. Parents with unrecognized and untreated ADHD can find it much more difficult to parent their children and have been demonstrated to make less use of parent training packages.

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### Box 4.3 Clinical interview with the parents

**General evaluation**
- Clarify presenting complaints
- Make systematic evaluation of symptoms
- Describe how problems developed
- Developmental history including previous professional reports
- Family history of ADHD
- Pregnancy and birth history (foetal growth, toxaemia, bleeding or severe infections during pregnancy, maternal diabetes or epilepsy, other maternal illness or traumas, poor maternal nutrition, maternal medication, nicotine, alcohol and drug use, gestational age, birth complications, birth weight, neonatal complications)
- Early developmental history (milestones for psychomotor development, language, attachment, sleep and feeding problems, growth and early temperament)
- Medical history (especially tics and epilepsy, psychosis—if adolescent)
- Medication (especially anticonvulsants, antihistamines, sympathetomimetics, steroids)
- Family functioning and family problems
- Social networks and other resources

**Specific questioning**
- The behaviours that comprise ICD-10 HKD and DSM5 ADHD diagnoses, and:
  - their relationship to current level of development
  - any situational variation
  - ages of onset
  - development over time
  - their presence in other family members
- A rating of impairment
- Related problems (e.g. behavioural and learning problems, emotional problems, tics, conduct disorder, alcohol problems)
- Parent completed rating scales

A clear understanding of past and current behaviour is essential for diagnostic definition, since only a small number of patients present the characteristic signs and symptoms of ADHD during assessment appointments. Whilst a clear display of symptomatic behaviour in the clinic room can be very helpful, the absence of symptoms at the office does not rule out the diagnosis. These children often are able to control the symptoms voluntarily for limited periods of time, or during activities in which they are highly interested. They can spend hours in front of the computer or TV, but cannot spend a few minutes in front of a book in the classroom or at home.

A detailed social and family history is of paramount importance. Clinicians should pay attention to family history of ADHD and in particular peri-natal history, since various studies have found a higher prevalence of ADHD in pre-term babies and low-birthweight infants. Careful follow-up of this risk group is important for the early identification of signs and symptoms that may indicate a possible diagnosis of ADHD.

As described in section 4.2, the use of standardized interview schedules and scales like the KIDDIE-SADS, DAWBA, SNAP-IV, and ADHD-RS to identify the signs and symptoms of ADHD is widely accepted, although many clinicians do not yet employ them on a routine basis.

### 4.3.2.2 *Separate interview with the child*

This is usually more helpful in addressing general adjustment and comorbidity than for assessing the presence or absence of diagnostic criteria which are usually more accurately described by parents, family members, teachers, and other observers (Box 4.4).

With respect to the observation of ADHD behaviours within the clinic setting, it is important to remember that children with ADHD, just like their healthy counterparts, will often moderate their behaviours in novel settings. It is therefore not uncommon for these children, who are described as perpetually 'on the go' by their parents, to appear well controlled for the first few clinic appointments. This should not usually be used as evidence against the presence of ADHD. It is, however, often very useful to make an assessment of the child's, language skills, social relatedness, and ability to use imagination as this may provide pointers towards (or away from) an autism spectrum disorder.

### 4.3.2.3 *Pre-school, kindergarten, and school information and school observations*

Information from school is essential for the diagnosis of ADHD. This can be gathered in various ways (Box 4.5). In our clinical practice we always ask for copies of all previous school reports

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**Box 4.4  Separate interview with the child**

**Should focus on**
- Functioning in the family, the school, and the peer group
- A general evaluation of psychopathology (especially emotional problems and self-esteem)
- The child's attitude to, and coping with, their disorder

Self-report rating scales may be helpful as an adjunct to an interview (especially for detecting emotional problems)

Observation of behaviour during the interview can be useful especially if ADHD or other behavioural problems are observed. However, a negative observation does not mean problems are not present and repeated observation is often required. An observer should focus on assessing:
- the presence of social disinhibition
- ability to concentrate and persist
- any evidence of language disorder

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**Box 4.5 Pre-school, kindergarten, and school information**

**Obtain information from teacher about**
- Behaviour and behaviour problems
- Development
- Social functioning
- Situational variation in behaviour and symptoms that may indicate comorbid or differential diagnoses

Standardized questionnaires can help to obtain a broad coverage of information (e.g. SKAMP, SDQ, CBCL, and Conners)

**Further written or telephoned reports may also be needed**
- For a full view of the child at school
- To assess the coping style of the teacher
- The teacher–child relationship

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and of any specific assessments that have been conducted within the school setting as well as a contemporaneous structured written report addressing current academic attainments, behavioural difficulties, and interpersonal relationships.

Where necessary, a structured telephone interview to clarify the presence/absence of ADHD symptoms and impairments is conducted with the class teacher using one of the instruments described above. If there is still doubt about the diagnosis or other aspects of functioning, a school observation is conducted focusing on the behaviours described previously in section 4.2.3 and Box 4.1, the interactional and coping style of the teacher, and the teacher–child relationship.

### 4.3.2.4 *Physical evaluation and investigations*

The physical evaluation is an important part of the assessment process and can also provide essential baseline measurements for the treatment phase. Clinical audit suggests that this is the part of the assessment most frequently missed out (especially in mental health settings), and therefore particular note of the recommendations described below should be taken when developing or reviewing care pathways. On the other hand, physical investigations (other than height, weight, head circumference, pulse, and blood pressure) are not routinely required and their use should be guided by the history and physical examination (see Box 4.6).

### 4.3.2.5 *Intelligence and cognitive testing*

The routine assessment of intelligence is not required for all cases. It can, however, be very helpful; for example, where there is a suspicion of a mild to moderate cognitive impairment or intellectual impairment. In such cases it is important to distinguish behaviours indicative of ADHD from those that are associated with delayed development. We are aware that lack of time and resources often restrict a clinician's ability to ask for intelligence testing but testing should always be considered when there is any problem related to classroom adjustment or progress. When time is scarce, a brief assessment of verbal performance (e.g. in the UK the British Picture Vocabulary Scale, BPVS) or the short Wechsler Abbreviated Scale of Intelligence (WASI) or equivalent is better than no assessment.

The neuropsychological heterogeneity inherent in ADHD (not all children with ADHD will necessarily have any one particular neuropsychological deficit) and the lack of specificity between particular tasks and particular psychiatric disorders (e.g. ADHD, autism spectrum

| Box 4.6  Physical evaluation and investigations |
| --- |

**Physical evaluation**
- Height, weight, and head circumference should always be recorded.
- Pulse and blood pressure (especially if considering medication).
- General examination is always needed and should include:
  - An assessment of general physical health
  - Any evidence of poor standards of care/abuse
  - Stigmata of congenital disorders (e.g. foetal alcohol syndrome, Williams syndrome, neurofibromatosis)
  - Vision check (Snellen chart)
  - Hearing check; in the UK and many European countries all children should already have had proper audiology testing. The assessing clinician should check whether this has happened and refer for audiometry if it has not.
  - Evidence of neurodevelopmental immaturity in gross and fine motor functions
  - Screen for motor and vocal tics
  - Cardiac examination if considering medication

**Investigations**
- These should not be routine but guided by history and physical examination
  - Where there is any evidence for compromised cardiac function an ECG (12-lead or 24-hour tape, depending on circumstances) should be carried out
  - Where there is a history suggestive of seizures an EEG should be carried out
  - If there is a developmental delay, chromosome estimation, and a DNA assessment for fragile X should be conducted
  - Audiograms are required if clinical evaluation has not ruled out significant hearing loss
  Brain scanning is <u>not</u> required unless there is a particular reason to suspect a brain lesion.

disorders, and schizophrenia are all associated with deficits in various executive functions) result in problems of sensitivity and specificity for neuropsychological tasks in the diagnostic assessment of ADHD. However, the identification of a neuropsychological deficit known to be associated with ADHD can be helpful in supporting a clinical diagnosis. They can also be of great assistance in helping to characterize strengths and weaknesses of patients and/or the presence of comorbid disorders like dyslexia and intellectual impairment. In particular, the identification of short-term memory problems and slow processing speed can be of practical help to teachers.

### 4.3.3 **Diagnosis and formulation**

Following the collection of information from the various sources, this needs to be integrated and a judgement made regarding diagnosis. Clinical training, skill, and experience are often required to reconcile conflicting information. The aim is to make a full formulation with diagnosis, differential diagnosis, a description of any predisposing, precipitating, and perpetuating factors, acknowledgement of any comorbid or co-existing disorders, and a description of any complicating factors (e.g. peer relationship problems, bullying, high expressed emotion at home, poverty, etc.). In cases where further treatment will be offered it is also helpful to integrate a formulation of the symptoms and problems that will be the focus of treatment (see Box 4.7 here and chapter 7).

## Box 4.7 Potential target symptoms and problems

Core ADHD symptoms
- Oppositional and disruptive behaviour in the home
- Oppositional and disruptive behaviour in the classroom
- Academic problems
- Peer group relationships
- Other associated symptoms (e.g. anxiety, mood instability, depression, dyspraxia, speech and language problems, etc.)

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## Chapter 5

# Pharmacological treatment

Alessandro Zuddas

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### Key points

- Drug treatment should be based on a comprehensive assessment and diagnosis including full medical history and physical examination.
- It should always be part of a comprehensive treatment plan that includes psychological, behavioural, and educational advice and interventions.
- Methylphenidate, amphetamine derivatives, atomoxetine, and guanfacine are effective treatments via distinct neurochemical mechanism. They should be used as the main pharmacological options for the management of ADHD in children and adolescents.
- Drug treatment should be closely monitored for both common and unusual (but potentially serious) side effects.

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## 5.1 Approach to treatment

Any treatment plan for ADHD must be based on a comprehensive diagnostic evaluation: the clinician should document that the child meets the criteria for a categorical diagnosis of ADHD, being aware of possible concomitant medical or psychiatric conditions or learning disabilities (see chapter 4). Rather than focusing just on the disorder, the child should be treated as an individual in her/his particular social context. Before starting treatment, it is important to identify (and quantify) the target outcomes for guiding therapy decisions during treatment. Depending on individual circumstances, both psychosocial intervention ('behaviour modification') and pharmacotherapy can be considered, (see chapters 6 and 7), as potential first treatments for children and adolescents with ADHD (Taylor *et al.* 2004; NICE 2008).

Stimulant medication (methylphenidate [MPH], dexamfetamine or amfetamine derivatives) and 'noradrenergic' medication (atomoxetine [ATX] and guanfacine) are the most effective psychopharmacological treatments for ADHD.

Racemic amfetamine is the oldest stimulant preparation used to treat ADHD and has been used since the seminal observations of Bradley in 1937; although more potent than MPH, amfetamines are less used in Europe and are not commercially available in many countries (IR-dexamfetamine has been licensed in Denmark, Finland, Germany, Ireland, Luxembourg, the Netherlands, Norway, Spain, Sweden, and the UK). However, recently an amfetamine pro-drug (lisdexamfetamine) has been licensed in the US (Vyvance®, Shire), several EU countries (Elvance ®, Shire), and in other parts of the world. The use of stimulants for the treatment of ADHD is well established and has been reviewed by the European ADHD Guidelines Group (Taylor *et al.* 2004; Banaschewski *et al.* 2006). MPH is licensed in the US and in most European countries as part of comprehensive treatment programs in children (over six years of age) and adolescents. Several different extended-release formulations have been developed.

More recently, a patch formulation (transdermal) has been approved in the US but uptake of this patch has been very slow.

Atomoxetine (Strattera®, Lilly) was the first non-stimulant medication officially approved for the treatment of ADHD. It has a license for children and adults in the USA, for children, and more recently also for adults, in many European countries and, with variable age indications, in many other parts of the world.

Guanfacine extended release (Intuniv®, Shire) has been approved for the once-daily treatment of ADHD children and adolescents aged 6–17 years by FDA and it has been submitted to EMA for approval and registration. In 2010, the US Food and Drug Administration (FDA) has approved a preparation of clonidine hydrochloride, extended-release tablets (Kapvay®, Shionogi Inc) alone or with stimulants for the treatment of ADHD in paediatric patients aged 6–17 years. This preparation is not available in the EU.

## 5.2 **Molecular mechanism of action of ADHD medications**

After synaptic release, monoamines (norepinephrine, dopamine, and serotonin) are taken up by specific active membrane transport proteins (norepinephrine transporter—NET, dopamine transporter—DAT, serotonin transporter—SERT, respectively) and, when in the cytoplasma, by specific vesicular transporter proteins (vesicular monoamine transporter 2—VMAT-2) into the synaptic vesicle. MPH, amfetamines, and ATX are effective via distinct neurochemical mechanisms.

### 5.2.1 **Amfetamines**

Racemic amfetamine contains equal amounts of d- and l-amfetamine isomer. The amfetamine *d* isomer (dexamfetamine) inhibits re-uptake via both membrane transporters and, at higher concentration, vesicular transporters. *D*-amfetamine also increases basal DA and NE release by binding to the vesicular monoamine uptake 2-transporter (VMAT-2) and inducing reverse transport through the plasma membrane into the cytoplasm. *In vitro*, affinity of *d*-amfetamine is higher for NET (which is found in the prefrontal cortex) than for DA (which is found in the striatum), and much lower for serotonin. The amfetamine *l*-isomer is much less potent (13-fold) than the *d*-isomer in inhibiting the accumulation of DA or NA into vesicles, and five to seven times less potent in inhibiting the synaptic membrane transport (Easton *et al.* 2006).

### 5.2.2 **Methylphenidate**

MPH is 40- and 70-fold less potent than dexamfetamine at inhibiting vesicular accumulation of DA or NA, but a similarly potent inhibitor of synaptic re-uptake of DA, and a slightly less potent in inhibitor of NE re-uptake. Racemic MPH consists of both *d*- and *l-threo*-enantiomers in a 50:50 ratio. The *d-threo*-enantiomer is pharmacologically more active than the *l-threo*-enantiomer (tenfold for norepinephrine re-uptake; 10- to 40-fold for dopamine re-uptake (Heal and Pierce 2006) (see Box 5.1).

### 5.2.3 **Atomoxetine**

Atomoxetine is a selective inhibitor of the synaptic re-uptake of NE. *In vitro*, ATX does not directly modulate DA transporter synaptic uptake or DA or NE vesicular transport. However, *in vivo* ATX specifically increases extracellular levels of DA in the prefrontal cortex but not the striatum, probably by modulating the cortical synaptic DA uptake via the NE transporter (Swanson *et al.* 2006). A summary of the molecular mechanisms of atomoxetine and other medications for the treatment of ADHD is shown in Figure 5.1.

**Box 5.1 From molecular mechanism to clinical effects**

Stimulants increase extracellular levels of dopamine (DA) and norepinephrine (NE) by blocking the respective monoamine transporters (amfetamines also increase catecholamine release from synaptic vesicles). Exactly how these actions relate to the stimulant effects on attention and performance is, however, still unclear. DA and NE decrease background firing rate of neurons, thus increasing noise-to-signal ratio. During cognitive tasks, methylphenidate (MPH) has been shown to increase cerebral blood flow (CBF) in dorsolateral prefrontal and posterior parietal cortices in healthy controls (Metha *et al.* 2000) and in the prefrontal cortex in adults with ADHD (Schweitzer *et al.* 2004); it appears to decrease metabolic activation of task-irrelevant brain regions, thus focusing activation and improving performance (Volkow *et al.* 2008).
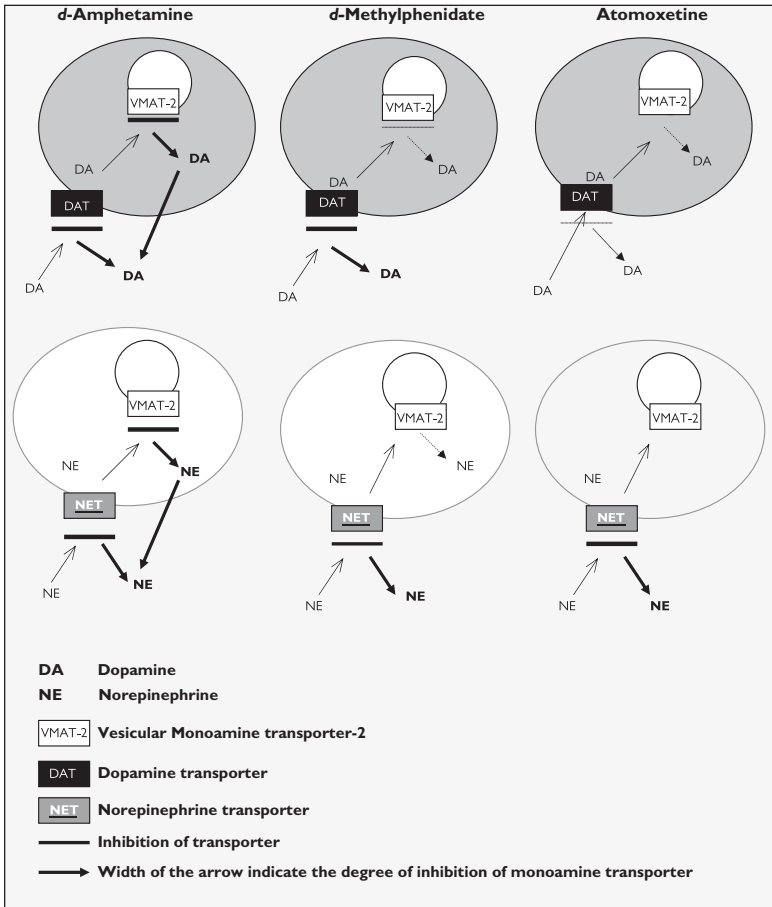
Figure 5.1 Molecular mechanisms of ADHD medication (Easton *et al.* 2006, modified).

### 5.2.4 **Guanfacine and clonidine**

Guanfacine is a selective alpha-2 noradrenergic-agonist with 15 to 20 times higher affinity for alpha-2A adrenergic receptors than for alpha-2B or alpha-2C receptors. Direct application of guanfacine on to neurons in dorsolateral prefrontal cortex increases the delay-related neuronal firing needed for working memory. In animal models, stimulating post-synaptic alpha-2A-adrenoceptor subtype, guanfacine can improve working memory attention regulation, and behavioural inhibition independently from its mild sedative actions. In monkeys, guanfacine also appears to improve impulse control during a delayed discounting task. It increases the ability to resist an immediate, small reward and facilitates waiting for a larger reward (Kim *et al.* 2012; Sallee *et al.* 2013 for a review). Being more selective for the alpha-2A receptor subtype than clonidine, which also binds with high affinity to alpha-2B, alpha-2C receptors, guanfacine is weaker than clonidine in producing hypotension and sedation (Arnsten *et al.* 2012 for a review).

Several studies, however, indicate that mechanisms of action observed from animal models do not always translate to humans. Studies in healthy normal adults have failed to find a positive effect of alpha-2 adrenoceptor agonists (including guanfacine) on cognition (Coull *et al.* 2001; Muller *et al.* 2005). In a controlled classroom trial with ADHD children and adolescents, no differences were observed in a choice reaction timed task (Kollins *et al.* 2011), although in a controlled trial in children and adolescents with ADHD and tics, guanfacine improved teacher-rated ADHD symptoms and positive continuous performance outcome measures (Scahill *et al.* 2001), and in adults, guanfacine has also been shown to modulate the influence of emotion control on cortical activation for cognitive control (Schultz *et al.* 2013; Salle *et al.* 2013).

## 5.3 **Pharmacokinetics and interaction with other drugs**

### 5.3.1 **Amfetamines**

Absorption of amfetamine is fast, with peak plasma levels occurring about three hours after oral administration. Food does not affect total absorption but does delay it. Metabolism is via various P450 enzymes and occurs mainly in the liver. Children eliminate amfetamine faster than adults, the elimination life of dexamfetamine being about one hour shorter in 6–12-year-old children (average nine hours) than in adults (average about ten hours). Acidification of urine increases urinary excretion of amfetamines. Ingestions of acidic substances such as ascorbic acid, or fruit juices, may lower absorption, whereas gastrointestinal alkalinizing agents, such as sodium bicarbonate, seem to increase absorption.

#### 5.3.1.1 *Onset and duration of action*

Consistent with the pharmacokinetics profile, the onset of action of amfetamines is rapid, within one hour after administration. For immediate release preparations, the duration of action is around four to five hours, which is slightly longer than for MPH, but still requires at least twice a day administration to ensure adequate coverage.

Mixtures of different *d*-amfetamine and *dl*-amfetamine salts formulated for immediate or sustained release are available as Adderall in the United States but not in Europe. Adderall XR® (Shire) 20 mg provides comparable plasma concentrations to two 10 mg doses of Adderall immediate release administered four hours apart. This method of administration results in ascending plasma levels of amfetamine up to a peak at about seven hours after dosing. This is followed by a gradual decline that results in low but detectable plasma levels 24 hours after dosing.

### 5.3.1.2 *Lisdexamfetamine*

Lisdexamfetamine is a pharmacologically inert molecule comprised of a dexamfetamine molecule that has been covalently attached to the essential amino acid, L-lysine. Lisdexamfetamine itself is not pharmaco-dynamically active.

After oral administration lisdexamfetamine is rapidly absorbed from the gastrointestinal tract, and thought to be mediated by the high capacity PEPT1 transporter. Lisdexamfetamine dimesylate is rapidly converted to dexamfetamine and l-lysine, which occurs by metabolism in blood primarily due to the hydrolytic activity on the surface of red blood cells (Pennick 2010). When injected or snorted the rise in plasma dexamfetamine is similar to that when the medication is taken orally, and it is likely that this contributes to a lower abuse potential compared to immediate-release stimulants.

Tmax of lisdexamfetamine itself is approximately one hour and the half-life less than one hour. After lisdexamfetamine administration, the Tmax of dexamfetamine is approximately 3.5 hours, with a half-life of about nine hours. Food does not affect the observed area under the plasma-concentration time curve (AUC) and Cmax of dexamfetamine but prolongs Tmax by approximately one hour (from 3.8 hours at fasted state to 4.7 hours after a high-fat meal). Pharmacokinetics of dexamfetamine after single-dose oral administration is linear (Boeller *et al.* 2010). There is no accumulation of dexamfetamine at steady state in healthy adults and no accumulation of lisdexamfetamine dimesylate after once-daily dosing for seven consecutive days. Lisdexamfetamine is not metabolised by cytochrome P450 enzymes. Amfetamine is oxidised to form 4-hydroxy-amfetamine, alpha-hydroxy-amfetamine or norephedrine. Norephedrine and 4-hydroxy-amfetamine are both active and each is subsequently oxidised to form 4-hydroxy-norephedrine. Following oral administration approximately 96% of the oral dose is found in the urine and only 0.3% recovered in the faeces over a period of 120 hours.

Lisdexamfetamine appears to have efficacy and tolerability comparable to other extended-release stimulant formulations used to treat ADHD, but reduced potential for abuse-related linking effects (Biederman *et al.* 2007; Coghill *et al.* 2013; Jasinski *et al.* 2009).

### 5.3.1.3 *Interaction with other drugs*

Amfetamine may potentiate stimulating effects of other drugs (i.e. serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs), and tricyclic antidepressants, bupropion, MAO inhibitors) on the cardiovascular or central nervous system. Ascorbic acid and other agents and conditions (diets high in fruits and vegetables, urinary tract infections, and vomiting) that acidify urine increase urinary excretion and decrease the half-life of amfetamine. Sodium bicarbonate and other agents and conditions (thiazide diuretics, diets high in animal protein, diabetes, respiratory acidosis) that alkalinize urine decrease urinary excretion and extend the half-life of amfetamine.

### 5.3.2 **Methylphenidate**

When delivered orally as an immediate-release preparation, MPH is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring about 1.5–3 hours after administration. Food delays the time to maximum plasma concentration from 1.5 hours when fasting to 2.5 hours after heavy breakfast: it is usually recommended to give the medication just before breakfast. MPH is primarily metabolized through de-esterification by the carboxyl esterase enzyme to ritalinic acid, which has no clinically significant pharmacological activity and is excreted in the urine. *D-threo*-methylphenidate undergoes enantioselective metabolism in the liver, which results in marked differences in the plasma concentrations of its isomers. The *l-threo* form is very rapidly metabolized and does not appear to contribute to the therapeutic effects. The elimination plasma steady half-life of *d-threo*-methylphenidate is about

3–3.5 hours. Because of this short-half life, steady state is never achieved during treatment and there is no carryover from one day into the next. Metabolism and pharmacokinetics are similar in school-age children and adults.

### 5.3.2.1 *Extended-release preparations*

Laboratory school studies suggest a close relationship between pharmacokinetics (PK) and pharmacodynamic (PD) properties. Optimal clinical effect appears associated with increasing plasma levels from morning to afternoon: preparations with bi- or tri-modal release systems ensure an initial sharp plasma peak occurring about 1.5 hours after dosing, followed by a second peak several hours later, followed by a gradual decline. Some products include a combination of immediate and extended-release MPH; they differ in the mechanics of the delayed-release system and in the proportion of immediate-release to delayed-release methylphenidate. Figure 5.2 shows the PK profile over time of some different formulations; the actions on behaviour parallel the concentrations in the blood.

Different delivery profiles provide the clinician with increased options when choosing which preparation to use for a particular patient, as well as a more flexible and sensitive individualized adjustment whilst retaining the benefits of an ER preparation. It should be

| MPH IR BID MPH (mg/mL) | % IR | % ER | CONCERTA® XL MPH (mg/mL) | % IR | % ER |
|---|---|---|---|---|---|
| | 100% | | | 22% | 78% |
| EQUASYM XL® MPH (mg/mL) | 30% | 70% | MEDIKINET RETARD® MPH (mg/mL) | 50% | 50% |
| RITALIN LA® MPH (mg/mL) | 50% | 50% | ADDERALL XR™ —○— Dextroamfetamine (mg/mL) —●— Levoamfetamine (mg/mL) | 50% | 50% |
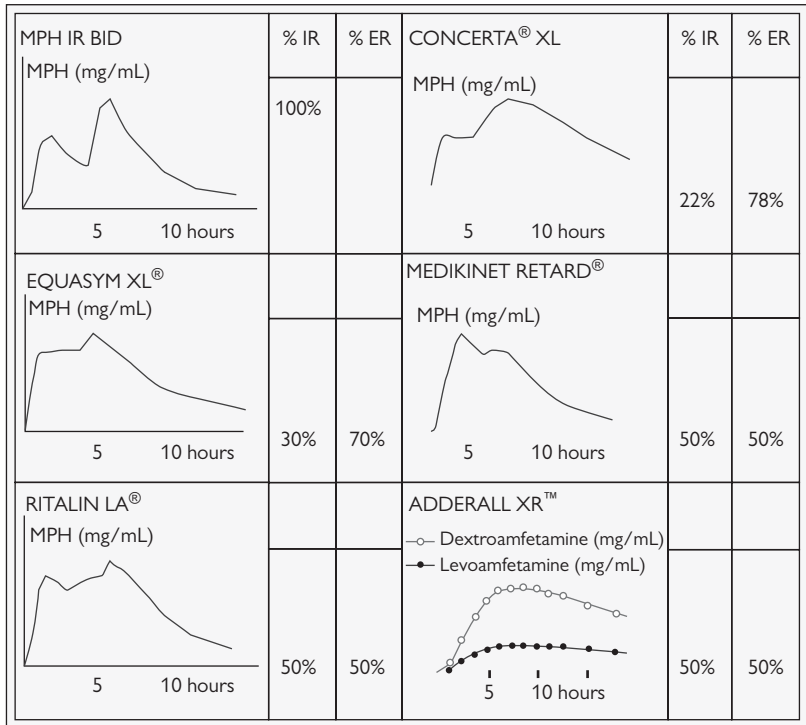
**Figure 5.2** MPH and amfetamine plasma levels over time with different preparations and their IR/ER proportion.

Figure 5.2 is reproduced from Banaschewski *et al.* (2006), with kind permission from Steinkopff, Heidelberg.

noted, however, that PK profiles may show considerable inter-individual variation. Caution should be observed when generalizing from aggregated profiles to individual patient cases. The onset of action, in particular, can be delayed or may be attenuated in the afternoon, requiring the concomitant administration with a low dose of immediate release preparation.

Recently a transdermal system that delivers racemic MPH through the skin directly into the bloodstream has been developed and made available in the USA. Racemic MPH is solubilized in acrylic in very high concentrations and mixed with adhesive to form concentrated pockets of drug. The concentration gradient results in an efficient diffusion of the drug out of the adhesive layer. Reproducible plasma concentrations within the same patient have been demonstrated, with intra-subject coefficients of variation of approximately 20%. With a nine-hours wearing time, the system the time course of clinical effectiveness was from two to 12 hours after skin application. Plasma concentrations, and probably efficacy, decline rapidly after patch removal. Since first-pass liver metabolism is avoided, the ratio of *l-* versus *d-threo*-methylphenidate concentration is significantly higher than after oral administration.

#### 5.3.2.2 *Interaction with other drugs*

MPH has little interference with the metabolism and pharmacokinetics of other drugs. It can inhibit the metabolism of anticonvulsants such as phenobarbital, phenytoin, and primidone, and of some antidepressants (tricyclics and SSRIs). There are potentially dangerous inter-reactions with cocaine and other sympathomimetic drugs, causing tachycardia, tremor, and nervousness more likely than either drug given in isolation.

Four cases of sudden death were reported in children with ADHD taking concurrent administration of MPH and clonidine, but no causal links between MPH treatment and cardiovascular adverse events or the occurrence of ECG abnormalities have been established (Tourette's Syndrome Study Group 2002).

### 5.3.3 **Atomoxetine**

ATX is metabolized mainly through the hepatic cytochrome P450 2D6 enzymatic system (CYP2D6) resulting in metabolites with clinically significant activity. About 5–10% of Caucasians and 2% of Afro–Caribbeans have genetically determined low CYP2D6 activity ('poor metabolizers'). In poor metabolizers, plasma levels of ATX can be tenfold higher compared to subjects with normal CYP2D6 activity ('extensive metabolizers'). Mean elimination half-life is about 22 hours in poor metabolizers compared to five hours in extensive metabolizers. At steady state the duration of brain NET inhibition appears to last longer than ATX plasma levels are detectable: once daily ATX is associated with a decrease of 3,4-dihydroxyphenylethylene glycol (DHPG), which is the main brain metabolite of norepinephrine and a biomarker of central NET inhibition, persisting for at least 24 hours. Interestingly, there also appears to be a dissociation between the pharmacokinetic and pharmacodynamic profiles for atomoxetine (ATX) with evidence that despite the relatively short half-life, even once-daily dosing can result in clinical effects that last throughout the day.

The onset of clinical effectiveness of ATX is slower than that of stimulants: as for tricyclic antidepressants (see section 5.6.4), it may vary between two and four weeks; maximum response is usually achieved after eight weeks of atomoxetine administration, although some patient may continue to improve for 36 weeks (Marchant *et al.* 2011).

#### 5.3.3.1 *Interaction with other drugs*

Concomitant administration of fluoxetine or paroxetine, drugs that inhibit the CYP2D6 activity, results in higher plasma levels of ATX. Likewise, slower metabolism of ATX and higher plasma

levels should be expected during concomitant use of other drugs that inhibit the CYP2D6 system Although there are case reports in the literature, and despite it having become common practice in some countries to combine ATX with stimulants where there appears to be a lack of treatment response with monotherapy, it must be noted that there has been no systematic investigation of concomitant use for this combination or for ATX with any other drug for the treatment of ADHD. In particular, safety data are lacking for this combination. Possible interaction between ATX and other drugs for ADHD treatment have not been systematically studied.

### 5.3.4 **Guanfacine**

Extended-release guanfacine (matrix-s tablets, GXR) is well absorbed: after oral administration, the time to peak plasma concentration is approximately five hours. Food intake significantly affects absorption: peak plasma concentration (Cmax) increases by 75%, the total drug exposure (AUC) by 40%. In plasma, guanfacine is approximately 70% bound to plasma proteins and it is primarily metabolized by hepatic cytochrome p450 (CYP) 3A4 microsomal enzymes. GXR is 16–17 hours, allowing once daily administration. Fifty per cent of an administered GXR dose is excreted unchanged in the urine. The pharmacokinetics of guanfacine is linear (first-order) and dose proportional. The pharmacokinetics of GXR differs from those with guanfacine immediate release (IR) tablets, with GXR resulting in 60% lower Cmax and up to 43% lower AUC compared to IR tablets (Elbe *et al*. 2014).

#### 5.3.4.1 *Interaction with other drugs*

Guanfacine does not inhibit or induce CYP enzymes but exposure to guanfacine may potentially be increased by concurrent use of CYP 3A4 inhibitors (e.g. clarithromycin, fluvoxamine, itraconazole, grapefruit juice) or decreased by concurrent use of CYP 3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort).

## 5.4 **Clinical efficacy**

### 5.4.1 **Short-term efficacy**

#### 5.4.1.1 *Methylphenidate*

There is substantial evidence supporting the efficacy and effectiveness of stimulants (MPH in particular) in reducing ADHD symptoms over treatment periods up to a year and in doses up to 60 mg daily. Numerous placebo-controlled randomized control trials confirm the substantial short-term benefit (SIGN 2001; Banaschewski *et al*. 2006; NICE 2008). Stimulants reduce restlessness, inattentiveness, and impulsiveness markedly and rapidly. Effect sizes on hyperactivity symptoms are typically between 0.8 and 1.1. The response rate both MPH and amfetamines is around 70% and if non-responders are treated with the second stimulant, the cumulative response rate is at least 95% (Efron *et al*. 1997; Hodgkins *et al*. 2012). The corresponding numbers needed to treat (NNT; a measure of outcome) are between three and five. Stimulants have also been documented to improve the quality of social interactions, decrease aggression and increase compliance. Patients with ADHD and comorbid anxiety or disruptive disorders have a robust response of their ADHD symptoms to stimulants as do patients who do not have these comorbid conditions. MPH effects on anxiety or oppositional defiant behaviour *per se* are, however, controversial. Nevertheless, taking stimulants, the hyperactive child is rated by peers as more cooperative, greater fun to be with, and is more likely to be considered to be a best friend. Medication may not enhance the hyperactive child's social judgement or eliminate his or her negative perceptions of his or her peers; a longer period of treatment may be required to counteract the negative reputation of a hyperactive child and to eliminate social deficits.

Medication usually starts with immediate-release MPH (see section 7.3.3), given three times a day in doses starting with 5–5–2.5 mg or 10–10–5 mg (depending on age and size of child), and should be monitored, collecting information from parent and teachers using simple rating scales. The dose should be titrated until a good clinical response (maximum dose 0.7–1.0 mg/kg/ dose, according to different guidelines; maximum dose 100 mg/day) or troublesome side effects occur. Long acting preparations may also be considered to start treatment (see chapter 7 for a fuller account of titration protocols).

### 5.4.1.2 *Lisdexamfetamine*

Lisdexamfetamine (LDX) has been the first drug registered according to the specific EMA Guideline on clinical investigation of medicinal products for the treatment of ADHD (EMA 2010): a three-arm design with the inclusion of an active comparator, multiple measures of clinical response including evaluation of symptomatic and functional efficacy and the evidence of the maintenance of effect assessed by a randomized withdrawal design. LDX was more effective than placebo on ADHD symptoms (effect size 1.8, NNT 2), was also effective in treating day-to-day problems associated with ADHD, and significantly improved quality of life (Coghill *et al.* 2013; Banaschewski *et al.* 2013). The randomized withdrawal of treatment after 24 weeks of open-label treatment indicated the benefit of continued LDX treatment (Coghill *et al.* 2014; see also section 5.4.3), with treatment-emerging adverse events generally consistent with those associated with stimulant treatment.

In comparing the LDX efficacy to methylphenidate, it should be taken into account that because of different pharmacodynamic characteristics, including the specific mechanism of action (see section 5.2.1), amfetamines are more potent that methylphenidate (5 mg dexamfetamine ≈10 mg methylphenidate). In titrating lisdexamfetamine it should also be considered that half of the molecular weight is due to the lysine, and that the different pharmacokinetics make it almost impossible to accurately calculate doses equivalents to methylphenidate. Usually 30 mg per day is considered a starting dose, which can be increased to 50mg and then 70 mg as required. Being associated with a relatively lower abuse potential than immediate-release methylphenidate, in the Americas and Australia lisdexamfetamine is registered as a potential first-choice treatment. In Europe, perhaps also considering the cost and the different reimbursement procedures, lisdexamfetamine is indicated for those who have not achieved optimal treatment with methylphenidate.

### 5.4.1.3 *Atomoxetine*

Atomoxetine (ATX) has been shown to be effective in decreasing hyperactivity, impulsivity, and inattention in school-age children with ADHD as compared with placebo with an effect size on hyperactivity symptoms of around 0.7 and NNT (see Box 5.2) of around 4 (Banaschewski *et al.* 2006). The treatment effect can be clinically evident at the end of the first week of treatment, but full therapeutic activity may not emerge until after four to six weeks of treatment, and in some cases may require even longer. The therapeutic benefit persists in time and is not subject to attenuation or tolerance.

ATX has been shown effective in reducing symptoms of both ADHD and comorbid anxiety, with a moderate effect size (0.5) for anxiety, relative to placebo. ATX has been shown a useful alternative in treatment-emergent or comorbid tics since it does not worsen tics and may even improve them (see also Table 5.1). Because of its lack of abuse potential, ATX have been also suggested as primary drug of choice in adolescents with ADHD and comorbid substance use disorder. ATX use as first-choice medication in specific patient populations is discussed in chapter 7.

### 5.4.1.4 *Clonidine and guanfacine*

The evidence for efficacy of clonidine to treat ADHD is weaker than that for stimulants and ATX. Evidence for its efficacy to reduce tics in children with ADHD and tic disorder is stronger.

## Box 5.2  Improvement and normalization: effect size and NNT

The calculation of effect sizes standardizes the magnitude of the difference in improvement (change) in drug and placebo groups so that a one-point difference indicates that the active treatment and placebo groups differ by one standard deviation on a particular outcome measure. This allows a direct comparison of treatment effectiveness across studies, including those that have used different outcome measures. A commonly used effect size index is the standardized mean difference (SMD: the difference in outcome scores between drug and placebo groups divided by the pooled standard deviation (of the placebo and medication group at end of treatment)).

The actual outcome may be better characterized by the concept of normalization and measured by the number needed to treat (NNT). Normalization rates are defined as the proportion of patients normalized; e.g., having no problems more than 'mild' (i.e. Conners scale T-score <63 or SNAP <1/item). The NNT corresponds to the expected number of patients needed to be treated to see one patient normalize in terms of symptoms with medication and would not have normalized on placebo therapy.

Effect sizes and NNTs for medications to treat ADHD (usually between 3 and 5) are better than those reported for most other psychiatric drugs. For example, the effect sizes and NNT for antidepressants to treat adult depression or obsessive-compulsive disorder are about 0.5 and 9, respectively, and for atypical antipsychotics to treat schizophrenia around 0.25 and 20 (Banaschewski *et al.* 2008).

## Table 5.1  Approach to common adverse events during stimulant treatment

| Averse event | Possible approach |
|---|---|
| Lack or loss of appetite (mostly more prominent at lunch, i.e., when medication is effective) | 1. If early in treatment, look for possible tolerance over time to this side effect<br>2. Decrease dose, if clinically possible<br>3. Increase caloric intake at breakfast and dinner<br>4. Monitor weight |
| Loss of weight | 1. Decrease dose (unless child is overweight)<br>2. Increase caloric intake at breakfast and dinner; add caloric snacks in between<br>3. Consider lower dose or no medication during weekend<br>4. Monitor weight: tolerance to this effect often develops |
| Early insomnia (difficulty falling asleep) | 1. If immediate-release prep.: allow no dosing after 3 p.m.<br>2. If extended-release prep.:<br>    a. reduce dosing,<br>    b. change formulation, or<br>    c. start treatment early in the morning and give medication before breakfast (more rapid absorption)<br>3. Be sure that there is an appropriate bedtime routine (e.g. reading)<br>4. Consider atomoxetine |
| Blunted affect ('zombie'-like appearance) | 1. Decrease dose, if possible<br>2. Try different preparation<br>3. Consider atomoxetine |
| Tics (new onset) | 1. Discontinue treatment and see if tics go away<br>2. Restart treatment and see if tics come back<br>3. Consider atomoxetine |

In children comorbid for ADHD and Tourette, a randomized controlled study comparing clonidine, MPH, and placebo, clonidine appeared to be most helpful for impulsivity and hyperactivity; MPH for inattention. The proportion of individual subjects reporting a worsening of tics as an adverse effect was no higher in those treated with MPH (20%) than those being administered clonidine alone or placebo (22%). Compared with placebo, measured tic severity lessened in all active treatment groups in the following order: clonidine + MPH, clonidine alone, MPH alone (Tourette's Syndrome Study Group 2002).

A recent meta-analysis showed that alpha-2 agonists (guanfacine and clonidine, both in immediate or extended formulation) as monotherapy are efficacious, with medium-effect sizes (0.56–0.59), in controlling ADHD symptoms in children and adolescents; no significant difference in effect size was observed between the two medications or the different formulations. In patients with insufficient response to ongoing psychostimulant therapy, alpha-2 agonists showed smaller effect sizes (0.32–0.36; Hirota *et al.* 2014).

### 5.4.2 **Long-term efficacy of stimulants and efficacy of combination with psychosocial intervention**

The long-term and distal effects of stimulants have been less well investigated, primarily because it is extremely difficult to run controlled studies over several years. Thus, it remains unclear if successful control of ADHD symptoms during childhood results in better prognosis in adult years. One large-scale, random allocation, non-blind trial in the USA focused on the comparison between careful medication management, intensive behaviourally oriented psychosocial therapy, a combination of the two, or a simple referral back to community agencies (which usually resulted in medication) (MTA Cooperative Group, 1999).

The main conclusions after 14-months' treatment were that careful medication was more powerful than behaviour treatment, and considerably more effective than routine medication in the community. The superiority of careful medication to behaviour therapy was particularly striking because behaviour therapy provision was much more intensive and prolonged than could be achieved by a community service. There were many advantages in adding medication to behaviour therapy, but relatively few to adding behaviour therapy to medication. The combination of behaviour therapy and medication did have some benefits: better control of aggressive behaviour at home; improving the overall sense of satisfaction of parents; possibly reducing the medication dosage; increasing the 'normalization' rate (reduction of problems to an average level of minor and below).

The follow-up at 36 months, 22 months after ending the active treatment phase of the study, at which point parents and children were free to choose the actual treatment, showed that all four original groups had a similar outcome, respectively improvement by comparison with pre-treatment baseline scores. Various explanations are possible: the effects of more intensive therapy disappear when the intensive treatment is stopped; self-selection of patients to treatments at the end of the randomization phase may lead to similar outcome (many children assigned to behavioural intervention started medication and a significant percent of those on intensive medication management actually withdrawn medication). The most favourable overall development was found in children who had been initially randomized to the MTA medication regime, whether or not they were taking medication at 36 months, suggesting some lasting benefit for some children with ADHD. (The reader is referred to section 7.4 for treatment monitoring issue.)

### 5.4.3 **Relapse prevention by atomoxetine and lisdexamfetamine**

In children and adolescents who had responded favourably to an initial 12-week, open-label period of treatment with ATX, ATX was superior to placebo in maintaining response for a subsequent nine-month period which was conducted under double-blind conditions. Interestingly, only 50% of the subject randomized to placebo relapsed to baseline severity (Michelson 2004). Following one year of treatment with ATX, continued treatment over the

following six months was associated with superior outcomes compared with blinded discontinuation with placebo substitution, but the magnitude of symptom relapse after drug discontinuation was often relatively modest, suggesting that subjects treated for a year with good results should be reassessed for their need for ongoing drug treatment (Buitelaar *et al.* 2006).

Following EMA guidelines, a relapse prevention study was carried out also with lisdexamfetamine. Children and adolescents who completed a 26-week open-label trial of LDX treatment were randomized 1:1 to their optimized dose of LDX or placebo for a six-week randomized withdrawal. Only 15.8% of patients receiv**i**ng LDX met treatment failure criteria (>50% increase in ADHD Rating Scale IV total score and two-point increase in CGI-S), compared with 67.5% of those receiving placebo. The rapid return of symptoms after LDX withdrawal indicates the need for continuing treatment (Coghill *et al.* 2014).

## 5.5  Safety

### 5.5.1  Stimulants and substance abuse

Stimulants are drugs of potential abuse. In animal models, both MPH and amfetamine display features typical of substances of abuse, such as compulsive self-administration, with neglect of other activities, including food intake. There are, however, important differences between therapeutic use and non-therapeutic abuse of stimulants that involve doses, route of administration, and social context. When abused, stimulants are typically injected or snorted with rituals of self-administration, powerful conditioning, and at doses that are much higher than therapeutic doses, in search of euphoria. For MPH, the reinforcing effects and 'high' are associated with the rapid changes in serum concentrations, and presumably rapid dopamine increases, associated with intravenous injection or insufflation, whereas the therapeutic effects are associated with slowly ascending serum concentrations and presumably smoothly rising dopamine levels found after oral administration. Euphoria is practically unknown among medicated children.

Concern has been raised that therapeutic use of stimulants may result in 'sensitization' and possibly increase the risk for substance abuse later in life. However, ADHD itself, associated with impulsivity, often impaired social judgment, and conduct disturbances, is a risk factor for substance abuse. Disentangling whether treatment of ADHD with stimulants results in a decrease (or an increase) in substance abuse in early adulthood in randomized clinical trials is practically impossible. Naturalistic follow-up studies do not support the contention that stimulant treatment increases risk for substance abuse (e.g. Mannuzza *et al.* 2008).

Stimulant medication prescribed for the treatment of ADHD can however be diverted by patients or families toward abuse (Wilens *et al.* 2008). Thus, history of substance abuse or the presence of current substance abuse in the family can, depending on the precise situation, be seen as either a relative contraindication for stimulant prescription, especially in the immediate release preparation., or as a reason for extremely close monitoring of a patient's stimulant use. The extended-release formulations of stimulants are less prone to diversion because these preparations cannot be easily crushed into powder for injection or snorting, and also because the once-a-day administration make parental supervision easier to enforce. Non-stimulant medications (i.e. atomoxetine) are another option for these patients.

### 5.5.2  Adverse events of stimulant medication

The common adverse effects of stimulants include decreased appetite, sleep disturbance, headaches, stomach aches, drowsiness, irritability, tearfulness, mildly increased blood pressure and pulse. Rare but more severe adverse events can include psychotic symptoms and sensitivity reactions requiring discontinuation of the medication.

Thus, stimulants are contraindicated in several circumstances, most of them uncommon in childhood: schizophrenia, severe depression, hyperthyroidism, cardiac arrhythmias, moderate to severe hypertension, angina pectoris, glaucoma, hypersensitivity, and concomitant use—or use within the last two weeks—of monoamine oxidase (MAO) inhibitors. Caution is advised in patients with motor tics, patients with known drug dependence or history of drug dependence, anorexia nervosa, or a history of suicidal tendency and during pregnancy or breastfeeding.

Strategies for dealing with side effects include monitoring, dose adjustment of the stimulant, adjustment in the timing of doses, switching medication, and, less commonly, adjunctive pharmacotherapy to treat the side effects (Taylor *et al.* 2004; Banaschewski *et al.* 2006; Graham *et al.* 2011; Cortese *et al.* 2013).

### 5.5.2.1 *Weight and growth*

Treatment with stimulants causes dose-related reductions in expected height and weight (Swanson *et al.* 2007; Faraone *et al.* 2008). Beside decreased food intake, weight gain can also be suppressed by increased activity and metabolic shifts (e.g. increased fat mobilization). These mechanisms can be related to direct medication effects or to secondary to changes in neuroendocrine hormone secretion: stimulants increase dopaminergic activity with in turn may inhibit GH secretion. Some studies also suggest that growth dysregulation may be an epiphenomenon of ADHD rather than a cause of its treatment, but more work is needed to confirm that hypothesis and to draw conclusions about the impact of long-term stimulant treatment on final adult height. Systematic reviews indicate that reductions in expected height and weight are, on average, small and appear to attenuate with time: nevertheless it is essential that physicians monitor for growth deficits to identify those children who will require a change in their medication regimen (Faraone *et al.* 2008; Durà Travé *et al.* 2012).

### 5.5.2.2 *Tics and Tourette's syndrome*

While Tourette's syndrome was once considered an absolute contraindication to stimulants, more recently several studies have shown that stimulants are quite effective in controlling ADHD in the context of Tourette's disorder and they do not inevitably worsen motor or vocal tics (Tourette's Syndrome Study Group 2002). Stimulants may be considered as an appropriate treatment option for children with ADHD and tic disorders, but careful monitoring during treatment is required: if the tics worsen, the stimulant should be suspended. It is critical to document the type and severity of tics before starting treatment in order to establish a baseline against which to assess treatment-associated changes.

### 5.5.2.3 *Pulse and blood pressure*

MPH may have a small but clinically non-significant effect (average increase <5 mmHg) on blood pressure and lead to a slight increase in pulse rate (average <5 bpm).

### 5.5.2.4 *Seizures and epilepsy*

Although longer-term effects of MPH and its effects in children with frequent seizures need to be studied, current evidence supports the use of MPH for the treatment of ADHD in those patients whose seizures are under control (Torres *et al.* 2008). When epilepsy is poorly controlled, frequency of seizures should be carefully monitored: if their frequency increases, or seizures develop *de novo*, then MPH should be stopped.

### 5.5.2.5 *Sleeplessness*

It is clinically important to distinguish children whose insomnia is an adverse drug effect from those children whose insomnia may be due to the recurrence—or worsening—of

behavioural difficulties as the medication effect subsides. For the first group of children, reducing the last dose of the day may be sufficient. For the latter group, an evening dose may be helpful.

5.5.2.6 *Other contraindications for stimulants*

Presence of florid psychosis or mania is a contraindication to the use of stimulants, which can worsen these symptoms by stimulating the dopaminergic transmission. In well-controlled bipolar disorder, use of stimulants for comorbid ADHD can be considered on an individual basis in combination with appropriate antimanic treatment.

### 5.5.3 Adverse events of atomoxetine

Common adverse effects associated with ATX include abdominal pain, nausea, and vomiting, decreased appetite with associated weight loss, dizziness, and slight increases in heart rate and blood pressure. These effects are normally transient and may not require discontinuation of treatment. ATX can increase blood pressure and heart rate. At a group level, these changes appear of little clinical significance, but there is individual variability and the clinician should measure vital signs before starting treatment and then periodically (at least monthly first, then at least quarterly) afterwards.

Very rarely, liver toxicity, manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported. Out of 351 spontaneous reports, three cases of reversible drug-induced liver injury were deemed probably related to the drug (Bangs *et al.* 2008). Six more case have been more recently reported by FDA (FDA 2009). Patients and caregivers should be alert to signs and symptoms of liver failure throughout ATX treatment: ATX should be discontinued and not resumed if a patient presents with jaundice or laboratory evidence of hepatotoxicity. Seizures are a potential risk for ATX. Suicide-related behaviour (suicide attempts and suicidal ideation) has been reported. In double-blind clinical trials, suicide-related behaviours occurred at a frequency of 0.44% in ATX-treated patients (one case of attempted suicide and five of suicidal ideation). As for stimulants, treatment with ATX can be associated with decreased appetite and weight loss.

### 5.5.4 Adverse events of alpha-2 noradrenergic agonists

Clonidine has prominent cardiovascular and central nervous systems effects that lower blood pressure and can result in symptoms of orthostatic hypotension, such as dizziness, palpitations, and rapid heart-beat, upon standing. Bradycardia is a possible side effect. Other common side effects include dry mouth and sedation.

The sedative effect of clonidine has been used to induce sleep in children with early insomnia, either idiopathic or consequent to use of stimulant medication. While this practice is apparently not uncommon in some communities, the potential risks or benefits have not been properly studied The most frequent adverse events of guanfacine, include somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. These usually emerge within the first two weeks of treatment and then remit spontaneously during treatment. Considerations about cardiovascular effects are similar as for clonidine: compared to placebo, reductions in mean systolic and diastolic blood pressure and heart rate were observed in GXR-treated patients. These were generally dose-dependent in nature. No serious QTc abnormalities were noted with GXR in the five RCTs. A precautionary statement regarding QTc prolongation was included in the Canadian SPC advising that the possibility of a placebo-adjusted QTc interval increase of 5 msec by GXR should be considered in at-risk patients (i.e. those with a known history of QT prolongation, with risk factors for *torsades de pointes* or taking medications known to prolong the QT interval). Rebound hypertension is a potential concern if alpha-2-agonists are suddenly stopped. Persistent blood pressure increases

of up to 10 mmHg have been observed in some individual at 30 days post-discontinuation, suggesting a gradual dosage decrements of no more than 1 mg every three to seven days when tapering off GXR (Elbe *et al.* 2014).

### 5.5.5 **Severe cardiovascular effects of ADHD medication**

In 2006, the FDA conducted a review on reports of sudden death in patients treated with ADHD medications using data from their adverse event reporting system (AERS).

The review identified 14 paediatric and four adult sudden-death cases reported with MPH between January 1992 and February 2005. None of them appears solely or directly related to MPH. Six of the 14 paediatric sudden deaths occurred in children with structural cardiovascular abnormalities that most likely preceded the use of MPH.

The safety review found seven cases of sudden death with ATX (three children and four adults) of which one had lymphocytic myocarditis and two had toxic levels of olanzapine or a possible seizure preceding death; none of these patients had prior history of cardiovascular problems or cardiovascular structural abnormalities. The review reported that none of the cases appears solely or directly attributable to ATX at therapeutic doses. The cases were highly confounded.

The review concluded that the rate of sudden death with MPH and ATX was below background rates available. No definitive conclusions can be drawn from the analyses of AERS cases due to the inherent limitations of the AERS and uncertainty regarding information on drug utilization and background incidence of sudden death.

Also the EMA's Committee for Medicinal Products for Human Use (CHMP) has recently reviewed MPH due to concerns over cardiovascular risks (hypertension, heart rate increases, and arrhythmias) and cerebrovascular risks (migraine, cerebrovascular accident, stroke, cerebral infarction cerebral vasculitis, and cerebral ischaemia). After reviewing all available data, the Committee concluded that there was no need for an urgent restriction to the use of MPH-containing medicines, but that new recommendations on prescribing and on pre-treatment screening and ongoing monitoring of patients are needed in order to maximize the safe use of these medicines (EMEA 2009). Specific recommendations are reported in Boxes 5.3 and 5.4.

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### Box 5.3 Precautions before starting medications

Drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural, and educational advice and intervention, full mental health and social assessment.

Pre-medication screening should include:

- full history and physical examination, including:
  - assessment of history of exercise syncope, undue breathlessness and other cardiovascular symptoms
  - heart rate and blood pressure (plotted on a percentile chart)
  - height and weight (plotted on a growth chart)
  - family history of cardiac disease and examination of the cardiovascular system
- an electrocardiogram (ECG) if there is past medical or family history of serious cardiac disease, a history of sudden death in young family members (i.e. a first-degree relative, younger than 40 years of age) or abnormal findings on cardiac history or examination (e.g. of syncope or undue breathlessness on exercise)
- risk assessment for substance misuse and drug diversion (where the drug is passed on to others for non-prescription use)

- Height and weight of treated patients treated should be monitored and compared to age-matched norms.
- Blood pressure and heart rate should be monitored regularly. Any problems that develop should be investigated promptly.
- Medications (ATX in particular) should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted.
- The use of stimulants or ATX could cause or worsen some psychiatric disorders such as depression, suicidal thoughts, hostility, psychosis, and mania. All patients should be carefully screened for these disorders before treatment and monitored regularly for psychiatric symptoms.
- There is a relative lack of information on the long-term effects of MPH. For patients who take medications for more than a year, doctors should interrupt treatment at least once a year to determine whether continued treatment is necessary.

For a recent extensive review on adverse events of ADHD medications see also Graham *et al.* 2011 and Cortese *et al.* 2013.

## 5.6 **Other drugs**

### 5.6.1 **Bupropion**

Bupropion is an antidepressant and has been shown to be better than placebo in decreasing ADHD symptoms in children. Its efficacy is however smaller than that of stimulants. The mechanism of action of bupropion remains unclear: it is a weak inhibitor of the presynaptic re-uptake of norepinephrine, dopamine, and serotonin. It is rapidly absorbed with plasma peak at about two hours and has a plasma elimination half-life of eight to 24 hours (mean 14 hours) in adults. Drug interactions are possible due to its extensive liver metabolism.

Bupropion can cause nausea, insomnia, and palpitations; it can also trigger tics and cause dermatological reactions, such as rash and urticaria, at times severe enough to lead to discontinuing the drug. Bupropion increases the overall risk for seizures, but this effect is very small if the dose is maintained within 300 mg/day. The possible effect of age on the risk for seizures has not been investigated.

### 5.6.2 **Tricyclics**

Tricyclics constitute the first generation of antidepressants: they were introduced in the 1960s and remained the usual treatment of mood and anxiety disorders in adults until the introduction of the selective serotonin re-uptake inhibitors in the late 1980s. Some of them have been tested also in the treatment of ADHD in both children and adults. Imipramine, desipramine, nortriptyline, amitriptyline, and clomipramine have been found to be more effective than placebo for the control of ADHD symptoms, but in general less effective than stimulants.

None of them has been approved by the FDA or EMEA for the treatment of ADHD: they were prescribed off-label for children with ADHD, but after the introduction of atomoxetine, they are rarely used for concerns about their potential toxicity, cardiovascular in particular. Sudden and unexplained deaths have been reported in children receiving therapeutic doses of tricyclic, most often desipramine. Some of these cases followed strenuous physical exercise. While a cause–effect relationship between therapeutic doses of tricyclic and sudden unexplained death has not been proven, the use of tricyclics has much declined after these reports. If treatment with a tricyclic is undertaken, careful pretreatment assessment

and monitoring during treatment is necessary. In addition, parents should be informed of the potential risks and advised to keep the prescribed medication in a safe place away from the child's reach.

Tricyclics inhibit the presynpatic norepinephrine re-uptake. They have also anticholinergic activity, which is responsible for some of their side effects such as dry mouth, constipation, tachycardia, and sedation, and quinidine-like effects, which are responsible for delayed electrical conduction in the heart and related potential cardiotoxicity. Blood pressure is sometime increased due to adrenergic stimulation.

Tricyclics are metabolized by hepatic microsomal enzymes, primarily the CYP2D6. On average, metabolism tends to be faster in children than in adults because of the greater hepatic parenchyma relative to body mass during development. The elimination plasma half-life of imipramine can range from six to 24 hours and that of desipramine from 12–76 hours in adults. Nortriptyline pharmacokinetics was studied in children and its elimination plasma half-life was found to range from 11 to 42 hours in 5–12-year-olds, and from 14–89 in 13–16-year-olds.

### 5.6.2.1 *Approach to treatment with tricyclics*

The tricyclic whose efficacy in ADHD has been best documented is desipramine. It is however unfortunate that most of the sudden deaths were associated with therapeutic doses of desipramine (in spite of the wider use of imipramine). It should be noted that desipramine is an active metabolite of imipramine, and that administration of imipramine results in plasma levels of desipramine. Despite the numerous unknowns about tricyclics and cardiotoxicity, it may be prudent, if a tricyclic is to be used at all, to consider imipramine or nortriptyline ahead of desipramine.

Before starting treatment, the child should receive a complete physical examination with ECG recording. Treatment should be considered only if the following limits are not exceeded on the ECG: 200 msec for the PR, 120 msec for the QRS, and 450 msec for the QTc, and the heart rate should be regular and not higher than 100 bpm. If there is personal history of arrhythmias, dizziness, fainting, palpitation, or heart abnormalities, a more thorough evaluation by a cardiologist is appropriate. Family history of sudden unexpected death or life threatening arrhythmias should be reason for avoiding use of tricyclic medication.

The starting dose of desipramine is usually about 10–25 mg once a day, then gradually raised in a few days to twice daily, and further adjusted based on clinical effects and side effects. Clinical effects can become evident in a few days, but full response may take weeks and the dose usually needs multiple adjustments. The usual therapeutic dose is between 0.7 mg/kg/day and 3.5 mg/kg/day. The ECG, pulse, and blood pressure are to be monitored when a steady state is reached (usually after four to five days of treatment) and each time the dose is increased above 3 mg/kg/day. Abrupt discontinuation of tricyclic treatment can trigger withdrawal symptoms, such as nausea, vomiting, headache, lethargy, and flu-like symptoms. To prevent withdrawal symptoms, the medication must be tapered off gradually, decreasing the dose by 10–25 mg every two to three days until complete discontinuation.

### 5.6.3 **Modafinil**

Modafinil is a 'wakefulness-promoting agent'.[1] It is marketed for the treatment of narcolepsy and has been occasionally used for the management of inattention in adults. Its mechanism is not clear (i.e. non-dopaminergic activating action on frontal cortex) but is unrelated to the sympathomimetic stimulants. Cases of Steve–Johnson's syndrome were reported during clinical trials in children, leading FDA to require new large randomized controlled trials: there is currently not enough data to consider modafinil an effective and safe medication for ADHD.

## 5.7 **Special populations**

### 5.7.1 **Pre-schoolers**

Most treatment research in ADHD has been conducted in children of six to ten years of age. The official label of MPH warns that this drug is not approved for use in children under six years old. Since amfetamine is an older drug and the label information reflects the lower regulatory standards 50 years ago, it is approved for use down to age three years. A recently completed, publicly funded, multi-site trial (Preschoolers with ADHD Treatment Study PATS, Greenhill *et al.* 2005) randomizing 160 children younger than six years to placebo or IR MPH 1.25, 2.5, 5 mg, or 7.5 mg three times daily found that the magnitude of the MPH effect (at 2.5–7.5 mg dose range) was somewhat lower than typically observed in school-aged children. MPH presented the typical profile of side effects of stimulant medication in older children, but the frequency and severity of adverse events (i.e. mood lability or reduced growth rate) were greater and led to treatment discontinuation in about 11% of cases. Continuous treatment for about nine to ten months was associated with a slight but detectable decrease in height and weight growth (Swanson *et al.* 2007).

### 5.7.2 **Children with autism spectrum disorder**

Contrary to previous system of classification, the recent DSM-5 allows a formal diagnosis of ADHD in the presence of autism spectrum disorder (ASD). A multi-site trial of MPH immediate release 7.5–25 mg/day given with three times daily dosing has been conducted in children with autism or other PDD and significant ADHD symptoms. This study indicated that this medication is effective in reducing ADHD symptoms severity but only in about 50% of the cases, a rate that is substantially lower than that observed in non-ASD children with ADHD (RUPP 2005). The proportion of children unable to tolerate the side effects of MPH was also correspondingly higher (18%) compared with normal children (less than 5%). Other smaller randomized double blind studies support these findings. MPH should therefore be considered for children with prominent ADHD symptoms in the context of ASD, but its relatively lower efficacy and tolerability must be taken into account. Two randomized double blind studies and a few open label studies show that atomoxetine moderately improve ADHD symptoms in patients with ASD, with adverse events similar to those observed in other studies with ADHD patients without ASD.

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## Chapter 6

# Psychosocial and other non-pharmacological treatments

Manfred Döpfner

> **Key points**
>
> - Psychosocial interventions for children and adolescents with ADHD include:
>   - psycho-education of the patient and their parents/teachers;
>   - family-based psychosocial interventions, in particular behavioural parent training;
>   - pre-school, kindergarten, and school-based psychosocial interventions;
>   - peer-focused behavioural interventions and social skills training;
>   - cognitive therapies for the child.
> - Other non-pharmacological interventions in children and adolescents which have at least some empirical support include neurofeedback and diet.
> - In adults, smaller studies provide some support for coaching and cognitive behavioural interventions, in both individual and group formats that support an individual's self-management strategies.

## 6.1 Introduction

Psychosocial treatments aim to reduce ADHD symptoms and other associated behavioural and emotional problems and thus increase the psychosocial functioning of the patient and his or her quality of life. Well-established psychosocial interventions for reducing ADHD symptoms and the other associated disruptive symptoms include psycho-education of the patient and parents/teachers, behavioural parent training including family interventions, teacher training, and behavioural classroom management strategies including interventions in pre-school, kindergarten, and school as well as peer-focused behavioural interventions with social skills training and cognitive–behavioural training of the patient (Taylor *et al.* 2004; Pelham and Fabiano 2008). However, recent meta-analyses question the robustness of the effects on ADHD symptoms (Sonuga-Barke *et al.* 2013).

Psycho-education is the basis of every treatment but the effects of psycho-education have not been well evaluated. Behavioural parent training and school-based behavioural interventions have been found to be the best established psychosocial interventions, while the effects of peer-focused behavioural interventions, social skills trainings, and cognitive–behavioural training of the patient have been less well studied. A combination of several of these interventions is often required since each has its own particular strengths and treatment objectives. This combined treatment is also often called multimodal psychosocial treatment. Other psychosocial interventions (e.g. psychoanalytically oriented treatment, play therapy, systemic family therapy) have either not been assessed regarding their empirical effects on ADHD symptoms or are not supported in this respect in empirical trials. Several

other non-pharmacological interventions (diet, neurofeedback) have at least some support (Sonuga-Barke *et al.* 2013).

Most of the empirical trials for non-pharmacological treatments have been conducted using young children with combined type of ADHD, a few with the primarily inattentive subtype of ADHD, and a few with adolescents or adults with ADHD. The following chapter describes content and empirical support of the different interventions as well as their treatment indications.

## 6.2 **Psycho-education**

Psycho-education for the patient and the parents is the basis of any treatment. The main aims of psycho-education are listed in Box 6.1.

The child and parents and, if consent is given by the family, the teacher are all interviewed in order to assess beliefs held about the causes of the specific problems and their potential solution. These then form the basis for informing the patient and his/her relatives about the evidence-based knowledge of what ADHD is, and for the development of a shared understanding of both the causes of the problem and the therapeutic interventions that are required. The information given should include all main areas of evidence-based knowledge about ADHD, especially symptoms, etiology, course, prognosis, and treatment, and should also cover what is *not* known. It is important to remember that education of children should be relevant to the child's level of development. The importance of psycho-education increases with the child's age. The psycho-education of pre-school children can be difficult, but all school-aged children should be offered it.

Although psycho-education is seen as a basic tool in the therapy of mental disorders, there are no studies which evaluate its effects in ADHD. Some indirect support comes from multimodal treatment studies showing symptom reductions during initial psycho-education and enhanced treatment effects by combining psycho-education with pharmacotherapy compared to pharmacotherapy alone (e.g. Doepfner *et al.* 2004).

## 6.3 **Family-based psychosocial interventions**

Behavioural parent training (BPT) has been shown to be effective in improving the child´s behaviour and decreasing maladaptive parental behaviour. In some studies additional positive effects on reducing parental stress and improving child classroom behaviour have also been shown. However, the generalization of treatment effects from the family to other situations (e.g. school) is the exception rather than the rule. BPT explicitly provides parents with a range of behaviour modification techniques that are based on social learning principles (see Box 6.2, adapted from Taylor *et al.* 2004).

Most training programs last between eight and 12 sessions. In spite of many differences in design and implementation between programmes, behavioural parent training is one of the most successful psychosocial interventions for the treatment of children with ADHD and it meets the criteria for being a well-established treatment with substantial evidence of efficacy (Pelham and Fabiano 2008).

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**Box 6.1  Aims of psycho-education**

- Development of a therapeutic relationship with the patient and the parents
- Collection of information about their individual health beliefs and attributions
- Establishment of what the patient, the parents (and teachers) knows about ADHD
- Definition of treatment goals as well as the development of a conjoint treatment plan

> ### Box 6.2 Components of behavioural parent training (adapted from Taylor et al., 2004)
>
> 1. Identification of specific problem situations, and specific behaviour problems within these situations.
> 2. An analysis of positive and negative consequences and contingencies of appropriate and problem behaviours together with the parents.
> 3. If coercive and unpleasant parent–child interactions occur very often, and positive parent–child interactions occur rarely, attempts should be made to enhance parental attending skills during supervised playtime sessions.
> 4. Teaching the parents effective methods of communicating commands, how to set rules and pay positive attention to their child's compliance.
> 5. The use of token systems in order to reinforce appropriate behaviour in specific situations.
> 6. The development together with the parents of *appropriate* mild negative consequences for problem behaviour. These consequences should be closely and consistently linked to the problem behaviour.
> 7. Teaching the use of response cost systems in order to reduce very frequent behaviour problems. Parents are taught to remove chips or points from a pool if the problem behaviour occurs. The remaining chips belong to the child and can be changed into backup reinforcers.
> 8. Teaching the use of time out from reinforcement as a punishment procedure for more serious forms of child non-compliance if negative consequences to problem behaviour are not effective. This intervention has to be explained very carefully to the parents and has to be monitored very carefully lest it become punitive.
> 9. In adolescence, teaching the use of contingency contracting rather than token systems or response cost systems and stress self-management procedures. The use of problem-solving and communication training as well as cognitive restructuring is supported with the aim of reducing parent–adolescent conflicts.

Behavioural parent training has demonstrated positive effects in individual (e.g Sonuga-Barke *et al.* 2001) as well as group settings (e.g. Pelham and Hoza 1996). Positive effects of parent training has been demonstrated for children of all age groups—for pre-school children at risk for ADHD (Sonuga-Barke *et al.* 2001, Hautmann *et al.* 2008) school aged children (Pelham, and Hoza 1996; Doepfner *et al.* 2004), and adolescents (McLeary and Ridley 1999), with regard to both ADHD symptoms and comorbid symptoms as well as on parenting. However, a recent meta-analysis found only small effects on parent-rated ADHD symptoms and no effects on more blinded assessment measures using stringent methodological criteria (Sonuga-Barke *et al.* 2013). However, for clinical practice unblinded parent ratings may be more informative. More robust effects were found on parenting and conduct problems (Daley *et al.* 2014), and change in parenting has been shown to be a mediator for child behaviour change (Hanisch *et al.* 2013). Little is known about the differential effects of parent or child characteristics on the outcome of these programmes. Sonuga-Barke, Daley, and Thompson (2002) reported that the presence of maternal ADHD resulted in less child improvement than non-ADHD maternal status when the mother participated in a BPT class, demonstrating a negative moderating effect of parental psychopathology on treatment outcome. Hautmann and colleagues (2010) found that severely impaired children profit most in a prevention trial with children at risk for ADHD.

Some but not all studies have shown an additional benefit can be achieved by combining parent training with medication. Firm conclusions about the additional effects of medication on parent training are difficult to draw from most of the studies which combine different intervention,s especially where studies have included additional interventions beyond the parent training and medication; e.g. additive school interventions or even more complex programs.

Self-help interventions for parents of children with ADHD use the techniques developed in BPT and sometimes add short telephone-based counselling sessions. These interventions have been shown to be effective in a number of trials especially in pre-school children (O'Brien and Daley 2011; Kierfeld *et al.* 2013).

## 6.4 **Psychosocial interventions in pre-school and school settings**

The main components of psychosocial interventions delivered in the pre-school and school settings are: the discussion of classroom structure and task demands with the teacher, the identification of specific problem situations and specific behaviour problems, the analysis of positive and negative consequences and contingencies of appropriate and problem behaviours, the enhancement of the differential attending skills of the teacher, and the implementation of token economy systems, response cost systems, and brief time out from reinforcement. The integration of the child as an active member in this therapeutic process is important (Taylor *et al.* 2004).

Using a higher-level classification classroom intervention can be distinguished from academic intervention.

- **Classroom interventions** include modifications of the classroom itself and strategies of behavioural classroom management.
- **Academic interventions** can be defined as school interventions that focus on promoting conditions conducive to improving academic achievement.

Teaching the teachers about ADHD as well as about treatment strategies (psycho-education) is important in order to increase the likelihood that the psychosocial interventions are implemented within the school. This also depends on the cooperation of the school in creating a setting within which the teacher can actively and willingly take part in the treatment of a child.

Another crucial point for the effective implementation of school-based interventions is the establishment of an effective collaboration between the home and the school. Conflicts between the two, which can be instigated by either party, ignoring the work of the other or working on different goals can lead to frustration of the teacher and/or the parents and reduce the effectiveness of the intervention.

### 6.4.1 **Classroom interventions**

The overall approach to teaching children with ADHD should involve paying attention to the structuring of the whole classroom environment and not only to specific tasks. A common intervention is the use of individual and separated desks which helps to decrease pupil distraction. The use of visual aids such as posters and signals can also be used to structure the classroom. Studies also show that traditional classroom settings with rows of desks and chairs and opposite-sex seating can increase task engagement and lead to lower levels of distractibility.

Other well-established behavioural classroom management interventions include specific behavioural techniques as praise, planned ignoring, giving effective commands, and daily report

cards as well as the use of contingency management techniques (e.g. incentives, reward programs, point systems, time out techniques).

Several reviews and meta-analyses have shown behavioural classroom management to be effective (Chronis *et al.* 2006; Daly *et al.* 2007; Fabiano *et al.* 2009; Pelham and Fabiano 2008). Most studies show effects on both classroom behaviour and social adjustment, but the effects on academic performance are less clear. Many studies have used single-subject designs and only a few have examined the effects of classroom interventions using a between-group design. Miranda (2006) demonstrated the effects of a multi-component classroom intervention which included psycho-education for the teacher, use of contingency management, instructional management procedures as well as changes in classroom environment, and use of self-instructional procedures. This programme resulted in significant improvements in ADHD symptoms, and reduced school problems and antisocial behaviour reported by both parents and teachers.

### 6.4.2 **Academic interventions**

Although it is well recognized that children with ADHD are at risk of significantly lower academic achievement and poor academic outcomes, very little treatment research has been conducted in this area. Peer tutoring, computer-assisted instruction, task and instructional modifications, and strategy training are all potential interventions that aim to increase on-task behaviour and thus enhance academic achievement.

Peer tutoring is an instructional strategy whereby two students work together on an academic task with one student providing assistance, instruction, and feedback to the other. All models of peer tutoring aim to increase on-task behaviour and enhance the pupil's attention. A well-described model is class-wide peer tutoring (CWPT; Greenwood *et al.* 1988). Tutoring is carried out by pairs, with praise and points for correct answers and correction with subsequent practising for wrong answers. CWTP has been shown to result in increased active engagement in academic tasks and reduction in off-task behaviour, with a subsequent improvement in academic performance by ADHD students (DuPaul *et al.* 1998).

Another method of academic intervention uses the modification of tasks and instructions (see Box 6.3). Task modifications involve revision of the curricula, whereas modification of instructions involves adapting the content and delivery of instructions to meet the needs of ADHD children.

Again, there are very few studies exploring the effects of task and instructional modification.

A very specific form of instructional modification is the use of computer-assisted instruction (CAI) to improve the academic achievements of students with ADHD. Specific instructional characteristics of CAI include: the highlighting of essential material, the use of multiple sensory modalities, the division of content material into smaller segments of information, the provision of immediate feedback about response accuracy, and limiting the presentation of non-essential

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**Box 6.3 Recommendations for altering academic tasks (Source data from: Barkley, 2006)**

- matching the tasks to each child´s abilities
- varying the presentation format and task materials to maintain interest and motivation
- brief and one-at–a-time presentation of academic assignments
- enthusiastic yet task-focused presentation with the possibility of frequent and active child participation
- interspersing academic periods with brief periods of physical exercise
- scheduling the more academic subjects into the morning hours
- reducing the length of written assignments
- allowing extra time for written tests

and distracting features. The few studies of CAI that have been conducted report an increase in both attention and on-task behaviour.

Strategy training is another form of academic intervention and is closely related to the strategies that are taught in cognitive therapy. Strategy training helps the student to develop a set of strategies which are specifically designed to address the demands of an academic situation and which can directly address the student's needs, e.g. taking notes or self-reinforcement.

## 6.5 Peer interventions and social skills training

Interventions aimed at increasing social skills were developed in an attempt to reduce the social problems which frequently result from the core symptoms of ADHD. These interventions focus on the development and reinforcement of appropriate social skills such as communication, cooperation, participation, and validation. Unfortunately traditional office-based social skills training produces minimal effects and the social validity of these interventions is therefore questionable. Several studies do, however, support the use of behavioural interventions aimed at reducing peer relationship problems in recreational settings—typically, summer treatment programs. These usually combine social skills training, a reward–cost system, and group practice as well as sport and membership skills. Positive effects including enhanced social functioning have been shown in several randomized controlled studies (Pelham and Fabiano 2008). In a comparably complex after-school program for middle scholars, Molina and colleagues (2008) targeted educational, social, and recreational skills, homework completion, and school and home behaviour in a ten-week programme and showed greater improvements in functioning of the active treatment group compared to a comparison group.

## 6.6 Cognitive–behavioural trainings of the patient

Cognitive–behavioural therapies all aim to promote self-controlled behaviour through the enhancement of problem-solving strategies. Several different types of cognitive–behavioural treatments aimed at helping children with ADHD have been developed. These have included a variety of techniques including verbal self-instructions, problem-solving strategies, cognitive modelling, self-monitoring, self-evaluation, and self-reinforcement. While earlier studies using these different types of cognitive–behavioural interventions could not demonstrate clinically important changes on either behavioural measures or academic performance in children with ADHD, a recent study (Abikoff *et al.* 2013) showed that organizational skills training was effective on several outcome measures. Moreover, there is some limited evidence that a combination of social skills training and problem-solving interventions can show positive effects if they are combined with intensive, multicomponent behavioural treatment packages.

Facilitating core skills of executive functioning or working memory is another recent approach. A meta-analysis however did show that cognitive trainings may have some effects on parent rated ADHD symptoms, but no substantial effects on ADHD symptoms in blinded outcome measures (Sonuga-Barke *et al.* 2013).

## 6.7 Multimodal psychosocial interventions

A multimodal psychosocial treatment approach, utilizing a combination of several of the psychosocial interventions described above, is often needed since children typically present with a variety of problems and each of these interventions focuses on different treatment objectives. It is therefore unsurprising that the majority of clinical trials have included treatment packages that included all or some combination of the behavioural interventions. Outcomes

have typically been measured for each domain independently, the suggestion being that the intervention component targeted at a particular domain was responsible for the outcomes in that domain and the conclusion being drawn that all components are necessary to bring about overall change in the child. Although this may be the case in most cases it remains an assumption that is not yet backed by empirical evidence.

In the Multimodal Treatment Study of ADHD (MTA; MTA Study Group 1999), the 'behavioural treatment' package included a course of behavioural parent training along with a school intervention, and a summer programme over the course of a 14-month intervention. With respect to ADHD symptoms, the behavioural treatment group was not significantly different from the community treatment comparison group—a randomly assigned condition receiving treatment as usual from community providers, 68% of whom received medication for ADHD during the treatment period. In addition, and often not reported, at 14 months the behavioural group was superior to the medication management group, who received the MTA medication algorithm, with respect to parent satisfaction with treatment and parent-perceived improvement in referring problems (Pelham *et al.* 2008), and on observed parenting skills (Wells *et al.* 2006).

Both the results of the MTA-study and meta-analyses of other trials using psychosocial interventions suggest that in the short-term the effect sizes of psychosocial interventions are roughly about the half that of stimulant medication for ADHD core symptoms. However, despite the superiority of the medication algorithm at the end of the active treatment phase, follow-up observational studies of the MTA groups did not find substantial lasting differential effects of the different treatment modalities in the long-term once the study treatments were withdrawn and the children and their families were free to choose what treatment they received from their local providers (Swanson *et al.* 2007).

Most of the studies discussed above have been conducted with the parents of children with combined-type ADHD. A programme that combined teacher consultation, parent training, and child skills training (skills for independence and social competence) was, however, shown to be effective in reducing symptoms as well as in increasing organizational and social skills in children with predominantly inattentive subtype ADHD (Pfiffner *et al.* 2007).

In view of our current lack of knowledge about which components of a multimodal treatment approach actually make a difference, a step-by-step approach may be an alternative to combining all the different interventions together at one point of time (Taylor *et al.* 2004; Doepfner *et al.* 2004). A more individually tailored adaptive multimodal treatment approach dependent on the particular problems shown by an individual and on the effects of each treatment step may be a good alternative for many children.

## 6.8 **Neurofeedback**

Neurofeedback, a specialized type of biofeedback, is an operant conditioning procedure that attempts to enhance self-regulation of brain activity. Over about 25–50 sessions, brain electrical activity is recorded by an electroencephalogram (EEG) and immediately fed back to the patient using visual or acoustic signals. Reinforcement is given when the patient changes their brain activity in a certain direction. These changes are supposed to have an impact on behavioural parameters. Neurofeedback for patients with ADHD aims to reduce activity within the theta-band and enhance activity in the beta-band. This pattern of brainwave activity is supposed to be related with an attentive but relaxed state and less hyperactive symptoms. A meta-analysis however did show that neurofeedback may have some effects on parent rated ADHD symptoms, but no substantial effects on ADHD symptoms in blinded outcome measures (Sonuga-Barke *et al.* 2013). Further controlled studies are necessary to establish

clinical efficacy and effectiveness and to learn more about the mechanisms underlying success-ful training.

## 6.9 **Food additives and restriction diets**

Numerous food additives have been proposed to have a substantial impact on ADHD symp-toms but only a few of these have been investigated in randomized controlled studies.

Essential omega-3 and omega-6 fatty acids are phospholipids which are contained in neu-ronal cell membranes of the brain. They are supposed to exert a positive effect on neurotrans-mission and so it has been hypothesized that a lack of those polyunsaturated fatty acids may play a major role in the pathogenesis of ADHD. These fatty acids cannot be synthesized by the human body and therefore have to be obtained from foodstuffs or added as food supplements.

Investigations of the effects of omega-3 and omega-6 fatty acid supplementation have reported inconsistent results. Some studies found no reduction in ADHD-symptoms after docosahexaenoic acid (DHA) supplementation was given while other trials with eicosapentae-noic acid (EPA), or combinations of essential fatty acids which include EPA, have been reported to ameliorate ADHD-related symptoms in populations with elevated ADHD symptoms (Richardson, and Montgomery 2005), or in patients with the inattentive subtype of ADHD (Johnson *et al.* 2009). Meta-analyses (e.g. Sonuga-Barke *et al.* 2013) did show small but robust effects. In a recent open-label study, strong and stable effects were found (Barragan *et al.* 2013)

Some food components have been postulated to have a negative impact on behaviour, and it has been supposed that the elimination or restriction of those components from the diets of children with ADHD will decrease ADHD symptoms. Such substances include sugar, several preservatives, food colourings, and potentially allergenic foodstuffs. The effects of restriction of potentially allergenic food are quite strong on unblinded measures but no effects were found on more blinded ratings. However, artificial food-colour exclusions result in a small but robust effect on ADHD symptoms (Sonuga-Barke *et al.* 2013). Further studies are needed to address the question of whether restricting these additives in the diets of children with ADHD will reduce their symptoms.

## 6.10 **Non-pharmacological treatment options for adults with ADHD**

In recent years there has been growing awareness for the need for non-pharmacological treat-ment options for adults with ADHD of which between 20% and 50% do not show significant symptom reduction with medication or who are unable to tolerate ADHD medications. Even those who do respond to medication often have only symptom reductions of 50% or less. Also, adults requesting treatment for ADHD usually have complex problems extending well beyond the core ADHD symptoms which are unlikely to respond to ADHD medication.

Non-pharmacological treatments for adults with ADHD include counselling, coaching, and individual or group cognitive–behavioural therapy. Unfortunately, these approached have received very little in the way of research investigation.

Counselling and psycho-education can be conducted in either an individual or a group setting and have considerable conceptual overlap with cognitive–behaviour therapy. Patients receive information about ADHD and are taught strategies to meet their individual goals. Although there are workbooks to support this approach (e.g. Weiss 1994), no studies have investigated the effects of these counselling approaches on adults with ADHD.

Coaching is defined as a supportive and pragmatic process. The patient and personal coach work together, usually via short daily telephone calls, with the aim of identifying goals and to

developing strategies to meet them (Barkley 2006). To-date, there is no standard methodology and no research has been done on this form of intervention for adults with ADHD.

Published accounts of the efficacy of cognitive–behaviour therapy for adult ADHD are at the earliest stages of empirical confirmation. Nonetheless, the studies provide encouraging findings, supporting the acceptability of this treatment approach, and suggesting that it can offer beneficial treatment outcomes for patients (Safren *et al.* 2004). Moreover, several recent trials did show encouraging effect supporting the efficacy of cognitive interventions (e.g. Solanto *et al.* 2010).

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# Organizing and delivering treatment

David Coghill and Marina Danckaerts

## Key points

- The delivery of treatment for ADHD can be broken down into several steps:
  - Deciding on the targets for treatment
  - Choosing, starting, and optimizing the first treatment
  - Monitoring treatment
  - Adjusting and switching treatments
- Treatment is about more than just symptom reduction; it also involves managing comorbid disorders and improving quality of life.
- The decision about whether to use a behavioural or pharmacological treatment as the first option is a complex one which depends on a range of different factors.
- It is essential to take baseline measures and to continue to monitor both positive and negative outcomes on a regular basis.
- When initiating medication treatments for ADHD the use of recognised titration protocols can help to ensure that treatment is optimized.
- Similarly, the use of a structured protocol for adjusting doses and switching medication will help ensure that evidence based treatment decisions are made whenever possible.

## 7.1 Introduction

Following diagnosis, all children with ADHD will require some form of intervention and most will require treatment over a relatively prolonged period of time. Psycho-education forms the cornerstone of treatment and should be offered to all those receiving a diagnosis and to their families. Additional treatments are usually indicated and, as described in the preceding chapters, there is now a broad range of therapeutic approaches available to manage the core ADHD symptoms of which the behavioural psychotherapies and medications are supported by the strongest evidence base (although see Sonuga-Barke *et al.* 2013). Many children will also require treatment for a range of other psychiatric and non-psychiatric disorders and other co-existing problems such as peer relationship and family difficulties. The material contained in this chapter draws heavily on work conducted by the European ADHD Guidelines Group (EAGG), and will attempt to present a clearly described implementable version of the evidence-based guidance and strategies for initiation, monitoring, and maintenance of ADHD treatment previously developed and published by this group (Taylor *et al.* 2004; Banaschewski *et al.* 2006; Graham *et al.* 2011; Cortese *et al.* 2013).

The four main sections will deal with deciding on the targets for treatment, initiating the first ADHD treatment, monitoring treatment, and adjusting and switching treatments. In each section we will make use of 'process diagrams' similar to those used in chapter 4. As before, each of these illustrates the tasks that have to be addressed at each stage of the clinical process. These process diagrams should not be seen as prescriptive and we suggest that they be used to stimulate discussion within teams and services and to help problem-solve any barriers to practice and to develop an evidence-based care pathway that works for their particular circumstances.

## 7.2 **Deciding on the targets for treatment**

Most children with ADHD will present with multiple problems in addition to their core ADHD symptoms and the associated impairments. This means that it is usually necessary to decide which problem or problems should be tackled first. Sometimes the decision is simple (e.g. child protection concerns clearly outweigh most other problems), but in most circumstances the choice depends on a combination of severity (actual and perceived), relative importance (to the child, their parents, the school, and the clinician), the availability of an evidence-based treatment, and pragmatic clinical decision making (e.g. poor peer relationships and academic functioning with low self-esteem are often judged to be secondary to ADHD symptoms, in which case it would seem sensible to treat the ADHD symptoms first and observe the impact of this on the other difficulties). Whilst it is of course possible to address several problems simultaneously, it is helpful if, when making a treatment plan, one is explicit about what one is and is not hoping to change in order that patient and parent expectations are managed. Making treatment targets explicit also helps set treatment goals and make accurate baseline measures so that treatment change can be monitored adequately with appropriate measures. Broad domains are described in Box 7.1. Within each of these domains it is then necessary to make specific, explicit, clear, achievable targets.

In clinical practice, several situations where a child/young person is suffering from more than one psychiatric disorder can present particularly difficult choices. This includes ADHD with comorbid depression, anxiety, Tourette's/tics, autism spectrum disorder, or substance misuse. These situations are discussed in more detail in section 7.3.

## 7.3 **Initiating the first ADHD treatment**

### 7.3.1 **Choosing the initial treatment**

When the decision is made to start treatment for ADHD, and after psycho-education is given to the child and his or her family, it is necessary to consider which treatment should be initiated first (see Figure 7.1). The first decision is whether to start with behavioural treatment (usually group parent training) or medication. There have been differences between the choices

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**Box 7.1  Potential target symptoms and problems**

- Core ADHD symptoms both at home and at school
- Oppositional and disruptive behaviour in the home
- Oppositional and disruptive behaviour in at school
- Academic problems
- Parent–child relationship and communication problems
- Peer relationships
- Other associated symptoms (e.g. anxiety, mood instability, depression, dyspraxia, specific learning disorders, speech and language problems, etc.)

| Trigger | • Child/young person is diagnosed with ADHD and decison to treat ADD symptoms is made |
|---|---|
| **Clinicians involved** | • Child and Adolescent Mental Health Services<br>• Developmental/behavioural paediatrics |
| **Aims** | • To choose the most appropriate initial treatment |
| **European Guidelines recommendations** | • All of those diagnosed with ADHD (and their families) should receive psycho-education<br><br>• Services that diagnose ADHD need to be able to offer/access a wide range of treatments (pharmacological and non-pharmacological)<br><br>• When the diagnosis is one of ICD—10 hyperkinetic disorder ('severe pervasive and impairing ADHD') the first-line treatment is usually medication unless there are contraindications to medication<br><br>• In those with less severe ADHD (DSM-IV ADHD—including inattentive type—but not hyperkinetic disorder) either behavioural treatment or medication can be considered<br><br>• Additional problems—e.g. reduced social compliance, poor self esteem, and family stress—will also usually need to be addressed and will require a broad range of therapeutic skills<br><br>• Comordid disorders—e.g. specific learning disorders (dyslexia), dyspraxia, and other psychiatric disorders—may necessitate alternations to the treatment plan or additional treatment |
| **Outcomes** | • Initial treatment choices are made using evidence based principles |

Figure 7.1 Choosing the correct first treatment.

traditionally made at this stage by European and US clinicians. In the US, medication is usually considered to be the first-line treatment for all ADHD, irrespective of severity. European clinicians have traditionally been more conservative and have reserved medication only for those meeting the much more restrictive ICD-10 criteria for hyperkinetic disorder (i.e. where symptoms from all three domains are present and impairing across more than one setting). Recently attitudes across Europe have changed and there has been an increase in the willingness to consider medication for children with less severe ADHD. Evidence has provided a degree of support for both views. Santosh *et al.* (2005) re-analysed data from the influential Multimodal Treatment of ADHD study (MTA study) and found that whilst for children with ICD-10-defined hyperkinetic disorder ('severe pervasive disabling ADHD'), a carefully crafted medication management was clearly more effective than an intensive behavioural programme, for those with less severe ADHD there was little difference between the two approaches. On the basis of these results, the EAGG recommended that unless there are contraindications, medication should be considered as a first-line treatment for children with hyperkinetic disorder. Whilst either medication or behavioural treatment (usually in the form of group parent training and/or school-based behaviour modification programmes) can be considered as the initial treatment for those with less severe ADHD (Taylor et al. 2004), with the implication that behavioural treatment will usually, but not always, be the most appropriate first option. In the UK, the National Institute for Health and Care Excellence (NICE 2008) has taken a similar, although rather less flexible, approach. It recommends that medication, as a first-line treatment, should be restricted to those with severe ADHD and that a group parent-training/education programme, either on its own or together with a group treatment programme for the child, should be offered to all and should be the first treatment for those with less severe ADHD. On balance we feel that the EAGG recommendations are appropriate in most circumstances. Whilst the recent systematic review of non-pharmacological treatments (Sonuga-Barke *et al.* 2013) suggested that parent training has not yet been equivocally demonstrated as having a specific impact on core ADHD, it may of course be helpful for oppositional behaviours and other more broadly defined behavioural problems.

There are of course situations where behavioural treatment may not be practical. For example, the presence of parental mental illness or substance misuse, language barriers or poverty in parents may all make behavioural treatment unfeasible. There are also situations where rapid change is required and this is more likely to occur with medication. Also some families will choose medication over behavioural treatments. In such circumstances *and* where a behavioural approach has been unsuccessful, medication treatment should also be considered as an option.

### 7.3.2 **Choosing the first medication**

There are now several medications and several formulations licensed for the treatment of ADHD (see chapter 5). It is therefore important to think about the general order in which these should be considered and under what circumstances these general rules should be broken. These questions were addressed in detail by the EAGG (Banaschewski et al. 2006). They decided that, on the basis of the available evidence, in most cases methylphenidate will be the first-choice medication. Atomoxetine may however be considered as first choice under particular circumstances such as:

- A current or past history of substance misuse
- In the presence of tics
- In the presence of anxiety
- Where there is a strong family preference to avoid stimulants

They also considered whether the immediate or extended-release methylphenidate preparations are to be preferred as first-line treatments and concluded that, where cost is important and a stimulant is being thought of, the cheaper and more flexible immediate-release preparation will usually be the first choice. However, an extended-release stimulant may be considered important to reduce stigma and increase privacy, where compliance needs to be addressed and to reduce the chance of diversion. In practice, many clinicians now start with an extended-release preparation and those that still initiate treatment with immediate-release methylphenidate usually switch most patients to an extended release preparation shortly after the dose is stabilized. Which extended-release preparation is chosen will depend on the desired profile of action required across the day.

An amfetamine pro-drug, lisdexamfetamine, has been licensed for the treatment of ADHD in several countries in North and South America and in Europe and Australia. In the Americas and Australia, the license is for general use including use as a first-line treatment. Available evidence suggests that lisdexamfetamine is at least as effective as methylphenidate and that it has a similar adverse event profile. It is also associated with a relatively low abuse potential and has a duration of action of around 13 hours. In these countries it would seem reasonable to consider lisdexamfetamine alongside the extended-release methylphenidate preparations as a potential first-choice treatment, although cost and reimbursement may be an important consideration. In Europe, the license for lisdexamfetamine covers use in those who have not achieved optimal treatment with methylphenidate, meaning that it should not generally be considered as the first medication treatment for ADHD.

### 7.3.2.1 *Special circumstances*

As noted in chapter 2, when ADHD occurs in association with other disorders alteration to the treatment plan is sometimes required. The following recommendations take into account the available evidence.

*ADHD + depression.* The clinician should determine which disorder requires addressing first. If it is the depression that is causing the most severe impairments and concern, then usual treatment guidelines for depression should be followed after which the ADHD symptoms can be addressed following the principles outlined above. Where the ADHD is to be treated first, stimulant medication, if required, should be titrated carefully as this may further lower mood. Otherwise treatment should follow the usual pathway with secondary treatments being offered for depression should this not resolve with treatment of the ADHD. The potential for drug × drug interactions should be remembered. This is particularly relevant for atomoxetine and fluoxetine, both of which are metabolised by CYP2D6 and co-prescription can lead to increased levels of both drugs.

*ADHD + anxiety.* Whilst there is some evidence to suggest that those with ADHD with comorbid anxiety disorders do not respond as well to methylphenidate as those without comorbid anxiety, this is not the same as saying that stimulants are ineffective in the presence of anxiety, and anxiety is not a contraindication. There is some evidence to suggest that atomoxetine may reduce anxiety symptoms in the presence of ADHD and it may therefore be considered in such cases. However, a further search for psychological stresses on the child is always in order, and if they cannot be simply alleviated, then psychological treatment may have more to offer than repeated drug trials.

*ADHD + tics.* Comorbid tics may sometimes be worsened by stimulants. This is not inevitable, and stimulants are sometimes useful even for the hyperactivity seen in Tourette's syndrome. Atomoxetine is an alternative and appears to be less likely to exacerbate tics. Where atomoxetine is ineffective and methylphenidate whilst effective is exacerbating tics (and a dosage

reduction does not lead to an improvement), or if the tics are continuing to cause significant psychosocial impairment, the use of a tic-reducing medication either as a monotherapy or in parallel with ADHD medication (e.g. clonidine, aripiprazole, risperidone, pimozide, tiapride) seems to be indicated. Behavioural therapy may be added for tics and obsessive symptoms.

*ADHD + autism spectrum disorder.* It is always appropriate for these cases to be seen by specialist services. There is little trial evidence, but we suggest that where ADHD is comorbid with autism, a trial of medication for the symptoms of ADHD should be considered. Medications should be started at the lowest practical dose and titrated slowly and carefully as these children are more likely to suffer from adverse effects, even at low doses. Methylphenidate itself is often the most helpful; atomoxetine, clonidine, guanfacine, and even risperidone and aripiprazole may have their place. Behavioural therapy, targeting the ADHD symptoms, is also widely applicable.

*ADHD + substance misuse.* There is little research evidence to guide clinicians when treating individuals with ADHD and an established substance-misuse disorder. Treatment plans should address both disorders and should include psychosocial interventions aimed at reducing substance misuse and relapse prevention. There are indications that effective treatment of core ADHD symptoms may enhance effective treatment of substance misuse. Pharmacological therapies for ADHD should be started with caution and under close supervision. Atomoxetine is unlikely to be abused and extended-release stimulants are likely to be less capable of being abused than their immediate-release counterparts.

### 7.3.3 **Initiating a new medication**

Clinical trials have shown that ADHD medications are very effective at reducing core symptoms and that in many cases both symptoms and impairment can be reduced such that impairment is minimal. This does however require the child to be treated with the right medication at optimal doses (see Figure 7.2). Not every patient will respond to every medication and, for the stimulants at least, it is important to recognize that it is not possible to predict the most effective dose from consideration of the patient's age or weight or the severity of their symptoms. It is therefore necessary to titrate patients onto each new medication whilst carefully measuring both their response to medication and any adverse effects (see chapter 4).

Key to this process is the routine use of standardized rating scales to measure treatment response and the routine assessment of adverse effects.

There are a wide range of available measures for assessing treatment response. In our clinic we favour the use of freely available measures and have chosen the SNAP rating scale (Swanson *et al.* 2005), used as a clinician-rated semi-structured interview with parents and patient, as our main measure of ADHD symptoms and response to treatment. The ADHD and oppositional defiant disorders section are used at each appointment as we find that giving the parents a chance first to discuss their child's opposition often helps them give a clearer and less prejudicial account of the ADHD symptoms. Teacher ratings, using the ten-item SKAMP questionnaire (Wigal *et al.* 1998), are also collected at each appointment. It is also helpful to rate global impressions using the Clinical Global Impressions Severity and Improvement scales (CGI-S and CGI-I; NIMH 1985) and the Children's Global Assessment Scale (CGAS; Shaffer 1983) which are quick and reliable ways of monitoring overall improvement.

For adverse effects it is helpful to have a standardized set of questions to rate the presence or absence of common adverse effects and to note whether or not these are impairing. Pulse, blood pressure, height, and weight should be measured and charted against age- and gender-matched norms (see chapter 5, Boxes 5.3 and 5.4).

| Trigger | • A decision is made to initiate ADHD medication for the first time |
|---|---|
| **Clinicians involved** | • Child and Adolescent Mental Health Services<br>• Developmental/behavioural paediatrics |
| **Aims** | • An effective treatment should result in 'considerable improvement with no problematic adverse effects'<br>• To stabilize on the most effective dose with the least adverse effects |
| **European Guidelines recommendations** | • Titration protocols should be used to ensure that patients is stabilized on the most effective dose<br>• The use of reliable standardised rating scales— e.g. ADHD-IV rating scale, SNAP, Conners' rating scales— for monitoring treatment effects<br>• Baseline measures should include documentation of levels/presence of both symptoms and potential adverse effects, including;<br>• Pulse and blood pressure— six monthly<br>• Height and weight—plotted on growth chart<br>• Appetite, tics, depression, irritability, withdrawl, spontaneity, perseveration |
| **Outcomes** | • patient is either stabilized on an effective and tolerable dose of medication or identified as a non-responder—either by virtue of 'non-response' or intolerable adverse effect |

Figure 7.2 Initiating a new medication.

It is essential that all of these measures are first measured at baseline, *prior* to the first dose of medication, in order that change can be assessed accurately. This is especially important for potential adverse effects as many children with ADHD will have issues with sleep, mood dysregulation, irritability and the like prior to treatment and this needs to be taken into account when assessing potential adverse effects of treatment.

### 7.3.3.1 *Titrating on to methylphenidate*

There are several different protocols for titrating on to methylphenidate. Perhaps the most common is the *forced dose titration* method whereby the child is started on a low dose (e.g. 5 mg of immediate release twice of three times per day, or the equivalent of an extended-release preparation). Baseline measures are recorded and the child is reviewed after approximately one week (either in person or by telephone), and baseline measures are repeated. Additional information from school is obtained using a standardized rating scale if possible. If the child has improved, and there is *no room for further improvement*, treatment is continued at the current dose. If there is either improvement with room for further improvement or no improvement, *and* there are no significant adverse effects, the dose is increased (e.g. to 10 mg immediate release) and the patient is reviewed a week later. Titration is continued either until there is no further room for improvement (remission, as a guide we use a total score of <18 on the ADHD symptoms of the SNAP), there are significant adverse effects, or the maximum routine dose is reached (usually 20 mg three times daily immediate release or with a pause at 15 mg three times daily in children <25 kg). The aim is to get maximum response, with minimum adverse effects, at the lowest required dose. The European Guidelines recommend a maximum daily dose of around 100 mg methylphenidate, but doses higher than 60 mg are normally only recommended where there is already a clear, but not yet optimal, response to the 60 mg dose. Thus at the end of the four-week titration period the clinician will have decided that the patient:

- has responded best to a particular dose
- has responded but cannot tolerate the optimal dose due to adverse effects, and either
  - shows an acceptable response, with no or tolerable adverse effects at a lower dose or,
  - does not show an acceptable response at a lower dose
- has not responded at any dose

Whilst we find this practice is acceptable to most families, an alternative strategy that is less intensive and may be more practical in some situations is for parents to give 5 mg of immediate release methylphenidate on a weekend/holiday morning and then to introduce a cognitively demanding task about one hour later, and observe general effect. If there are no adverse effects 10 mg can be given on another weekend/holiday morning (and 15 mg on another in teenagers). Parents draw conclusions as to tolerability and likely effect. If this is favourable they can discuss with prescriber extending the trial to mornings only during school week with the teacher measuring effect with a standardized rating scale. Where effectiveness is established it is still necessary to optimize dose and again one should aim for maximum response, with minimal adverse effects at the minimum dose. It is important to remember that some adverse common effects such as loss of appetite or sleep problems can sometimes be managed by adjusting routines or the timing of doses.

### 7.3.3.2 *Titrating on to dexamfetamine*

Clinicians titrating patients on to dexamfetamine can follow the same procedures described for methylphenidate but with reduced doses (5 mg methylphenidate ≈ 2.5 mg dexamfetamine).

### 7.3.3.3 *Titrating on to lisdexamfetamine*

A similar approach to that described for methylphenidate can be used but with a starting dose of 30 mg, increasing to 50 mg and then 70 mg as required. It is important to note that due to the differences between lisdexamfetamine and dexamfetamine (described in detail in chapter 5), it is not possible to calculate equivalent doses of these two medications. Therefore whilst response to dexamfetamine suggests that a patient is likely to respond to lisdexamfetamine it is still necessary to independently titrate when switching between one and the other.

### 7.3.3.4 *Titrating on to atomoxetine*

As atomoxetine is prescribed in a mg/kg fashion, it is generally simpler to titrate than the stimulants. The standard protocol for titration on to atomoxetine is to initiate treatment at a dose of 0.5 mg/kg to reduce difficulties with initial adverse effects (especially nausea, which we inform patients is very common but usually transient), increasing to 1.2 mg/kg after one week and then continued at this dose. Many of those who are going to show a response will report some positive effects after three to four weeks; however, in our clinical experience there is a small group of patients who, whilst showing no response at around eight weeks do report significant benefits at around 12 weeks. We therefore recommend that patients are made aware of this and that treatment is continued for 12 weeks before a decision about non-response is made. If there is a response to 1.2 mg/kg but there remains room for improvement, it is acceptable to increase the dose up to 1.8 mg/kg.

## 7.4 **Monitoring treatment**

Having established and stabilized effective and optimized treatment, it is necessary to put systems in place to monitor ongoing treatment (see Figure 7.3). Whilst a proportion of patients will probably continue to do well with minimal intervention, many will require more careful monitoring either to ensure continued clinical response or to minimize the impact of adverse effects such as the sleep and appetite difficulties common with stimulants. Others will require additional support and/or treatment for other types of problems such as mood lability, peer and family relationship difficulties, etc. The results of the MTA study suggested that a carefully crafted and applied medication management system is superior to that which was traditionally available in the community. Group treated under MTA medication management protocol were:

- treated with doses of methylphenidate 10 mg/day greater
- had three—times-daily dosing versus twice-daily dosing
- started treatment with intensive 28-day double-blind titration trial
- received more in the way of supportive counselling and reading materials
- had their dosage adjustments informed by monthly teacher consultation with the pharmacotherapist

The routine follow-up of treatment response and adverse effects is important and should be given adequate time and consideration. It is important to get feedback from teachers and young people as well as parents. This can help achieve optimal symptom control and avoid anomalous situations arising such as a rather high dose of medication being arrived at from parent feedback before the message gets through that teachers are concerned about undue subduing of the child. It is not necessary for senior medical staff to conduct all continuing care clinics. Indeed, if a well-thought-through protocol is designed and implemented it is possible for junior medical staff and nurses to conduct high-quality continuing care clinics. The same protocol, assessment schedule, and measurement tools can be used for continuing care clinics as were used when initiating and titrating on to medication.

| Trigger | • Child/young person has been stabilized on a treatment regime |
|---|---|
| **Clinicians involved** | • Child and Adolescent Mental Health Services<br>• Developmental/behavioural paediatrics<br>• Primary care staff |
| **Aims** | • To monitor the impact of treatment<br>  • To ensure treatment is still required<br>  • To ensure that treatment results in an adequate continued response without problematic adverse effects<br>• To identify non-responders, relapsers and those with new or as yet untreated problems |
| **European Guidelines recommendations** | • A regular (at least six monthly), and as required, review supervised by a specialist (who may be working with primary care staff in a shared care setting)<br>• The continued use of reliable standardized rating scales (e.g. ADHD-IV rating scale, ANAP, Conners' rating scales) and/or specific treatment targets are helpful for monitoring treatment effects<br>• If no medication measures should include documentation of levels/ presence of both symptoms and potential adverse effects, including;<br>  • Pulse and blood pressure (ECG not routinely required unless there are specific cardiac risk factors)—six monthly<br>  • Height and weight (plotted on growth chart)—six monthly<br>  • Appetite, tics, depression, irritability, withdrawal, spontaneity, perseveration—each visit |
| **Outcomes** | • Nobody on treatment that they don't require<br>• The majority of those on treatment will be optimally controlled with no problematic adverse effects<br>• Those who require a switch of treatment or additional treatment are identified |

Figure 7.3 Monitoring treatment.

Although rarely made explicit, the key aim of most clinical care is not just to reduce symptoms but also to improve quality of life. Various studies have identified that ADHD severely impairs a person's quality of life and evidence is emerging that treating ADHD can relieve at least some of this burden (Danckaerts *et al.* 2010) Although to-date mainly used in a research setting several validated measures of quality of life are now available to the clinician at relatively little cost (e.g. PEDS-QL and CHIP-CE). More widespread use within routine clinical practice can help to ensure that the clinician is focusing on the whole picture and not just on core symptoms.

It is good practice to ensure routinely and regularly that an individual continues to require medication. With stimulants it is generally recommended that an individual has a planned withdrawal from medication at least once a year in order to assess whether symptoms return. In reality this will usually occur naturally and in an unplanned fashion when a patient forgets to take his or her medication and others around them either notice the difference or will comment that there seemed to be no difference between days when medication was taken and when it was missed. A continued need for medication is more difficult to demonstrate with atomoxetine in view of its different mechanism of action and in particular because it has a more long-term pharmacodynamic effect. If a short withdrawal of atomoxetine results in a recurrence of symptoms, then one can conclude it should be restarted. If, however, symptoms do not immediately return after a short-term withdrawal, it is still possible that they will return after a longer break. In itself this situation does not raise any problems as we can withdraw medication and wait to see if symptoms return. The problem for many families is that if symptoms do return after a moderate to long withdrawal it is possible that it will take time to get another appointment at the clinic, and that even when atomoxetine is restarted it may take several weeks for the symptoms to resolve again. During this time the patient will continue to have difficulties that they and their family, understandably, will see as having been avoidable. There is no simple solution other than to ensure that withdrawal is monitored closely and that the patient has quick and easy access to the clinic as required.

It is also essential to remember that the management of ADHD involves a lot more than just the management of the core ADHD symptoms. Comorbidity is very common as are other personal, interpersonal, and systemic issues. These will often require treatment in their own right. It is not uncommon for clinicians and patients/parents to be working to different agendas at a continuing care clinic with the clinician, for example, wanting to discuss the response of ADHD symptoms to medication and the parents wishing to discuss other issues such as problems they are having interfacing with school or their child's peer relationships, etc. For this reason we have found it helpful to be explicit that the routine continuing care clinic has a dual purpose to both monitor treatment and *identify* 'other problems'. We do not necessarily try to fix these 'other problems' in the routine continuing care clinic, where time may be very limited. Instead, separate appointments are made to ensure that these issues are managed in the most appropriate manner by the most appropriate person, and that adequate time is devoted to this important aspect of the clinical process.

Although around one-third of those with ADHD will no longer suffer from ADHD-related impairments in adulthood, many young people continue to have significant symptoms of ADHD or have other co-existing conditions that continue to require treatment past the normal cut-off age for paediatric and child and adolescent mental health services. For these individuals it is therefore very important to consider their ongoing treatment requirements and make arrangement for their care to be passed on to the appropriate adult services (see section 5.7.3). Usually this will be to adult psychiatry. It is important that time is taken to ensure that there is a smooth transition between services and that all relevant details of the past and anticipated future treatment and services that the young person will require are passed on. It is often helpful for there to be a formal meeting involving the child and adolescent mental health service and/or paediatrics and the adult psychiatric services to discuss the handover of care.

Clearly the young person should be involved in the planning and where appropriate, so too their parents or carers.

The precise timing of transition will vary locally but should usually be completed by the time the young person is 18 years old. Clear recommendations regarding transitional care by NICE (NICE 2008) and elaborated on by Young and colleagues (2011).

## 7.5 **Adjusting and switching treatment**

Where there is a failure to respond to a particular treatment or when a patient is unable to tolerate a treatment due to adverse effects it is necessary to consider either adjusting or switching treatment. In general, although the need for change may have been recognized within primary care, such alterations to the treatment plan should usually be carried out by specialists within child and mental health services or paediatrics. Particularly in the case of suspected non-response there are several general considerations that need to be addressed in all cases before deciding on what action to take. These include reviewing dosage (always ensure an adequate dose has been applied before switching treatment), addressing compliance issues (motivational interviewing may help compliance and if on an immediate-release preparation try an extended-release one), and diagnosis and assessing whether the apparent non-response is actually due to a co-existing disorder or problem that is not currently being treated.

When the lack of response is due to intolerable adverse effects or is indicative of the patient being resistant to that particular form of treatment, the recommendations for switching treatments vary depending on the current and past treatment history. For further suggestions about the management of adverse effects see Graham *et al.* (2011) and Cortese *et al.* (2013).

Suggested responses to various situations requiring a switch of treatment are described in Table 7.1.

## 7.6 **I want to implement evidence-based practice in my clinic but am not sure how to get started**

Chapters 4 and 7 of this book provide a framework for developing an evidence-based protocol for assessing and managing ADHD based on the European ADHD Guidelines (Taylor *et al.* 2004; Banaschewski *et al.* 2006). Whilst translating evidence into routine clinical practice is never easy, it is possible. It requires dedication, willingness to self-reflect critically, a team that works together as a unit and who are willing to embrace change. And whilst it does require time and resources, it does not necessarily require either a significant investment of money or huge numbers of staff. It can also be very satisfying to practice in the knowledge that you are doing all that you can to ensure each patient receives the right treatment at the right time.

It is not possible to provide a recipe for change that will work in every setting. ADHD care is delivered in very diverse settings each with its own history and barriers to change, and within a wide range of healthcare systems that require the clinician to organize their care in very different ways.

However, it is possible to present some general guidelines that will facilitate the development of evidence-based care pathways. One effective strategy is to address the need for change with a problem-solving approach and utilize the concepts of clinical audit to monitor and inform cycles of change. Possible steps are outlined in Box 7.2. A detailed description of how these issues were addressed in one particular service along with the supporting clinical documentation can be found in the work by Coghill and colleagues (2014).

### Table 7.1 Switching treatments

| **Current treatment** | **Suggested interventions** |
| --- | --- |
| Mild to moderate ADHD either unable to adhere to, or failing to respond to, a first line behavioural intervention (after a trial of around two months) | Initiate a trial of methylphenidate |
| Suboptimal response to methylphenidate as a first-line treatment | Ensure dose has been optimized |
| | Address any compliance issues |
| | Switch to lisdexamfetamine or, if not available, dexamfetamine or atomoxetine |
| Methylphenidate not tolerated as a first-line treatment | Switch to either lisdexamfetamine, dexamfetamine, or atomoxetine |
| Suboptimal response to atomoxetine as a first-line treatment | Ensure dose has been optimized and that treatment has continued for long enough (~12 weeks) |
| | Address any compliance issues |
| | Switch to either methylphenidate, lisdexamfetamine or dexamfetamine |
| Atomoxetine not tolerated as a first-line treatment | Switch to either methylphenidate, lisdexamfetamine, or dexamfetamine |
| Failure to respond to (or tolerate) methylphenidate, lisdexamfetamine, dexamfetamine, and atomoxetine | Seek advice from regional/national specialist |
| | Try alternative medications; |
| | • Alpha-2 agonist (clonidine, guanfacine) |
| | • Bupropion |
| | • Tricyclic antidepressant |
| | • Mood stabilizer |
| | • Nicotine patch |

Note: these recommendations will continue to change as new treatments, drugs/preparations become available. It is therefore important that the clinician stays up-to-date with new advances in the field.

### Box 7.2 A problem-solving approach to implementing evidence-based practice

- Agree on standards of practice to be followed (local, national, international evidence-based guidelines)
- Measure current practice against these standards
  - This could be against the complete guidelines or only particular sections.
  - This could be done by a single clinic or a group of services
- Identify where practice is adequate and where improvements need to be made to achieve the agreed standards
- Identify the current barriers to implementing these standards of care
- Spend time as a team problem solving and identifying the steps required to overcome these barriers and achieve implementation of evidence-based practice in your workplace
- Implement agreed changes
- Reassess practice against the standards
- Continue with this process until the team are happy that practice meets standards (both your own and those set out in guidelines)

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# ADHD in adults

Philip Asherson and Jan Buitelaar

## Key points

- ADHD persists into adult life in around two-thirds of cases and can affect people throughout the lifespan.
- Associated clinical features of adult ADHD such as mental restlessness, sleep problems, and emotional instability overlap with and can mimic other common mental health disorders.
- Clinical response of ADHD symptoms and impairments to stimulants and atomoxetine is well established and recommended by national and international guidelines.
- ADHD is often seen in adult mental health settings and should be on the differential diagnostic checklist for all clinicians working with mental health disorders.

## 8.1 Introduction

Although services for ADHD are well established in childhood with rapid service development across much of Europe since the mid-1990s, this is generally not the case for ADHD in adults. Although clinical services for adults with ADHD started to be developed locally at the end 1990s, these were rather pioneering initiatives.

A key milestone in the development of clinical services for adults with ADHD was the publication of the National Institute of Health and Clinical Excellence (NICE) guidelines in 2008, which for the first time included recommendations for clinical management across the life span (NICE 2008). Other guidelines published for ADHD in adults include those from the British Association of Psychopharmacology (Nutt *et al.* 2007), the European Network Adult ADHD (Kooij *et al.* 2010), and the Canadian ADHD Resource Alliance (<http://www.caadra.ca>). These guidelines are remarkably consistent, indicating the high level of agreement among clinical experts in this field.

These developments come as no surprise to those working with children and adolescents with ADHD, who are aware of the frequent persistence of the disorder beyond the adolescent years (Faraone *et al.* 2006a), and because ADHD is seen in around 20% or more of parents of children with ADHD (Faraone *et al.* 2000). As more children are being diagnosed and treated, the demand for transition services to adult mental health has grown and undiagnosed cases in adults are increasingly being identified for the first time. Yet until recently, ADHD has not been recognized as a treatable condition by most adult mental health psychiatry and psychology services, including those where high rates of ADHD have been established such as forensic, addiction, and personality disorder services. Outside adult mental health, ADHD impacts on education, work, family, and social life, so there is a need for a wider range of

professionals to be trained in recognizing the disorder and providing necessary support and accommodations. The recognition of ADHD in adults as a common disorder leading to a wide range of psychosocial impairments means that all those involved in adult mental health require training, whether it is to recognize the condition and make appropriate referrals, or for those with more direct responsibility for the delivery of effective mental health to adult patients with ADHD.

## 8.2 **Definition of ADHD in adults**

ADHD in adults should not be viewed as a distinct condition but rather a continuation of the childhood disorder. As such, the criteria are similar to those for childhood ADHD, although some adjustment should be made for the age-appropriate presentation of ADHD symptoms in adults. In general there is a change away from the more externally observable symptoms of hyperactivity and impulsivity, towards the internalizing symptoms of inner restlessness and inattention (Biederman *et al.* 2000; Larsson *et al.* 2006). However, both sets of symptoms can be prominent throughout the life span. A list of age-appropriate examples of ADHD symptoms in adults is provided in Box 8.1.

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**Box 8.1 Age-adjusted ADHD symptoms for use with adults (with permission from Asherson 2005)**

**Inattention**
- Often fails to give close attention to detail. Difficulty remembering where they put things. In work this may lead to costly errors. Tasks that require detail and are tedious (e.g. income-tax returns) become very stressful. This may include overly perfectionistic and rigid behaviour, needing too much time for tasks involving details in order to prevent forgetting any of them.
- Often has difficulty sustaining attention. Inability to complete tasks such as tidying a room or mowing the lawn, without forgetting the objective and starting something else. Inability to persist with boring jobs. Inability to sustain sufficient attention to read a book that is not of special interest, although there is no reading disorder. Inability to keep accounts, write letters, or pay bills. Attention however often can be sustained during exciting, new, or interesting activities like using the Internet, chatting, playing computer games, etc. This does not exclude the criterion when boring activities are not completed.
- Often does not seem to listen when spoken to. Adults receive complaints that they do not listen, that it is difficult to gain their attention. Even where they appear to have heard, they forget what was said and do not follow through. These complaints reflect a sense that they are 'not always in the room', 'not all there', 'not tuned in'.
- Fails to follow through on instructions and complete tasks. Adults may observe difficulty in following other people's instructions. Inability to read or follow instructions in a manual for appliances. Failure to keep commitments undertaken (e.g. work around the house).
- Difficulty organizing tasks or activities. Adults note recurrent errors (e.g. lateness, missed appointments, missing critical deadlines). Sometimes a deficit in this area is seen in the amount of delegation to others such as secretary at work or spouse at home.
- Avoids or dislikes sustained mental effort. Putting off tasks such as responding to letters, completing tax returns, organizing old papers, paying bills, establishing a will. One can enquire about specifics then ask why particular tasks were not attended to. These adults often complain of procrastination.

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*(continued)*

Box 8.1 Continued

- Often loses things needed for tasks. Misplacing purse, wallet, keys, and assignments from work, where car is parked, tools, and even children!
- Easily distracted by extraneous stimuli. Subjectively experience distractibility and describe ways in which they try to overcome this. This may include listening to white noise, multi-tasking, requiring absolute quiet, or creating an emergency to achieve adequate states of arousal to complete tasks; many projects going simultaneously and trouble with completion of tasks
- Forgetful in daily activities. May complain of memory problems. They head out to the supermarket with a list of things, but end up coming home having failed to complete their tasks or having purchased something else.

Hyperactivity
- Fidgets with hands or feet. This item may be observed, but it is also useful to ask about this. Fidgeting may include picking their fingers, shaking their knees, tapping their hands or feet, and changing position. Fidgeting is most likely to be observed while waiting in the waiting area of the clinic.
- Leaves seat in situations in which remaining seated is usual. Adults may be restless. For example, frustrated with dinners out in restaurants, unable to sit during conversations, meetings, and conferences. This may also manifest as a strong internal feeling of restlessness when waiting.
- Wanders or runs about excessively or frequent subjective feelings of restlessness. Adults may describe their subjective sense of always needing to be 'on the go', or feeling more comfortable with stimulating activities (e.g. skiing) than with more sedentary types of recreation. They may pace during the interview.
- Difficulty engaging in leisure activities quietly. Adults may describe an unwillingness/dislike to ever just stay home or engage in quiet activities. They may complain that they are workaholics, in which case detailed examples should be given.
- Often 'on the go' or acts as if driven by a motor. Significant others may have a sense of the exhausting and frenetic pace of these adults. ADHD adults will often appear to expect the same frenetic pace of others. Holidays may be described as draining since there is no opportunity for rest.
- Talks excessively. Excessive talking makes dialogue difficult. This may interfere with a spouse's sense of 'being heard' or achieving intimacy. This chatter may be experienced as nagging and may interfere with normal social interactions. Clowning, repartee, or other means of dominating conversations may mask an inability to engage in give-and-take conversation.

Impulsivity
- Blurts out answers before questions have been completed. This will usually be observed during the interview. This may also be experienced by probands, as a subjective sense of other people talking too slowly and of finding it difficult to wait for them to finish. Tendency to say what comes to mind without considering timing or appropriateness.
- Difficulty waiting in turn. Adults find it difficult to wait for others to finish tasks at their own pace, such as children. They may feel irritated waiting in line at bank machines or in a restaurant. They may be aware of their own intense efforts to force themselves to wait. Some adults compensate for this by carrying something to do at all times.
- Interrupts or intrudes on others. This is most often experienced by adults as social ineptness at social gatherings or even with close friends. An example might be inability to watch other struggle with a task (such as trying to open a door with a key) without jumping in to help.

## 8.3 **DSM-5 criteria for adult ADHD**

Under DSM-5 there are changes to the criteria from the previous DSM-IV that reflect the growing understanding of the disorder and its diagnosis in adults. Since these are helpful to our understanding of the diagnosis of ADHD in adults, they are reviewed here.

### 8.3.1 **Symptom thresholds**

The symptom thresholds have been lowered to five out of nine items (from six out of nine in DSM-IV) in either the inattentive or hyperactive/impulsive domains beyond the age of 17 years. This is consistent with research that shows that a lower threshold of symptoms is a good predictor of impairment in the adult years (Kooij *et al.* 2005). Although an even lower threshold of four items in either domain was also recommended this was not adopted, presumably to minimize the potential for over diagnosis. Nevertheless, it should be recognized that some individuals subthreshold to the symptom criteria of five out of nine items in either domain will still be functionally impaired by persistence of ADHD symptoms and might therefore warrant treatment. Under DSM-5 these cases are referred to as 'ADHD in partial remission'.

### 8.3.2 **Age of onset**

Several symptoms should be present before the age of 12 years. The age of onset criteria have changed in two ways. First, the criteria have changed from before the age of seven years. This reflects literature that reports no distinction in the clinical presentation, course, or outcome of those whose ADHD symptoms became apparent before or after the age of seven years (Faraone *et al.* 2006b; Kieling *et al.* 2010; Rohde *et al.* 2000). This change also addresses the problem that many adults are unable to provide a clear retrospective account of their symptoms and behaviors before the age of 12 years, and that the estimated age of onset of symptoms is sometimes reported as later than the true age of onset (i.e. had prospective data been collected) (Barkley *et al.* 2007).

The other key change is that age of onset relates only to the presence of symptoms, with impairment from the symptoms no longer a requirement. This recognizes the situation for some individuals where impairment from the symptoms of ADHD during childhood and adolescents can be relatively mild. This is usually seen in moderately severe ADHD where there is strong infrastructure of support at home and school, or in individuals with above-average intelligence who have enough capacity to compensate. Impairments from ADHD can then emerge in young adults when individuals leave home and need to manage their daily lives without such external supports. Furthermore, mental health problems related to ADHD, such as emotional lability, sleep problems, and low self-esteem, may become more troublesome for individuals as they grow older.

When considering the age-of-onset criterion, it needs to be considered whether this means that the full syndrome should be present before the age of 12 years, or whether the presence of 'several symptoms' (i.e. three or four) in either symptom domain is sufficient. Within the context of European psychiatry the view is generally held that since ADHD in adults is a continuation of the childhood disorder, it is expected that the full syndrome (i.e. six or more symptoms in either domain) should be present before the age of 12 years (Kooij *et al.* 2010). In contrast, strict application of the DSM criteria only requires 'several symptoms' to be present before the age of 12. Application of the less stringent criterion will contribute to variation in prevalence estimates for ADHD in adults. For example, in the epidemiological survey from Kessler (2006), the childhood criteria applied was two or more ADHD symptoms before the age of seven years, with an estimated prevalence of 4.4% (Kessler *et al.* 2006).

### 8.3.3 **Several symptoms in two or more settings**

This requirement remains the same in childhood and adulthood and reflects that pervasive nature of neurodevelopmental disorders across situations and environments. In adults this is usually evaluated by enquiring after the presence of symptoms in social, education, and occupational settings. Adults with ADHD may, however, report that they function well for certain tasks which are particularly salient to individuals, such as sports activities or computer games, while being impaired in many other situations and tasks.

### 8.3.4 **Symptoms interfere with or reduce quality of social, educational, or occupational functioning**

Here the range and type of impairment in adults needs to be considered. These fall into two main categories. First, those that impact on daily function, such as difficulty performing educational or occupational activities or difficulty socializing. Functional impairment may, however, be minimal in some cases, particular when symptoms are less severe and where effective coping strategies have been developed. Nevertheless, the chronicity of ADHD symptoms can be a continued source of distress to individuals or affect different aspects of their lives. Some common impairments and their assessment are listed in Box 8.2. Increasingly the role of emotional dysregulation that is often seen to accompany ADHD in adults, has been identified as an independent source of impairment (Barkley and Fischer 2010; Skirrow and Asherson 2013).

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**Box 8.2 Assessment of impairment**

- *Quality of life*. Mood lability, a short fuse, and constant efforts to correct scatter-brained mistakes are frustrating and demoralizing. Low self-esteem and dysthymia related to ADHD symptoms and impairments. Distress from symptoms such as ceaseless distractible thought processes, physical restlessness, and sleep problems,
- *Family life*. Even where an adult with ADHD feels fine, interviewing of the patient's spouse/family may reveal significant dysfunction. Emotional dysregulation may be a particular source of difficulty with family relationships. Disorganization and forgetfulness may be disruptive of family life.
- *Work*. While some ADHD individuals find work that is compatible with their symptoms, they may be impaired by not being able to move in new directions in which they would otherwise have desired to move. Others may be functioning in attention-demanding professions, but at great emotional cost and without much success. Work may not be commensurate with their intelligence and educational background. This is usually experienced as under-achievement. When severe, adults with ADHD are not able to retain themselves in any kind of employment.
- *Relationships*. ADHD is hard on relationships and some adults with ADHD give up on their capacity for intimacy and lead an isolated existence. They may be unaware of the ways in which their ADHD-caused behaviour patterns have contributed to relationship failures.
- *Education*. Many adults with ADHD are impeded from obtaining an education appropriate to their potential (usually assessed by IQ). A history of academic failure, under-achievement, or erratic performance represents academic impairment.
- *Activities of daily life (ADL)*. Even a high-functioning individual with ADHD may have difficulties with ADL such as shopping, cleaning, dressing, or managing money. The deficit is not seen in what the individual can do, but in what he/she actually does, thus direct observation or an informant is required to assess this properly.

NICE guidelines indicate that for the diagnosis of ADHD impairments should be of at least moderate severity (NICE 2008). The clinician needs to assess whether an individual is impaired relative to his or her own potential, or relative to expected norms. Impairment should be to a degree that most people would consider requires some form of medical, social, or educational intervention. Without a specialist professional or higher level of intervention to ameliorate the problems, there is likely to be long-term adverse implications for the person affected, as well as problems in the short and medium term. Impairment should be pervasive, occur in multiple settings, and be at least of moderate severity. Significant impairment should not be considered where the impact of ADHD symptoms is restricted to academic/work performance alone, unless there is a moderate to severe impact in other domains.

## 8.4 **Prevalence of ADHD in adults**

The persistence of ADHD into adulthood has been investigated by follow-up studies of children with ADHD. Persistence of the disorder was first highlighted in the 1970s when there was a growing awareness that minimal brain dysfunction (MBD) persisted into adults, and that adults showed similar treatment effects of stimulants on symptoms of MBD to that seen in children (Wood *et al.* 1976). Follow-up studies conducted by several groups were subsequently included in a meta-analysis that concluded that 15% of children with ADHD still met full DSM-IV criteria by the age of 25. However, they also found that an additional 50% met criteria for ADHD in partial remission, meaning that although they were subthreshold to the full criteria, there was persistence of ADHD symptoms from childhood leading to clinically significant impairments (Faraone *et al.* 2006a). In another study reporting on the outcome of children with ADHD at a mean age of eight years, and followed up to a mean age of 41 years, 22% were found to have current ADHD compared to 5% of controls (Klein *et al.* 2012). Other studies report higher rates of persistence, perhaps related to the age at which cases were first ascertained and the severity of the cases at the outset of the studies (Mannuzza *et al.* 2003).

Several community surveys and meta-analyses have now been conducted to estimate the prevalence of ADHD in adults across multiple countries. Two meta-analytic studies reached similar conclusions. Using a meta-regression method, Simons estimated a pooled prevalence of 2.5% (95% CI 2.1–3.1) for DSM-IV ADHD using data from the United States, New Zealand, Netherlands, and Italy (Simon *et al.* 2009). Fayyad included data from six European (Spain, Netherlands, Italy, Germany, France, and Belgium), and four non-European (USA, Mexico, Lebanon, and Columbia) countries and estimated an average prevalence of 3.4% with a range of 1.2–7.3%. Prevalence was relatively low in lower-income countries (1.9%) compared to higher-income countries (4.2%) (Fayyad *et al.* 2007). As in prevalence studies of childhood ADHD, the wide range of prevalence estimates is largely explained by methodological differences, particular the thresholds used to define individual symptoms, impairments from the symptoms, and situational pervasiveness.

## 8.5 **Clinical presentation of ADHD in adults**

Central to the assessment of ADHD is the evaluation of the 18-symptom items that define the condition. Examples of age-appropriate descriptions of ADHD symptoms to the adult population are listed in Box 8.1. One area of ADHD that has been relatively neglected in children and adolescents is the focus on subjective experiences of ADHD symptoms. This is because the criteria for ADHD are traditionally based on parent and teacher reports of child behaviour, rather than focusing on subjective accounts of mental phenomena reported by patients. Examination of such mental phenomena is, however, central to the classification of many adult psychiatric disorders, and a phenomenological

approach can also be applied to ADHD. Symptoms that are commonly reported by adults with ADHD include excessive mind wandering (or mental restlessness), physical restlessness, and mood lability.

### 8.5.1 **Mental restlessness**

Mental restlessness in ADHD is related to the concept of mind wandering, which occurs when one's mind drifts away from a task and focuses on internal thoughts and images unrelated to the task or situation at hand (Stawarczyk *et al.* 2013). In adults with ADHD, mind wandering is often experienced as excessive, intrusive, and interfering with normal functions of attending to tasks, organization, and planning (Brookes *et al.* 2005). The occurrence of u*nwanted thoughts* is included as a description of being *easily distracted* in DSM-5. Individuals report ceaseless mental activity, thoughts that are constantly on the go, or a mind that is constantly full of thoughts. Thought processes are experienced as uncontrolled, with multiple thoughts occurring at the same time or the mind flitting from one topic to another. These observations raise the possibility that the intrusion of poorly controlled thought processes could lead to known difficulties in ADHD such as sustaining attention, planning ahead, and forgetfulness. Furthermore, many adult patients with ADHD describe excessive mind wandering as one reason for the sleep difficulties that often accompany ADHD (Gau *et al.* 2007). This phenomenon of mental restlessness was first described by Alexander Crichton in 1798. More recently, Shaw and Giambra (1997) found that students with ADHD reported higher levels of task-unrelated thoughts. Nadeau (1997) noted that adults with ADHD have difficulty with internal distractions such as daydreaming and a constant flow of thoughts. Some adults with ADHD may at the same time experience the positive side of mind wandering; their mental associations may turn into creative and novel ideas that can be expressed and acted upon.

### 8.5.2 **Physical restlessness**

This is a subjective phenomenon that is thought to reflect the internal experience of physical activity. For this reason, under DSM-5 subjective restlessness is considered to be equivalent to the childhood symptom of 'often runs about or climbs in situations where it is inappropriate'. Similarly, feeling uncomfortable when staying seated for a long time, as in restaurants or meetings, is considered to be equivalent to the childhood symptom of 'often on the go, acting as driven by a motor'. A related phenomenon is the problem of adults with ADHD who are unable to relax or engage in leisure activities. Some adults with ADHD may be able to focus their excess energy on sports activities in which they sometimes excel.

### 8.5.3 **Emotional dysregulation**

Emotional dysregulation (ED) such as low frustration tolerance, irritability, and mood lability, is a commonly associated feature of ADHD that can be used to support the diagnosis (DSM-5). Although recent research has highlighted that some degree of ED is common in adults with ADHD, the non-specific nature of the symptoms, which occur in several other adult-onset psychiatric disorders, is one of the reasons why this is not considered a core diagnostic feature of ADHD in adults. There is an ongoing debate about the degree to which ED reflects a core domain of ADHD in adults. Arguments in favour of this conceptualization include the common co-occurrence of ED in adults with ADHD (Barkley and Fischer 2010; Barkley and Murphy 2010; Skirrow and Asherson 2013), the strong phenotypic correlation between measures of ED and ADHD (Skirrow and Asherson 2013), and evidence that treating ADHD with methylphenidate (Reimherr *et al.* 2007; Rosler *et al.* 2010) or atomoxetine (Reimherr *et al.* 2005) has a similar effect size on ED as on the core ADHD symptoms of inattention and hyperactivity/impulsivity. For these reasons we recommend that adults

presenting with chronic difficulties with emotion regulation or mood instability should always be screened for ADHD.

## 8.6 **ADHD and impairment**

Impairment is central to the diagnostic construct of ADHD. This criterion is particularly important to the diagnosis of ADHD because the symptoms that define the condition are continuously distributed throughout the population and there is no point of rarity between those with and without the clinical disorder (Chen *et al.* 2008). How impairment is defined will therefore have a major impact on who is diagnosed and treated for ADHD.

In adults, impairment covers a wide range of symptoms and behaviours and their functional consequences (Box 8.2). Most prominent are functional psychosocial impairments including difficulties in higher education, occupation, and family and social relationships. Behavioural problems can be severe leading to more serious problems such as addiction disorders (van de Glind *et al.* 2013a), antisocial behaviour leading to criminal convictions (Lichtenstein and Larsson 2013), and high rates of serious driving offences (Chang *et al.* 2014). Other impairments are reflected in mental health symptoms such as difficulty getting to sleep, low self-esteem, and constant physical and mental restlessness. Adults with ADHD are also more likely to have co-occurring neurodevelopmental disorders like autism, dyslexia, and general learning difficulties, as well as comorbid mental health disorders such as anxiety, depression, bipolar disorder, and borderline personality disorder (Kessler 2007; Kooij *et al.* 2010; Philipsen 2006; Skirrow *et al.* 2012).

### 8.6.1 **Impairments reflecting executive dysfunction**

Some of the most common impairments linked to ADHD in adults are behavioural and functional problems related to *executive dysfunctions*. Brown in his executive dysfunction model of ADHD describes multiple areas of functional impairments that he considers reflect a lack of executive control (Brown 2008). He describes impairments in several areas of executive dysfunction:

- *Activation:* organizing, prioritizing, and initiating work
- *Focus:* focusing, sustaining, and shifting attention to tasks
- *Effort:* regulating alertness, sustaining effort and processing speed
- *Emotion:* managing frustration and regulating emotions
- *Memory:* utilizing working memory and accessing recall
- *Action:* monitoring and self-regulating of activities

These domains of impairment are highly characteristic of symptoms and impairments seen in adults and may be particularly sensitive and specific to the diagnosis (Kessler *et al.* 2010). Similarly, descriptions of behaviours thought to reflect executive dysfunction in adults with ADHD are provided by Barkley (Barkley 2010). Unfortunately, from a theoretical perspective, there is poor concordance between neurocognitive tests of executive function and the behavioural descriptions of executive dysfunctions, so it remains an open question as to the main underlying neurobiological and cognitive processes that underlie these behavioural impairments. Nevertheless, this does not negate their importance as reflecting highly characteristic impairments that are seen in adults with ADHD. The Behaviour Rating Inventory of Executive Function (BRIEF—adult version) is increasingly being used for their systematic evaluation and has been shown to show significant improvements following medical treatments (Adler *et al.* 2013; Gioia *et al.* 2002).

## 8.7 **Diagnostic procedures**

To establish the diagnosis of ADHD in adults, both current and retrospective behaviour and mental state should be considered, with a developmental history of the onset and development of the symptoms and impairments of ADHD. The most characteristic clinical picture is of the onset of symptoms and impairment during early to middle childhood, with persistence of similar symptoms and impairments to the time of the assessment as an adult. Unlike most adult mental health disorders, with the exception of trait-like conditions such as personality disorder and other neurodevelopmental conditions, the symptoms of ADHD do not reflect changes from the premorbid mental state. Rather, they reflect enduring traits that are sustained throughout development. Although rating scale and neuropsychological measures are frequently used in specialist ADHD clinics, these are not sufficiently good predictors of the diagnosis. Like other mental health disorders, ADHD is a clinical and behavioural phenotype best evaluated by clinical diagnostic interview, with supporting evidence from informants, such as parents or siblings concerning childhood symptoms, or a partner for current symptoms and functional impairment.

### 8.7.1 **Screening for ADHD in adults**

The first step in the diagnostic process is the use of either screening questionnaires or clinical acumen to identify those that are likely to be affected by ADHD. The Adult ADHD Self Report Scale (ASRS) is widely used and includes the full DSM 18-items which have been reworded better to reflect the condition in adults (Adler *et al.* 2006). The short version consisting of a subset of only six of these items was shown to have good sensitivity and specificity when used in a community survey (Kessler *et al.* 2007). Although sensitivity tends to be high for the ASRS, specificity may be low in some populations, such as patients with comorbid disorders such as addictions (van de Glind *et al.* 2013b). Alternatives that are widely used include simple DSM-IV item checklists such as those published by Russell Barkley, including informant and retrospective versions for the childhood symptoms of ADHD (Barkley and Murphy 1998).

Whatever screening tool is used, rating scales should never be employed to establish the diagnosis, since there will always be a proportion of cases either wrongly identified or missed. Rather, as in children, the diagnosis remains a clinical one and is established following a detailed clinical assessment. Screening tools have the additional value of providing baseline data, which can then be repeated during a course of treatment to track the course of any improvements in the symptoms of ADHD. It is further recommended that impairment scales are used to track clinical and functional improvements beyond the core symptoms of ADHD. Impairment scales recommend for use in this way include the Adult ADHD Quality of Life Scale (AAQOL), the Weiss ADHD Impairment Scale, and the Barkley Impairment Scales.

### 8.7.2 **Diagnostic interviews for ADHD in adults**

Semi-structured interviews have been developed and provide a good basis on which to establish the diagnosis. The two most widely used are the Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein *et al.* 2001) that is a licensed instrument, and the Diagnostic Interview for ADHD in Adults (DIVA) (Kooij 2012) (<http://www.divacenter.eu>). Both interviews take a similar approach to the systematic evaluation of each of the DSM 18-symptom items for both current symptoms in adulthood and retrospective symptoms from childhood. Parents and older siblings are useful informants when evaluating childhood and adolescent symptoms, whereas partners can also be very helpful for providing more information on current symptoms and behaviours. The DIVA was introduced to provide a readily accessible

diagnostic approach that is free for healthcare professionals to access and will assist with the accurate diagnosis of ADHD in adults. DIVA has been translated into numerous languages and formatted as a mobile app. By providing detailed lists of examples of both symptoms and impairments the DIVA is an excellent training tool as well as diagnostic instrument for use in routine clinical practice.

## 8.8 **Difficulties with diagnosing ADHD in adults**

ADHD in adults is often said to be a particularly difficult disorder to diagnose accurately because the symptoms and impairments overlap with other common mental health disorders, as well as normal behaviour. However, this view is not generally held by clinicians once they gain experience of the diagnostic and treatment process, who view the diagnostic problems as no more or less complicated than those seen for other mental health conditions. Here we highlight some of the specific difficulties faced by clinicians in relation to ADHD in adults.

### 8.8.1 **Distinction from normal behaviour**

A common question is the level of symptoms and impairments required to establish the diagnosis and the need for treatment. The issue arises most commonly with high-functioning patients who have developed effective strategies to manage ADHD symptoms such as disorganization and forgetfulness, and who may therefore appear at first glance to be unimpaired. The general question can be a tricky one, since the symptoms of ADHD are seen to varying degrees throughout the population, making it difficult to provide a definitive threshold. While this can present as a diagnostic difficulty in some cases, the problem is no greater than that faced every day by healthcare professionals working with other common mental health conditions such as anxiety and depression, where similar issues arise. How impaired should someone be before we choose to offer then treatment?

In practice, reasonable thresholds need to be applied on the basis of the level of severity, reflected in personal distress to self and others and levels of functional impairment from the symptoms. One important difference from an episodic disorder is the chronic trait-like characteristic of ADHD symptoms. Unlike episodic disorders from which people can recover, ADHD symptoms are present over extended periods of time. As a result, relatively mild symptoms (experienced on a daily basis) can lead to moderate to severe levels of impairment. Careful attention must therefore be paid to the impairments from the symptoms of ADHD, and individual coping skills, and not just a focus on the diagnostic checklist of symptoms.

### 8.8.2 **Distinction from comorbid disorders**

The other common difficulty can be the distinction from comorbid disorders, including anxiety, depression, bipolar and borderline personality disorders, as well as substance-abuse disorders and antisocial personality disorder. However, before diagnosing someone with comorbid ADHD plus another disorder, care must be taken to ensure that the diagnosis is not better explained by a single underlying condition. Clearly it can be as detrimental to patients to misdiagnose someone with ADHD who has another underlying disorder as it is to misdiagnose other conditions with ADHD, because the treatments and expected outcomes are very different for the different conditions. One of the most common examples of the mistaken diagnoses is between ADHD, bipolar disorder, and borderline personality disorder (Asherson *et al.* 2014), mainly because of the common co-occurrence of emotional instability in all three conditions. It is therefore critical to pay close attention to the specific features of each condition that help to make the diagnostic distinctions.

When considering the relationship of ADHD to comorbid conditions, there are three main categories that should be considered: symptoms of ADHD that mimic other disorders; neurodevelopmental disorders that often accompany ADHD; and the development of other disorders where ADHD acts as a developmental risk factor.

## 8.9 Symptoms of ADHD that mimic other disorders

ADHD is itself a 'symptomatic condition' with symptoms that overlap with and may therefore mimic other conditions. Examples of these are listed in Table 8.1. Notably, some of the symptoms that overlap with other conditions are not listed as core symptoms of ADHD (DSM-5 or hyperkinetic disorder (ICD-10), although they are commonly seen to accompany ADHD in adults. These include symptoms such as initial insomnia (difficulty falling asleep) and restless sleep, emotional dysregulation, mental restlessness, and restless agitation. A recent investigation of 41 adults with a clearly defined diagnosis of ADHD, carefully selected for having no comorbid disorders or being influenced by alcohol, drugs, or prescription medications, nevertheless found increased rates of mental health symptoms compared to healthy controls. These included somatic complaints, fatigue, sleep problems, irritability, physical health worries, mild dysthymia, depressive ideas, anxiety, worrying, avoidance behaviour, panic, compulsions, and obsessions (Skirrow and Asherson 2013). It is therefore important to be aware that many symptoms seen in ADHD overlap with those seen in other conditions.

### 8.9.1 Neurodevelopmental disorders

ADHD shares genetic risk factors with other neurodevelopmental disorders including autism, specific learning difficulties (e.g. dyslexia, dyscalculia), general learning difficulties (e.g. lower IQ), and developmental coordination disorder (e.g. DCD, dyspraxia). It is therefore not uncommon that these disorder or traits co-occur in adult patients with ADHD, adding to the impairments and difficulties faced in everyday life. Unlike ADHD symptoms, these comorbid neurodevelopmental traits are not expected to respond to the drug treatments used to control ADHD symptoms.

### 8.9.2 ADHD as a developmental risk factor

When ADHD co-occurs with another mental health disorder, we can view ADHD as a developmental risk factor. Disorders that occur at higher rates in adolescents and adults with ADHD include anxiety, depression, and bipolar disorder, borderline and antisocial personality disorder,

### Table 8.1 Symptoms associated with ADHD that mimic other disorders

| Disorder | Symptoms associated with ADHD that mimic other disorders |
| --- | --- |
| Anxiety | Mental restlessness, ceaseless thoughts, restlessness, poor sleep, avoidance of situations (e.g. queues, social situations) |
| Depression | Initial insomnia and restless sleep, impulsive eating, low self-esteem, unstable moods, impatience and irritability, concentration problems |
| Borderline personality disorder | Chronic symptoms emerge from childhood/adolescence, impulsive behaviour, mood instability, angry outbursts, impaired social relationships |
| Bipolar disorder | Mood instability, motor restlessness, mental restlessness and distractible mind, distractibility and difficulty concentration, over talkativeness |

and alcohol and drug dependency. The mechanisms for such developmental comorbidities are generally unknown and may include one or more of the following.

1.  Shared genetic and environmental risk factors.

2.  ADHD generates exposure to risky environments for other disorders. For example, repeated negative educational and social experiences leading to low self-esteem and depression; school expulsion leading to increased psychosocial risks for antisocial behaviour.

3.  ADHD may enhance the impact of other risk factors. For example children with ADHD with the COMT genotype are more likely to develop antisocial behavioural problems. This is an ADHD by genetic interaction since no genetic risk for antisocial behaviour from the COMT genotype is seen in the non-ADHD population (Caspi *et al.* 2008).

4.  Multiple risk factors. In many cases both innate characteristics of ADHD will combine with environmental exposure to risky environments. An example of this is addiction disorders which occur at increased rates in adolescents and adults with ADHD. In studies of addiction units across Europe, it was found that around 12% of addiction patients meet diagnostic criteria for ADHD (Huntley *et al.* 2012; van de Glind *et al.* 2013a). The reasons for this association is likely to be multifaceted, including increased exposure to environmental risk factors for addiction, poor self-regulation and impulsivity leading to an increase in risk-taking behaviour and self-treatment of ADHD symptoms such as physical and mental restlessness and sleep problems.

## 8.10 **Treatment of ADHD in adults**

Treatment of ADHD in adults is similar to that in children. The medications used in childhood ADHD are all effective in adults, although effect sizes in studies of adults tend to be slightly lower than those seen in children. In addition to drug treatments psychological treatment programs have been developed using principles of psycho-education, cognitive behavioural therapy, and/or dialectical behaviour therapy. In nearly all cases the studies of psychological treatments have been as an adjunct to medical treatment, so there is very limited information on the effectiveness of psychological treatments without the concurrent use of medication. Novel treatments such as mindfulness training and neurofeedback are not sufficiently studied in adults with ADHD to provide clear guidance at this time. Similarly, alternatives to conventional drug treatments, such as essential fatty acid supplementation or dietary restrictions have not been adequately studied in adults with ADHD. Based on these considerations, clinical guidelines currently emphasize the use of drug treatments as first line when treating adults with ADHD, although this should always form part of a comprehensive treatment programme that addresses psychological, behavioural, and educational or occupational needs (Kooij *et al.* 2010; NICE 2008).

## 8.11 **Drug treatments for ADHD in adults**

### 8.11.1 **Methylphenidate**

Methylphenidate is the most studied medication in adults with ADHD. In Europe, both immediate-release and extended-release formulations are available, providing considerable flexibility to fine-tune the use of methylphenidate. Two meta-analyses come to similar conclusions about the effectiveness of methylphenidate in the treatment of ADHD, with average effect sizes of around 0.5 in patients without addiction disorders (Castells *et al.* 2011; Koesters *et al.* 2009). Koesters (2009) found no significant effects among a small number studies that included patients with addiction disorders.

### 8.11.2 **Dexamfetamine and lisdexamfetamine**

Dexamfetamine has been available as an immediate-release medication in some but not all European countries for many years. Overall there are fewer studies of dexamfetamine in adults with ADHD and greater concerns about the abuse liability compared to methylphenidate,1although there is no evidence to support this conclusion. In most European countries, dexamfetamine is viewed as a second-line medication, although this may be largely related to the lack of alternatives to immediate-release preparation and is in sharp contrast to the frequent use of amphetamine-based medications, such as Adderall®, in the United States. More recently, lisdexamfetamine has been marketed in Europe and at the time of writing has a license for use in children in most European countries. Although recommended as a second-line medication, available evidence indicates that efficacy and adverse effects are similar to those seen for methylphenidate. Since lisdexamfetamine is a pro-drug of dexamfetamine it has several potential advantages for use in adults. Abuse potential is not altered by the route of administration since the rate-limiting step on the release of dexamfetamine is hydrolysis on the cell membranes of erythrocytes. As a result dexamfetamine is released slowly throughout the day, giving a sustained and stable effect for around 10–12 hours.

### 8.11.3 **Atomoxetine**

This is the first medication for ADHD to be widely licensed for first-time use in adults with ADHD in most European countries. Current clinical guidelines recommend that atomoxetine is used as a second-line medication, mainly on the basis of the slightly lower effect size estimated across studies. Meta-analyses of efficacy studies for atomoxetine provide an estimate of around 0.4 (Cunill *et al.* 2013) for atomoxetine, compared to around 0.5 for methylphenidate. No head-to-head studies of atomoxetine with methylphenidate in adult ADHD currently exist. One potential advantage of atomoxetine is the relatively slow onset and offset of the medication effects and extended symptom control. The stability of these effects may be particularly useful when the off–on effects of stimulants are problematic. For example, in those where ADHD is associated with extreme irritability or where untreated ADHD in the evenings leads to severe sleep problems. Atomoxetine is recommended as the first-line treatment in patients with co-occurring addiction disorders and may be better tolerated in some patients with anxiety disorders.

### 8.11.4 **Other medications**

Alternative medications for ADHD in adults are less widely studied and are less commonly used in Europe. Drugs used as third line include bupropion, guanfacine, clonidine, and tricyclic antidepressants. It is unclear how many adult patients who do not respond to stimulants or atomoxetine, or suffer from significant adverse effects from these medications, show an adequate clinical response to third-line medications. Bupropion is often cited as the first choice among these alternative medications, although in the US the use of guanfacine has been increasing since it was licensed as a specific treatment for ADHD.

## 8.12 **Treatment algorithm for adults with ADHD**

Current guidelines recommend the use of methylphenidate, dexamfetamine (or lisdexamfetamine), and atomoxetine in the treatment of adults with ADHD. First-line is usually methylphenidate because of the higher effect size reported across studies compared to atomoxetine, and because of the availability of a range of extended-release preparations in Europe compared to dexamfetamine. However, within Europe there are regulatory and reimbursement restrictions that vary from country to country for different medications for ADHD in adults, which have a major impact on local prescribing practice.

Table 8.2 Key differences between stimulants and atomoxetine in the treatment of ADHD in adults

| Stimulants | Atomoxetine |
|---|---|
| Short duration of action | Sustained action |
| Rapid onset | Slow onset (several weeks) |
| Individual titration (expert) | Standard dosing (non-expert) |
| Potential on-off effects / rebound | Sustained effect |
| Fine control over symptom level | General reduction in symptoms |
| Multiple dosing, depending on clinical need/ response | Once-daily dosing |
| Potential for diversion/abuse | Limited diversion/abuse potential |
| May precipitate anxiety | Unlikely to precipitate anxiety |
| Effects wear off relatively quickly and regular dosing a requirement | Effects wear off very slowly and missed doses may not lead to symptom change. |
| Good effects in most people. Retain fine control over level of symptoms. Useful when stable 24-hour effect is undesirable, not needed, or not wanted. | Useful for high-risk patients and patients needing a stable effect. First line for alcohol or drug abuse. Useful for patients with poor compliance (where due to forgetfulness) or stable effects are desirable. Consider in patients with comorbid anxiety. |

The different clinical properties of each type of medication and the availability of different drugs and formulations should be considered when selecting the appropriate medication for each individual patient. Table 8.2 provides a list of the main characteristics that can be used when considering between stimulants and atomoxetine. There is little to distinguish methylphenidate from dexamfetamine on the basis of efficacy or the way the medication is used, so we compare immediate-release and extended-release stimulants, and atomoxetine.

One key difference between stimulant and non-stimulant medications is the need for skillful titration when using stimulant medications. There is wide variability in the clinical response to dosing, so that optimal treatment can only be provided by careful titration to the optimal dose for each individual patient, balancing the dose required for adequate control of ADHD symptoms and adverse effects. There is little evidence that simple mg/kg formula is relevant when using stimulants because of the extensive response heterogeneity to different doses regardless of weight.

When using stimulants it is usual to start at a low dose and gradually titrate upwards until there is good control of the symptoms of ADHD or limiting adverse effects become apparent. A choice needs to be made between immediate-release stimulants and extended-release formulations. Immediate-release methylphenidate and dexamfetamine both have effects that are apparent to patients for around three to four hours, while extended release preparations vary from six to twelve hours, depending on the formulation used. Dosing decisions are based on three main questions:

1. How long do the effects of each dose last?
2. What dose is needed at each dosing point to provide adequate control of symptoms?
3. For how long and in what times of the day does the patient need good control of ADHD symptoms?

The answers to these questions vary between individuals and the range of stimulant preparations allows for individually tailored dosing regimens to be achieved.

The process of titrating stimulants contrasts with the much simpler dosing regimen for atomoxetine in adults, in which there is a target maintenance dose of 80–100 mg in adults with ADHD. It is recommended to start at 40 mg for one week, and then to immediately increase to the final dose of 80 mg. In the majority of cases this approach is fine, however some experts prefer to start lower and increase the dose more slowly to reduce the risk of adverse effects leading to the early cessation of the medication. When using atomoxetine, patients need to be informed that the effects are relatively slow to develop, and that a period of at least eight weeks is required on the maintenance dose of 80–100 mg to ensure an adequate trial of the medication. Nevertheless, for the majority of individuals who are going to respond to atomoxetine, significant treatment effects are apparent by six weeks.

### 8.12.1 Adverse effects

The adverse effects in adults are similar to those seen in children and adolescents. Common side effects of stimulants in adults include decreased appetite, insomnia when taken in the evenings, headaches, and nervousness or dysphoria. In most cases these are transient or mild and only occasionally require the medication to be stopped or changed. Decreasing the dose, altering the stimulant, or changing to a non-stimulant medication should be considered if the symptoms persist. Atomoxetine can cause constipation, dry mouth, nausea, and erectile dysfunction. All drug treatments for ADHD can cause minor but statistically significant increase in heart rate and blood pressure so it is recommended that adults with ADHD should have their blood pressure and heart rate checked at baseline and periodically throughout treatment. Here we discuss briefly some specific considerations when treating adults with ADHD.

#### 8.12.1.1 *Cardiovascular risk*

The main additional concern is whether there are long-term effects, particularly on the cardiovascular system for patients on medication for long periods of time, or for those entering the age of risk for cardiovascular problems like hypertension and myocardial infarctions. In fact, based on available evidence there are no additional long-term risks. Nevertheless because both stimulants and atomoxetine can increase pulse and blood pressure, these should be measured after each increase in dose and at three to six-month intervals. Importantly, pulse and blood pressure should be measured before starting treatment to provide a baseline for each individual patient. Electrocardiograms are not advised unless there is a specific indication such as dysrhythmia or known or suspected structural heart deficit. If in doubt it is advisable to get a cardiovascular health check with the primary care physician or for more serious problems seek advice from a cardiologist.

#### 8.12.1.2 *Anxiety*

Treating anxious patients with stimulants can be a problem because stimulants can exacerbate somatic symptoms of anxiety. This can be a particular problem for those with comorbid anxiety, especially when accompanied by somatic symptoms such as panic attacks. Where anxiety is a problem, stimulants should be titrated slowly starting with a low dose. In some cases anxiolytic medication should be used at the same time, or patients referred for CBT. Atomoxetine is not thought to cause an increase in anxiety and would be a good choice in anxious patients who cannot tolerate stimulants.

#### 8.12.1.3 *Sleep problems*

Sleep problems are well established when taking stimulants, particularly in the evening. Nevertheless, many patients actually report improvements in their sleep and are tempted to

take small doses of stimulants in the evening to reduce the level of ADHD symptoms when they are trying to fall asleep. Typically patients complain that initial insomnia is secondary to mental and physical restlessness in the evenings. Although not well studied this phenomenon is thought to be to occur for around 50% of adult patients with ADHD. The skillful use of stimulants may therefore be to time the last dose so that at least some effects on the control of ADHD symptom remain in the evening. In contrast, where stimulants cause a sleep problem the solution may be to take the last dose earlier in the day, or to switch to a non-stimulant like atomoxetine.

### 8.12.1.4 *Erectile dysfunction*

This is a particular problem with atomoxetine affecting around 10% of men. Male patients should therefore be warned of this in advance. However, in most cases this adverse effect is short lived and wears off after a few weeks.

### 8.12.1.5 *Mania and psychosis*

These are rare (but potentially serious) adverse effects despite the potentiation of both dopamine and noradrenergic signalling by stimulants and atomoxetine. Risk may be higher in those with a previous history of psychosis or mania when ADHD medications should be used with caution. Where psychosis occurs it is advised to stop ADHD medications immediately and treat the psychosis in the usual way. Further consideration can then be given to the need to restart ADHD treatment once the psychosis has been treated and is stabilized.

## 8.13  **Treating ADHD in patients with comorbid disorders**

Treating patients with ADHD and comorbid disorders is in most cases approached in the same way as treating non-comorbid ADHD. However, there are specific considerations to consider with different co-occurring problems. As described above, the first step is to ensure that the symptoms do indeed reflect another condition rather than the broader clinical presentation of ADHD. This requires a detailed assessment of both ADHD and the comorbid condition. Although there are many symptoms of ADHD that overlap with those of other conditions, this does not usually confound the diagnosis when a full developmental history and review of the diagnostic criteria are completed. Care must be taken not to confuse the common symptoms that frequently co-occur with ADHD, such as chronic emotional instability, low self-esteem, and sleep problems as an indication of a co-occurring condition in the absence of other indicators of a comorbid disorder. In general it is usual to treat any condition that reflects a significant departure from the premorbid mental state first. Clinical judgment may be needed to decide which disorder is driving the current level of symptoms and impairments, and in some cases it will be appropriate to treat two conditions at the same time.

### 8.13.1  **ADHD and depression**

ADHD is often accompanied by chronic dysthymia, emotional instability, and sleep problems. In such cases ADHD is usually treated first. In cases where there is a distinct change in mood from the premorbid mental state, consistent with the onset of a depressive episode, depression is usually treated as the priority.

In evaluating mood symptoms that are often seen to accompany ADHD in adults, the differential diagnosis is largely determined by the time course of the symptoms and the association with other features of mood disorders. Note, however, the overlap with symptoms such as restlessness and agitation, emotional instability and fatigue that are also seen in ADHD. Adults with ADHD have often experienced psychosocial and symptomatic

impairments over many years, so that some level of lowered self-esteem or low motivation linked to low mood is not uncommon. In these cases, where the mood state is consistent with the impairments linked to ADHD, treating ADHD is the priority. In contrast, when there is development of a distinct period of depression, then treating depression becomes the priority. It is usually best to treat depression first in such cases, because the onset of depression can make the accurate diagnosis and evaluation of ADHD more difficult. Depression should always be treated first when severe, particularly when there is a potential risk of self-harm or harm to others.

In some patients already in treatment for ADHD, depression may present as a worsening of their ADHD symptoms. Thus, depression should always be investigated when patients report that their medication is not working as well as usual. This also means that it may not be possible to evaluate the effectiveness of ADHD treatments in people who present with co-occurring depression. Data on the combined use of antidepressants and stimulants are lacking, although clinical experience suggests that the combination of antidepressants with stimulants is effective and safe, with care to monitor potential adverse effects, particularly pulse and blood pressure.

### 8.13.2 **Bipolar disorder**

The distinction between ADHD and bipolar disorder is usually easier to make in adults compared to children. Bipolar is characterized by the occurrence of hypomania or mania in distinct episodes. Care should be taken not to confuse chronic mood instability and frequent mood swings throughout the day with bipolar disorder. One way to make the distinction is the ability of most adults with ADHD to control emotional instability during clinical interviews, although angry outbursts due to frustration can occur. This is in contrast to the sustained change from the premorbid state that characterizes bipolar episodes. As for depression, there should also be a distinct change in mood state when establishing the presence of bipolar symptoms. ADHD in contrast has an earlier age of onset and a chronic persistent course, and the mood swings are generally less extreme, occur several times a day, and are interspersed with periods of normal mood. Grandiosity is not a feature of ADHD. In ADHD, thoughts may be ceaseless and unfocused (excessive mind wandering) but are not speeded up and do not show flight of ideas. Such excessive mind wandering in ADHD reflects distracted thought processes which are usually viewed as problematic by ADHD patients, rather than the feelings of enhanced cognitive ability described during hypomanic/manic episodes.

Bipolar disorder should always be treated first and ADHD further evaluated once there is a return to the usual mood state for that person. It is not usually recommended to treat ADHD in people with bipolar disorder, although in some cases with dual pathology and ADHD with moderate to severe impairment, the use of stimulants and atomoxetine can be considered. There is a lack of an evidence base for how best to proceed, but it is recommended that ADHD should only be treated in bipolar patients if they are treated with mood stabilizers. ADHD treatments should be stopped temporarily during hypomanic/manic episodes, but if needed could be restarted afterwards. Patients should be warned of the potential for ADHD medications to destabilize bipolar disorder.

### 8.13.3 **ADHD and anxiety**

Individuals with ADHD commonly report high levels of anxiety on rating scales. However, a more detailed enquiry about the psychopathology shows that in some cases the ADHD syndrome can mimic aspects of anxiety, or anxiety is a natural consequence of ADHD-related impairments. In such cases the primary treatment should target ADHD. Examples include individuals with ADHD who have difficulty coping with social situations (especially social groups)

because they are unable to focus on conversations and tend to tune out. They may as a consequence worry about how they will cope in such situations (i.e. an understandable concern) and as a result avoid group interactions. A similar scenario can occur with simple tasks such as shopping because of their experience of forgetting things, high levels of disorganization, and intolerance of having to wait in shopping queues. The difficulties coping with simple everyday tasks that most of us take for granted are a source of considerable concern and are often accompanied by avoidance of stressful tasks and poor self-esteem. In combination with ceaseless mental activity, these legitimate concerns and responses take on the appearance of a mild to moderate anxiety state, although lacking the somatic manifestations of anxiety disorders. Some patients try to cope with disorganization by getting overly rigid and perfectionist, in order to have some control over the chaos. This behaviour can mimic obsessive–compulsive disorder, but does not have the function to divert from anxiety. Rather it serves to control problems with forgetfulness and disorganization related to ADHD. As with the major affective disorders, the key to understanding the comorbid symptoms is to focus on the precise phenomenology and consider whether they have a similar onset and time course to the ADHD symptoms and the extent to which they may reasonably be a consequence of core ADHD symptoms.

It is also the case that many individuals with ADHD will develop more typical anxiety states and it will then be important to consider whether primary treatment should be targeted at the anxiety disorder. A judgement will need to be made on the severity of the anxiety and the strength of the current relationship between the anxiety and the ADHD symptoms. There are two main ways to treat ADHD with anxiety. First, treat the anxiety first with either an anxiolytic or CBT. This may be appropriate where the anxiety is a more severe immediate problem that the ADHD. However, it is often the case that anxiety is related to ADHD symptoms and impairments. In such cases a dual approach can be taken, with the use of an anxiolytic at the same time as starting stimulants or atomoxetine. Stimulants should be used at low dose and only slowly increased in dose in anxious patients. Atomoxetine may be the drug of choice because it does not usually exacerbate anxiety symptoms and has been used effectively in a study of ADHD that included patients with generalized anxiety disorder (Adler *et al.* 2009; Ravindran *et al.* 2009). Finally, psychological interventions for anxiety are more likely to succeed once ADHD symptoms are controlled with medication, consistent with the evidence that is accruing for multimodal approaches including both medication and psychological treatments (see below).

### 8.13.4 **ADHD and substance-abuse disorders**

ADHD is seen in around 10% of adult patients with addiction disorders (Huntley *et al.* 2012; van de Glind *et al.* 2013c). The links between ADHD and substance-abuse disorders most likely reflect at least three mechanisms. First, ADHD is itself associated with novelty seeking, a known risk factor for substance abuse disorders. Secondly, many patients report the use of drugs (usually cannabis) and alcohol as a way to suppress ADHD symptoms such as mental and physical restlessness. Thirdly, ADHD is associated with an increased exposure to psychosocial risk factors including educational failure, adverse peer group influences, and earlier exposure to drugs. The development of conduct disorder is a further risk factor for substance-abuse disorders in young people with ADHD.

The most common forms of drug misuse in ADHD are alcohol and cannabis. These are easily available and patients with ADHD symptoms often describe using these drugs to reduce the hyperactive/impulsive symptoms of ADHD. Some individuals find they have difficulty getting off to sleep without some form of self-medication. The use of these drugs is not always at a harmful level but regular use of any drug is of potential concern. More serious levels of drug and alcohol abuse are also seen in adults with ADHD, yet currently across Europe ADHD comorbid with serious substance abuse or addiction disorders is rarely treated, despite potential benefits to patients.

Potential benefits of medical treatment include: increased level of function; increased level of interest in daily activities; reduced need to 'self-medicate'; increased levels of self-control and reductions in impulsivity. The evidence base is not, however, very encouraging, with methylphenidate showing no significant effects in a meta-analysis of a subgroup of studies that included patients with substance abuse disorders (Koesters *et al.* 2009). Atomoxetine is usually recommended as the first-line choice, due the reduced potential for abuse compared to stimulants and by providing a more stable form of treatment, without the on–off effects often seen with stimulants. When using stimulants patients with substance-abuse disorders should be given extended-release medications that are relatively difficult to abuse. Treatment should usually be conducted with close liaison between ADHD and addiction specialists, or by alcohol and drug teams acquiring expertise in the treatment of comorbid ADHD.

### 8.13.5 **ADHD and personality disorders**

The relationship of adult ADHD to personality disorders is of considerable interest since both reflect trait-like alterations of behavioural symptoms that develop out of childhood and adolescence. The high rates of emotional instability and behavioural disturbances in many adults with ADHD further complicate the distinction between the types of disorders. Based on current evidence, ADHD should be treated when it appears alongside other behavioural disturbances, perhaps reflecting a co-occurring personality disorder. For example, patients with borderline personality disorder and ADHD may well benefit from the improvements in function, as well as reductions in restlessness and emotional instability that are often seen when treating adults with ADHD.

In people with a personality disorder, ADHD should be diagnosed in the usual way, with care taken to elicit the symptom criteria, age of onset, pervasiveness, and impairment criteria that are used to define ADHD. Further research is, however, needed to identify predictors of good and bad clinical response, since these remain unknown. Care must also be taken not to mistake the behavioural impairments and emotional instability that is often seen in severe ADHD with a personality disorder. The main issue for diagnosis and treatment is therefore to recognize when there is evidence for ADHD and to treat accordingly. While the diagnostic focus should be on the main symptoms that define inattention, overactivity, and impulsivity, it is also important to remember that mood instability and impulsivity are common components of the ADHD syndrome. For this reason it is often useful to make particular enquiries about symptoms that are more specific to ADHD such as short attention span, variable performance, distractibility, forgetfulness, disorganization, physical restlessness, and over-talkativeness rather than focus on the occurrence of maladjusted and disruptive behaviours (which do not define ADHD).

## 8.14 **Psychological treatments**

Psychological treatments are often needed when treating adults with ADHD because not all patients want medical treatments, there is often only a partial response of symptoms and/or impairments, or drug treatments may not be tolerated. Because ADHD is a neurodevelopmental condition that starts during childhood, patterns of maladaptive behaviour have often developed over time and become entrenched. Some individuals have specific areas of need, such as students in higher education who require learning support and the occupational needs of people in work. Medical treatment of ADHD in adults should therefore always form part of comprehensive treatment program that addresses psychological, behavioural, and educational or occupational needs (NICE 2008).

Psychological treatment should begin with psycho-education, which should be offered to all patients with ADHD, either as part of a formal psycho-education program, or as part of the

diagnostic and treatment process by individual clinicians. However, more specific benefits have been demonstrated when using specialized forms of treatment such as cognitive–behavioural therapy (CBT), with most evidence coming from the use of psychological treatments as an adjunct to medication.

CBT and related approaches for ADHD provide a structured approach that typically includes practical advice on organizing, planning, day-to-day problem solving, and identifying solutions by breaking down overwhelming tasks into achievable steps. Patients may be taught skills to manage problems related to distractibility and procrastination, sustaining motivation, and improving their reactions to stressful or challenging situations. Randomized controlled trials show reductions in ADHD symptoms and ADHD-related impairments both on and off medication, although it has been difficult to control adequately for all non-specific effects of the treatment process in these studies. In qualitative research, patients report that they greatly value the addition of psychological treatments and expect a multimodal approach to be adopted (Matheson *et al.* 2013). Greater access to psychological treatments for ADHD is therefore a priority for the further development of effective ADHD treatment services for adults.

Several different approaches have been taken with open trials of dialectical behavioural therapy, group metacognitive therapy, combined medication and CBT, cognitive–behaviourally orientated group rehabilitation and mindfulness meditation training, all showing initial promising results on ADHD symptoms and impairments (Knouse and Safren 2010). Several randomized controlled trials have been conducted in recent years that overall support the use of psychological treatments as an adjunct to medication, although there are limited data to clarify the potential role of psychological treatments in the absence of medication. More recently, a large multicenter study has been conducted in Germany by Philipsen and colleagues (Philipsen *et al.* 2014) consisting of 433 patients randomized to four treatment arms: manualized dialectical behavioral therapy-based group psychotherapy (GPT) plus methylphenidate or placebo; or clinical management including supportive counselling plus methylphenidate or placebo. At the time or writing the findings from what may be a pivotal study are yet to be released. Previous RCTs laid a strong foundation for this work. Safren and colleagues evaluated a 12-session CBT program compared with relaxation therapy and basic psycho-education in 86 adults with ADHD on medication. They found significant improvements in ADHD symptoms and clinician ratings of impairment in the CBT group, which were sustained for 12 months (Safren *et al.* 2010). In another study, Solanto and colleagues developed a 12-week meta-cognitive therapy program which targeted problems with time management, organization, and planning. They found significant benefits to the inattentive symptoms of ADHD of their treatment program compared to supportive training (Solanto *et al.* 2010). Philipsen and colleagues found benefits to both medicated and unmedicated patients following a structured group course with skills training (Philipsen *et al.* 2007). Weiss and colleagues found benefits of CBT to symptoms and impairments of patients with or without medication, although this study was study randomized to drug treatment rather than CBT (Weiss *et al.* 2012). Bramham and colleagues investigated a brief group CBT intervention with waiting-list controls. The CBT group had significant improvements in knowledge about ADHD, self-efficacy, and self-esteem compared to the control group (Bramham *et al.* 2009). Stevenson and colleagues developed a cognitive remediation program with retraining of cognitive functions, helping participants to develop coping strategies and work on restructuring their environment. Comparing treatment groups to waiting list controls they found greater reductions in ADHD symptoms and better levels of organization and self-esteem (Stevenson *et al.* 2002).

## 8.15 **Conclusion**

The persistence of ADHD into adulthood is now well established and there is a rapidly developing and sophisticated evidence base for the diagnosis and treatment of ADHD in adults. Substantial progress has been achieved in recent years with rapidly increasing awareness of the impact of ADHD on adult psychopathology. Service delivery is improving across Europe, although service provision is often inadequate and restricted to specialist services. However, this is not a sustainable model of service delivery in the longer term due to the very large numbers of people presenting with mental health problems related to ADHD. We therefore envisage that as healthcare professionals and primary care physicians become more familiar with the clinical management of ADHD in adults, these services will increasingly move into generic mental healthcare provided by shared care protocols between primary and secondary care services. At the same time further investigations are urgently needed to evaluate the impact of treating ADHD in different adult healthcare services including primary healthcare, addiction services, personality disorder services, and forensic services where there are still large numbers of undiagnosed or untreated adult patients with ADHD.

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# Appendix

This appendix contains addresses and links to ADHD self-help organizations which might be useful for the reader. The authors do not guarantee the accuracy, relevance, timeliness, or completeness of this information. Further, the inclusion of addresses of and links to particular organizations does not guarantee their quality or importance, nor do the authors intend to endorse any views expressed, or services offered, of these organizations or of the information provided on their websites.

## Global Networks

AD/HD Global Network
North America: PO Box 3700, McAllen TX 78502, USA
South America: Colonia 1767 apt. 11, Montevideo 11200, Uruguay Europe: Ben-Gurion Drive 161, 60437 Frankfurt, Germany Australia: PO Box 204, Chatswood, NSW 2057, Australia
Email: info@global-adhd.org
Website: <http://www.global-adhd.org>

ADHD-Europe
Website:<http://www.adhdeurope.eu>

Latin American League for ADHD
Website: <http://www.tdahlatinoamerica.org>

## National Networks

### Argentina

La Fundacion Trastorno Por Deficit de Atención e Hiperactividad, Ernestina Montefusco de Pergolini, Castelli 313, Drive 4, Code Postal
San Martín 164, Dto 4B - Ramos Mejía Bs. As., Argentina
Email: info@tdah.com.ar
Website: <http://www.tdah.org.ar>

### Australia

Canberra & Queanbeyan ADD Support Group, Inc.
ADDACT
PO Box 717, Mawson ACT 2607 or c/- SHOUT, Pearce Centre
Bldg 1, Collett Place, PEARCE ACT 2607
Tel: 02 6290 1984 business hours; 02 6287 4608 6–9 p.m. after hours
Email: addact@shout.org.au
Website: <http://www.addact.org.au/index.php/adhd-adults/>

ADDult with ADHD (NSW) Inc ADHD Centre Office (by appointment)
3/51 Wicks Road North Ryde
Postal Address: PO Box 22 Epping NSW 1710
ABN 87 819 863 019 CFN 22782 INC9877265
info@adultadhd.org.au
Tel: 02 9889 5977
Fax: 02 9889 5988
Website: <http://www.adultadhd.org.au/>

Learning & Attentional Disorders Society of WA (Inc)
Suite B, The Niche 11 Aberdare Road NEDLANDS WA 6009
Phone: (08) 9346 7544 Fax: (08) 9346-7545
Email:lads@cnswa.com
Website: <http://www.ladswa.com.au/>

## Austria

ADAPT—Aufmerksamkeitsdefizit/Hyperaktivitaetsstörungen—Arbeitsgruppe zur Förderung
von Personen mit AD/HS und Teilleistungsschwaechen,
Adresse (Postadresse): Kohlmarkt 12/13, 1010 Wien
Tel: +43(0676) 516 56 87 (mobile)
Fax: +43 1 879 75 48
Email: verein_adapt@yahoo.com
Website: <http://www.adapt.at/>

## Belgium

Association 'Hyperactivité et troubles associés—TDA/H Belgique',
Aderess: 4 Rue de la Probité - 1050 Bruxelles
Tel: 0471 21 92 66
Email: info@tdah.be
Website <http://www.tdah.be/>

Centrum Zitstil omgaan met ADHD
Kruishofstraat 341 2610 Wilrijk
Tel: +32 (03) 8303025
Fax: +32 (03) 8252072
Email: info@zitstil.be
Website <http://www.zitstil.be/>
<http://adhd-edu.be/>

## Brazil

Associação Brasileira do Déficit de Atenção (ABDA)
Prof. Paulo Mattos
Tel: (21) 2295-0921
Email: abda@tdah.org.br
Website: <http://www.tdah.org.br/>

## Canada

CADDRA: Canadian Attention Deficit Hyperactivity Disorder Resource alliance
3950 14th Ave, suite 604
Markham, Ontario L3R 0A9, Canada
Tel: 416-637-8583 Fax: 905-475-3232
Website: <http://www.caddra.ca/>

CADDAC—Centre for ADD/ADHD Advocacy, Canada
3950 14th Ave, Ste 604 Markham, ON L3R 0A9
Tel: +1 416 637 8584
Fax: +1 416 385 3232
E-mail: info@caddac.ca
Website: <http://www.caddac.ca>

### Croatia

ADHD I JA
Sajmišna 1 (dvorište Arcusove zgrade) 10 370 Dugo Selo
Tel: 01/2752-071
Fax: 01/2752-071
Mobile: 099/7367-605
E-mail:adhd-i-ja@net.hr
Website: <http://www.adhd-i-ja.hr/>

Buđenje—udruga za razumijevanje ADHD-a
Kačićeva 4, 10 000 Zagreb
Tel: 098-997-8915
Email: budenje@gmail.com
Website: <http://www.budenje.hr/>

### Cyprus

ADD-ADHD Cyprus
P.O. Box 12187, 2341 Nicosia, Cyprus
Tel: +357-22446592
Mobile: +357-99651995
Email: info@add-adhd.org.cy
Website: <http://www.add-adhd.org.cy/>

### Denmark

ADHD-foreningen
Pakhusgården 50 5000, Odense C Danmark
Tel.: +45 70 21 50 55 CVR: 12771975
Email: info@adhd.dk
Website: <http://adhd.dk/>

### Estonia

Target Enterprise Estonian Children's Fund
Lai 31/Suurtüki 1, 10133 Tallinn, Estonia
Tel/fax: +372 64 111 88
Email: info@elf.ee
Website: <http://www.elf.ee/>

### Finland

ADHD-liitto ry - ADHD Association in Finland
Pakarituvantie 4 FIN-00410 HELSINKI
Phone: +358 50 354 4325 Fax: + 358 9 454 111 23
E-mail: adhd@adhd-liitto.fi
Website: <http://www.adhd-liitto.fi/

Association for Adults with ADHD in Finland, Suomen
AD/HD—Aikuiset ry, c/o Ritva Kohijoki, Lepistöntie 5, 05400 Jokela,
Tel: +359 (040) 521 2645
Email: sihteeri@adhd-aikuiset.org
Website: <http://www.adhd-aikuiset.org>

## France

HyperSupers TDAH France
4, Allée du Brindeau 75019 PARIS
Tel: 09 66906519
E-mail: info@TDAH-France.org
Website: <http://www.tdah-france.fr/>

## Germany

zentrales adhs-netz
Koordination Hannah Liebermann,
Universitätsklinikum Köln (AöR) Robert-Koch-Str. 10 50931 Köln
Tel: (0221) 478 – 89876
Fax: (0221) 478 - 89879
Website: <http://www.zentrales-adhs-netz.de>

ADHS Deutschland e.V., Poschingerstraße 16, 12157 Berlin, Postfach
41 07 24, 12117 Berlin
Tel:+49 (030) 85 60 59 02
Fax: +49 (030) 85 60 59 70
E-Mail: info@adhs-deutschland.de
Website: <http://www.adhs-deutschland.de/Home.aspx>

## Gibraltar

Email: Giselle addersgibraltar@yahoo.com

## Greece

Email: info@specialeducation.gr
Website: <http://www.specialeducation.gr/frontend/index.php>

## Great Britain

National Attention Deficit Disorder Information and Support Service—ADDISS, PO Box 340,
Edgware, Middlesex HA8 9HL
Tel: +44 (020) 8952 2800
Fax: +44 (020) 8952 2909
E-mail: info@addiss.co.uk
Website: <http://www.addiss.co.uk/>

Chelmsford ADHD/AS Support group
C/O 241 Rutland Road Chelmsford Essex CM1 4BW
Stephen Challen 0786 612 9728
Email: steve@adhdplus.support
Website: <http://www.adhd-support.org.uk/>

## Hong Kong

ADD Adult Support Group, Therapy Associates Limited,
19/F Kennedy Town Centre, 23 Belcher's Street, Kennedy Town, Hong Kong,
Tel: +852 2869-1962
Fax: +852-2869-7770
Email: tal@talhk.com
Website: <http://www.talhk.com/>

Focus on Children's Understanding in School
Room 1504, 15 / F, CLI Building, 313 Hennessy Road, Wan Chai
Tel: (852) 2849 8218
Fax: (852)3019 7644
Email: info@focus.ord.hk
Website: <http://www.focus.org.hk/>

## Hungary

Alternatív Terápiás Központ
2053 Herceghalom, Sándor Móricz tér 5
Telefon +36-70-6155-244 Fax: +36-23-530-123
E-mail:adhdmagyarorszag@vipmail.hu; adhdmo@gmail.com
Website: <http://www.adhd-magyarorszag.com/>

## Iceland

ADHD Association in Iceland,
Háaleitisbraut 13, 108 Reykjavík, Iceland
Tel: +354 581 1110
Email: adhd@adhd.is
Website: <http://www.adhd.is/>

## Ireland

INCADDS Unit 17a, Rallybane Enterprise Centre, Galway, Ireland
Tel: (091) 755090
Email: info@incadds.ie
Website: <http://www.incadds.ie/>

Hadd Family Support Group, Carmichael Centre for Voluntary
Groups, Carmichael House, North Brunswick Street, Dublin 7
Tel: +353 (01) 8748349
Email: info@hadd.ie
Website: <http://www.hadd.ie/>

## Italy

Associazione Italiana Famiglie ADHD,
Via dei Montaroni, 27 – 00068 Rignano Flaminio (RM)
Tel: +39 0761 508126
Fax: +39 06 233227628
Information: info@aifa.it
E-mail: segreteria@aifa.it
Website: <http://www.aifaonlus.it/>

AIDAI
Sede Legale: Via Fratelli Cairoli, 24, 06125 Perugia
Tel. 39 075 3722518,
Fax: 39 075 5899147
Email: aidai@libero.it
Website: <http://www.aidaiassociazione.com/>

Italian National ADHD Registry
A description (in Italian) of the Italian National ADHD Registry with information for parents and clinician can be found at the Italian National Institute of Health (Instituto Superiore di Sanità-ISS)
Viale Regina Elena, 299
00161 - Roma (I)
Tel: 06 4990.3300
Fax: 06.4990.2827
Email: adhd@iss.it
Website: <http://www.iss.it/adhd/>

## Japan

NPO Edison Club, 924, 1-1-1, Toyooka, Iruma-Shi,
Saitama, 358-0003
Fax: +81 4 2962 8683
Email: info@e-club.jp
Website: <http://www.e-club.jp/>

## Luxembourg

Spontan ADD
Centre Barblé 203, route d'Arlon B.P. 62 L-8001 Strassen
Luxembourg
Tel: 691 444 920
Email: treffp@pt.lu
Website: <http://www.treffadhs.lu/>

## Malta

The ADHD Family Support Group, PO Box No. 2, St Julians STJ
1001, Malta
Tel: +356 21 233 749
Email: info@adhdmalta.org
Website: <http://www.adhdmalta.org>

## Netherlands

Impuls—Vereniging voor volwassenen met ADHD en aanverwante stoornissen, Postbus 93,
3720 AB Bilthoven
Tel: +31 (030) 225 50 50
Fax: +31 (030) 225 24 40
Email: arga.paternotte@balanslb.demon.nl
Website: <http://www.impulsdigitaal.nl>

## New Zealand

ADHD Association Inc
PO Box 9063 Newmarket 1149 Auckland
New Zealand
Tel: (09) 625 1754
Email: adhd@clear.net.nz
Website: <http://www.adhd.org.nz>

### Norway

ADHD Norge Storgata 10A 0155 Oslo
Tel: 67 12 85 85
Email: post@adhdnorge.no
Website: <http://www.adhdnorge.no/>

### Peru

Asociación Peruana de Déficit de Atención
Website: <http://deficitdeatencionperu.com/>

### Poland

Poradnia Polskiego Towarzystwa ADHD
ul. Kazimierza Wielkiego 29
30-074 Kraków
Tel: 609 454 809
Email: poradnia@ptadhd.pl
Website: <http://www.poradnia.ptadhd.pl/>

### Saudi Arabia

ADHD Support Group and ADHD Society
PO Box 94037 Kendi Plaza, Diplomatic Quarters
Riyadh 11693
Kingdom of Saudi Arabia
Tel: +966114815455
Email: info@adhd.org.sa
Website: <http://adhd.org.sa/en/>

SPARK
1008 Toa Payoh North, #03-08 Singapore 318996
Email: SPARK_Singapore@yahoogroups.com
Website: <http://www.spark.org.sg/index.html/>

### South Africa

Attention Deficit and Hyperactivity Association of South Africa
(ADHASA)
Postal Address: ADHD Support Group P.O. Box 3704,
Randburg 2125 Republic of South Africa.
Tel: (011) 888-7655
Email: rscox@icon.co.za; marinavzyl@yahoo.com
Website: <http://www.adhdsupport.co.za>

### Spain

ADANA Fundación (Ayuda Déficit de Atención, Niños, Adolescentes y Adultos) Barcelona,
Isabel Rubio
Avenida Tibidabo, 15, Planta Baja
08022 Barcelona
Tel: +34 93 254 60 98
Email: info@fundacionadana.org
Website: <http://www.fundacionadana.org/>

Federación Española de Asociaciones de Ayuda al Déficit de Atención e Hiperactividad, Colegio San Carlos, C/Del Romeral, n° 8, Tentegorra, 30205 Cartagena Murcia
Tel: 968 52 82 08 -650 96 88 34
E-mail: adahimurcia@hotmail.com; penchom@cesmurcia.es
Website: <http://www.feaadah.org/>

FAHYDA
Federación Andaluza de Asociaciones de Ayuda al Trastorno Hipercinético y Déficit de Atención
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## Sweden

Riksförbundet Attention
Tjurhornsgränd 6 121 63 Johanneshov
Tel: 08-120 488 00
Email: kansliet@attention-riks.se
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## Switzerland

Verein für Eltern und Bezugspersonen von Kindern sowie für
Erwachsene mit POS/AD(H)S, Elpos Schweiz,
Sekretariat Affolternstr. 125 8050 Zürich
Tel: 044 311 85 20
Email: info@elpos.ch
Website: <http://www.elpos.ch/>

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Attention Deficit Disorder Association
PO Box 103, Denver PA 17517
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Website: <http://www.add.org>

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