Eur Child Adolesc Psychiatry [Suppl 1]
13 : I/7–I/30 (2004) DOI 10.1007/s00787-004-1002-x

ORIGINAL CONTRIBUTION

European clinical guidelines for hyperkinetic disorder – first upgrade

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Abstract *Background* The validity of clinical guidelines changes over time, because new evidence-based knowledge and experience develop. *Objective* Hence, the European clinical guidelines on hyperkinetic disorder from 1998 had to be evaluated and modified. *Method* Discussions at the European Network for Hyperkinetic Disorders (EUNETHYDIS) and iterative critique of each clinical analysis. Guided by evidence-based information and based on evaluation (rather than metaanalysis) of the scientific evidence a group of child psychiatrists and psychologists from several European countries updated the guidelines of 1998. When reliable information is lacking the group gives a clinical consensus when it could be found among themselves. *Results* The group presents here a set of recommendations for the conceptualisation and management of hyperkinetic disorder and attention deficit/hyperactivity disorder (ADHD). *Conclusion* A general scheme for practice in Europe could be provided, on behalf of the European Society for Child and Adolescent Psychiatry (ESCAP).

Key words ADHD – HKS – guidelines – European – children

Introduction

Hyperkinetic disorder is a persistent and severe impairment of psychological development resulting from a high level of inattentive, restless and impulsive behaviour. Its onset is in early childhood: by definition before the age of 7, nearly always before the age of 5 and frequently before the age of 2 years. It often persists into adolescence and adult life, and puts sufferers at risk for a range of abnormalities in personality development. The adverse outcomes include delinquency and other antisocial behaviour and underachievement in school. Longitudinal studies indicate that the inattentive and restless behaviour is a developmental risk. It is not just a marker to some more fundamental kind of disadvan-

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tage. The treatment of severely hyperactive behaviour is therefore a major target for child mental health services.

The importance of treating hyperactivity is established. It has been hard to establish European guidelines, because a variety of different clinical traditions have evolved within Europe [143], and there has been widespread public controversy about the disorder and possible over-prescription in the United States. In 1998 an approach to European guidelines was produced by a group of experts, including some of the present authors [169]. Since then, however, a good deal has changed. Professional consensus has emerged in most countries, reflected in published national protocols [25, 33, 70]. The use of treatments for hyperactivity and attention deficits has increased markedly, especially for stimulant medication [22, 139]. Scientific knowledge has increased rapidly [134]. There is therefore a need for revision and update of these "European guidelines" and we have aimed at achieving this on behalf of ESCAP (European Society for Child and Adolescent Psychiatry). The revision has been greatly helped by discussions at the European Network for Hyperkinetic Disorders (EUNETHYDIS). Practice does, of course, vary between countries and centres; and these guidelines are therefore intended as a statement of evidence-based or consensus-driven general principles rather than detailed protocols for clinical management. The development of specific protocols will need to take place at the local level, involving other stakeholders such as users and purchasers of service; we hope that these guidelines will form a useful framework.

Influences on pathogenesis

The exact aetiological pathways of AD/HD are unknown. AD/HD aggregates within families with a 3–5 times increased risk in first-degree relatives [45]. Twin studies have found considerable heritability with genetic factors contributing 65 % to 90 % of the phenotypic variance in the population [173]. High heritability must not be confused with genetic determinism and some caution should be adopted in counselling families about causes.

Molecular genetic studies have found associations with variations in genes for the dopamine receptors 4 (DRD4 7-repeat allele) and 5 (DRD5 148bp-allele), and the dopamine transporter (DAT1 10-repeat allele) [30, 46, 94]. While the 10-repeat allele of DAT1 has been associated with an increased expression of the transporter [49, 99], the 7-repeat allele of DRD4 seems to encode a receptor that is subsensitive to dopamine [5].

Preliminary evidence suggests aetiological influences of the receptor genes DRD1 [101] and 5-HT(1B) [66, 118], the Taq 1 polymorphism of the dopamine beta hydroxylase gene [31, 148], and the SNAP-25 gene, which is involved in the regulation of neurotransmitter release [12, 100].

Each of these risk alleles increases the relative risk for AD/HD only slightly (odds ratios: 1.2–1.9), consistent with the hypothesis that, in most cases, AD/HD is a complex disorder influenced by the interaction of multiple aetiological factors, each of minor effect. However, some rarer genes, including fragile X and resistance to thyroid hormone, may show large effects. Some genes involved may have pleiotropic effects. Thus, it has been suggested that AD/HD and reading disability [6, 147, 185], and AD/HD and autism [6, 147] share genetic susceptibility factors.

There are also associations with a variety of environmental risks, including prenatal and perinatal obstetric complications, low birth weight, prenatal exposure to benzodiazepines, alcohol, or nicotine, and brain diseases and injuries [24, 51, 97, 98, 166, 171]. Severe early deprivation, institutional rearing, idiosyncratic reactions to food, and exposure to toxic levels of lead are also considered to have aetiological importance [17, 127, 130, 170]. The quality of relationships within the family and at school can be considered as maintaining or protective factors [17, 130]. Gene-environment interactions seem likely (e. g. DAT-10 allele multiplies the risk of maternal prenatal smoking [77]), but have not yet been studied extensively.

Studies using structural and functional brain imaging, electrophysiology and transcranial magnetic stimulation have shown various abnormalities in frontal, temporal, and parietal cortical regions, basal ganglia (striatum), callosal areas, and cerebellum [13, 14, 23, 28, 29, 47, 102, 111, 126, 157, 163, 176, 190]. The morphological abnormalities seem to be evident early, non-progressive, and not a result of stimulant treatment [29].

Converging evidence from a variety of sources suggest that catecholaminergic dysregulations are centrally involved. The molecular genetic findings above, the effectiveness of stimulants and noradrenergic substances [4], some animal models [e. g., 128, 138], and functional imaging studies – which suggest altered DOPA decarboxylase activity in the striatum and prefrontal areas [42, 43], as well as increased striatal dopamine transporter binding capacity [37, 84] – are all in keeping with this.

Neuropsychological and electrophysiological studies have found various alterations in higher-order cognitive functions [9, 114, 142], motivational processes [129], and more basic information processing stages [13, 83, 135, 149, 174, 188]. The tests used are summarised in the Appendix.

Some research evidence suggests heterogeneity at several levels: phenotypic [e. g., 16], neuropsychological [e. g., 150], psychophysiological [e. g., 7, 23, 125], and genetic [e. g., 107, 175, 186]. There may be multiple developmental pathways from aetiological factors to behavioural symptoms [151, 152].

Prevalence

Several studies converge on a *point prevalence* for hyperkinetic disorder of about 1.5 % in the primary school age population – which is the age at which the problem is most likely to be referred for specialist attention [163]. In the UK, the rates are similar in studies stemming from the 1970s and 1990s – a period during which the recognition of the disorder changed greatly. The *administrative prevalence* – the rate at which the disorders are in practice recognised – varies vary greatly between different European countries, from approximately zero to nearly 2.5 % [81]. Attention deficit without hyperactivity has received less research attention, but is troublesome for something like another 1 % of the school age population [166].

The prevalence of the broader category of AD/HD is, obviously, higher. The estimates vary from about 4 % to 19 % but the usual figures adopted are those of the DSM IV estimates of 3–5 % [26]. The exact figures found in studies probably depend more upon the cut-off that is chosen than on any major differences between populations [163]. Hyperactive behaviour is distributed continuously in the population, and the exact cut-off taken is somewhat arbitrary. In some populations – for instance, the Chinese population in Hong Kong – careful diagnostic measures have suggested that there may be a lower prevalence of disorder than in Europe [88]. Interestingly, however, the apparent prevalence taken from rating scales was higher in Hong Kong than in Western populations – perhaps illustrating the extent to which the disorder is socially defined and influenced by the concern that adults feel for these behaviours in different cultural settings. Methodological differences, however, usually make it hard to compare rates between countries.

Diagnosis

The diagnosis of hyperkinetic disorders follows the ICD-10 criteria.

The DSM-IV category of AD/HD is more broadly defined and is a commoner diagnosis. In both schemes, the behaviours to be recognised are very much the same. The differences come in the ways that the symptoms are weighted and combined into categories:

The ICD-10 diagnosis of hyperkinetic disorder is the narrower category, and it appears that nearly all cases of hyperkinetic disorder should be included within AD/HD. The additional criteria of ICD-10 are that all three problems of attention, hyperactivity and impulsiveness should be present; that more stringent criteria for pervasiveness across situations are met; and that the presence of another disorder such as anxiety state is in itself an exclusion criterion – the expectation is that most cases will have a single diagnosis.

Both these diagnostic schemes have their advantages and disadvantages and a narrower or a broader definition will be suitable for different purposes. Many European clinicians prefer to use the wider definition of AD/HD. We see no contradictions involved. Indeed, it is helpful to use both concepts. In the assessment of an individual child, the first question then becomes whether the criteria for AD/HD are met, i. e. whether there is any target problem for investigation and management. If there is, then one should proceed to a finer grain of classification. Does the child also meet the criteria for hyperkinetic disorder; or, if they fall only into the wider definition, is it possible to assign an alternative type of psychopathology?

Impairment

Diagnosis requires that there should be clear evidence of clinically significant impairment in social, academic, or occupational functioning. This requirement is essential not only for AD/HD but for all mental disorders, in order to differentiate disorders from ubiquitous symptoms and variations of behaviour. 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.

A valid instrument for the assessment of impairment is the Children's Global Assessment Scale (CGAS) by Shaffer et al. [144]. The CGAS runs from 0 to 100 with 0 indicating a child with the most severe disorder and impairment and 100 the most healthy and well functioning child. Cut-offs have been proposed in order to differentiate normal functioning from severe problems in need of treatment [144, 161]. The multiaxial classification of child and adolescent psychiatric disorders by the WHO has introduced a similar scale to measure the level of psychosocial functioning [187]. Axis six of the multiaxial scheme (MAS) runs from 0 indicating superior/good social functioning to 8 reflecting gross and pervasive social disability. Both CGAS and Axis six of the MAS are suitable for the clinical assessment of psychosocial impairment resulting from mental disorders in children and adolescents.

The CGAS has also been influential for the definition of AD/HD according to DSM-IV. A cut-off point of 60 on the CGAS – indicating a level of clinical impairment that requires treatment – has been used in order to define the number of symptom criteria for AD/HD. In a field trial it was found that 5 symptoms of AD/HD had to be present in order to arrive at the CGAS cut-off point of 60 [85]. In order to be conservative and avoid false-positives the numbers were increased by one to 6 (or more) symptoms of inattention and hyperactivity-impulsivity.

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Comorbidity

The co-existence of other types of psychopathology is very common. The reasons appear to be different in different forms [54].

Conduct disorder

Oppositional defiant and conduct disorders are very common in hyperactivity, and genetic influences overlap. They should often be seen, not necessarily as a differential diagnosis or a comorbid condition, but as a complication. Longitudinal studies indicate that in primary school-aged children hyperactive behaviour is a risk factor for conduct disorder, that it appears over time even in children who showed a pure pattern of hyperactivity without conduct disorder at the beginning of their problems, and that conduct disorder does not give rise to hyperactivity in the same way [164].

Emotional disorders

Much less is known about the reasons for the frequent coexistence of hyperactivity and problems of anxiety and depression. Some children may develop low self esteem and insecurity as a result of failures at school and interpersonal relationships

Specific learning disorders

Children with hyperkinetic disorders are more likely to show neurodevelopmental delays of various types. Language milestones are achieved later than normal, expressive language is unduly simple, sensory motor coordination is often impaired, handwriting is poor, and reading ability is behind that expected for chronological age [166].

McGee and Share [91] suggest that children with onset of hyperactivity after school entry are more likely to have behaviour problems confined to school, and to show specific learning difficulties. The suggestion is therefore that some children may enter school with their cognitive function compromised by neuropsychological deviations. The attendant stress in adjusting to classroom demands leads to disturbances in the control of activity and attention. For other children, a primary disturbance of attention and impulse may give rise to secondary academic problems, either through inability to cope with the work or aversion to it.

Pervasive developmental disorders

Children with autism often show hyperactive behaviour, and autistic symptoms are sometimes seen in the hyperactive. Research is now on its way to clarify the relationship between them. Clinically, children with hyperkinetic disorder and an autistic type of social impairment will sometimes show a partial response to stimulants (though caution is needed in view of possible adverse effects). It is therefore desirable to recognise both disorders when they are present. The ICD-10 (but not the DSM) scheme includes a diagnosis of "Hyperkinesis with stereotypies". This is in our experience usually accompanied by social impairment and best seen as a part of the autism spectrum.

Tic disorders

A number of children with AD/HD develop comorbid tic disorders during their early school years [124]. In these cases, the degree of psychosocial impairment is usually determined by AD/HD and it may be the target for therapy.

Developmental coordination disorder

AD/HD 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 [53, 76]. If significant interference with academic achievements or activities of daily living is observed, treatment with stimulants seems to be indicated: it may improve motor coordination and increase the motivation of the child for further sensorimotor training.

Bipolar disorder

The main DSM-IV inclusion criteria for mania are elated mood and/or grandiosity. There is still some controversy about the existence and definition of preadolescent mania [65, 67, 79]. More work is needed on the phenomenology and diagnosis of mania in children, on its natural history and on its familial correlates. Nevertheless, some studies which describe high rates of overlap between AD/HD and mania exist. This might have implications for treatment approaches in such cases, but consensus is not reached yet.

Substance abuse

The relationship between AD/HD and Substance Misuse Disorders is complex and relatively understudied. Elevated rates of AD/HD are reported among those seeking treatment for opiate, cocaine and other substance use disorders. Those with AD/HD were younger at presentation and reported earlier onset of drug abuse, more frequent and intense drug use, higher rates of alcoholism and higher rates of previous treatment [90]. These studies however all have the problem of retrospective reporting of AD/HD symptoms by adults with current substance misuse problems. Prospective studies of referred and non-referred children with AD/HD followed up into adolescence and early adulthood also report increased rates of drug use and abuse, including smoking, in AD/HD groups [71]. It is not surprising that this association is much stronger in samples followed up into early adulthood than in those only followed up into adolescence as those in the younger age range are not fully through the peak age of substance misuse risk (e. g. 19 to 22 years). Whilst controlling for comorbid disorders (particularly conduct disorder) substantially weakens, and in some samples completely accounts for this association [90], there is some evidence that non-comorbid AD/HD in adults does act as an independent risk factor for substance misuse [183].

Differential diagnosis

The separation of autism spectrum from hyperactivity is not based on excluding hyperactive features but on detecting the presence of autistic types of impairment.

Anxiety and mood disorders are sometimes the cause of hyperactive behaviour, because they make children agitated and preoccupied. They are best assessed by the combination of psychiatric interview with the child and a careful history of emotional symptoms. Acute adjustment disorders can readily be distinguished by their time course, even when activity and attention changes are seen. Attachment disorders should also be considered in the differential. Some children who have had massive and prolonged disruption of attachment relationships in early childhood show a rather characteristic course in which an initial period of indiscriminate clinging to adults is followed, during school years, by a pattern of inappropriately outgoing and inattentive activity, with an unreserved contact with strangers and often a lack of deep and trusting relationships.

Chronic brain syndromes may present with hyperactive behaviour, as with other psychiatric syndromes: brain dysfunction is therefore not a differential diagnosis, but a possible cause. Mental retardation can coexist with hyperkinetic disorders, and does not exclude the diagnosis. The clinician needs to judge whether the disturbance of activity and attention is too severe to be accounted for by the known developmental level of the child.

Conduct disorders without any attention deficit may sometimes give difficulty in the differential. This comes especially because uncontrolled behaviour is the norm in oppositional defiant disorders. It may be difficult to tell – especially in a younger child – whether an apparently inattentive pattern of failing to do activities is in fact due to defying adult expectations to conform. It may be necessary to follow children over some time, until the pattern is clarified. It is often not until school entry places demands upon attention that it is possible to be clear whether there is an impairment. During that period the clinician should be aware of the possibility of misdiagnosis both ways.

Work-up

At the level of primary care, the first responsibility is to detect the symptoms of AD/HD. Parental checklists, and accounts from teachers, are valuable in order to make sure that these are indeed the presenting problems rather than the commoner difficulties of sleep or conduct disturbance. Physical examination should be done to make sure that there is no evident underlying physical illness, hearing should be checked, and any history of epilepsy sought. If the symptoms of AD/HD are causing social impairment, then the next step should be referral to a community child mental health service, or if this is not available to developmental paediatrics. Even in the private sector, a multidisciplinary approach is to be preferred.

At the level of secondary care, responsive advice should always be provided. If the problem does not resolve, then a comprehensive diagnostic assessment should be undertaken. Assessment should comprise clinical interview with the parents, and separately with the child; obtaining kindergarten, preschool or school information; testing intelligence, achievement, attention and impulsivity as indicated; making behavioural observations during clinical examinations and testing; and physical evaluation. The child must be seen on more than one occasion; AD/HD symptoms must be evaluated carefully against what is expected at that developmental level; the assessment needs to be full enough to find any alternative explanation of the symptoms that may be present, and any significant comorbidity. It is unlikely that a single-handed doctor will be able to provide such a depth of assessment without multidisciplinary input. Nevertheless stimulants should only be prescribed after a full assessment has been made.

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Clinical interview with the parent(s)

General evaluation should clarify presenting complaints, make a systematic evaluation of psychopathological symptoms, and describe how problems developed. The developmental history is important and should include previous professional reports. One needs to reach an adequate account of affected family members (relevant to a genetic aetiology), pregnancy and birth history (foetal growth, toxaemia, bleeding or severe infections in pregnancy, maternal diabetes or epilepsy, other maternal illnesses or traumas, poor nutritional state of the mother, use of medication, nicotine, alcohol or drugs, 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; medication (especially anticonvulsants, antihistamines, sympathomimetics, steroids) and (if adolescent) history of psychosis.

The assessment also needs to be sufficiently detailed to address family functioning and family problems (e. g. financial problems, problems of other family members, parental conflicts), coping styles of the parents, expressed warmth and hostility, social network and other resources.

Specific questioning should include the behaviours that comprise the ICD-10 and DSM-IV diagnoses, any situational variation in them, their times of onset and development, and their presence in other family members – together with that of related problems (such as behavioural and learning problems, emotional problems, tics, conduct disorder, and alcoholism). Symptoms of comorbid and differential diagnoses should be asked about (see above; in adolescents one should also consider borderline personality disorder, substance abuse, and schizophrenic disorders).

Parent rating scales are useful as a supplement to the interviews, not a replacement. They have the advantage of systematic cover but the disadvantage of uncertainty about how the parents make the ratings. Halo and adaptation effects are to be expected. See Appendix 1.

Interview with the child

The child's self-report is helpful, especially if the child is 6 or older, but more for general adjustment and comorbidity than for the presence or absence of diagnostic symptoms. It should therefore be focussed on functioning in the family, the school and the peer group; general evaluation of psychopathology (especially emotional problems and self-esteem); and the children's attitudes to and coping with their disorder. Self-report rating scales may be useful, as a supplement to the interview, especially for detecting emotional problems in children of 9 years or more.

Behavioural observation during clinical examinations and testing is very useful when problems are shown. Hyperkinetic symptoms, however, may not be present in a novel and arousing setting, so repeated assessment is often needed. The examiner should also assess social disinhibition, the ability to concentrate and persist, and any evidence of language disorder. Classroom observation (for instance, by an educational psychologist) is very helpful but not always feasible.

Kindergarten, preschool or school information

If parents agree, it is essential to obtain information from the teacher (or nurse or other caregiver) about behaviour and behaviour problems, developmental and social functioning, situational variation in behaviour, and symptoms indicating comorbid or differential diagnoses. Standardised questionnaires are a good way of obtaining systematic coverage. See the Appendix for available scales; it helps to use both broad band rating scales and rating scales specifically developed to assess AD/HD symptoms. Written or telephoned reports are also needed, both for a full view of the child at school, and to assess the coping style of the teacher and the teacher-child relationship.

Psychometric tests

Currently, there are no psychological tests, which are diagnostic of AD/HD. Hence, we provide here some principles by which psychological assessment might be undertaken. There are a wide variety of tests, which are useful in the assessment of children with AD/HD. In the appendix we include a list of tests and key references from which each country can search for normative equivalent tests.

Standards by which tests should be evaluated include validity, reliability, age/sex norms and, preferably, parallel versions. Important for clinical work is the differential diagnostic validity of tests. Assessment of IQ is useful to determine academic performance versus academic potential. From a neuropsychological point of view, tests whose specific brain activation areas are already known (e. g. from fMRI and other neural imaging research studies) have clear advantages in testing, when appropriate control tests are also carefully chosen. A further consideration is follow-up of patients. A test that has norms has an advantage for comparing children with their peers. However, if the intention is to measure stability, decline or improvement with long-term follow-up (i. e. *within* subject comparison), careful inspection of the test-retest reliability and the standard

error of the test is required, before conclusions can be drawn.

Lack of resources often means that priorities have to be set; but testing should always be considered when there is any problem related to classroom adjustment or progress. When time is scarce, a short WISC or equivalent is better than no assessment. Speech and language tests are needed when there is evidence of difficulty in communication. Tests of attention and impulsivity have developed markedly in recent years. They are still essentially research tools, and have not been standardised for individual diagnosis, but they can give clues to the nature of the problem in an individual case (see Appendix).

Physical evaluation

Height, weight, and head circumference should always be recorded. A general examination is always needed, including assessment of physical health and any evidence of breakdown of care, and any stigmata of congenital disorder (e. g. foetal alcohol syndrome, Williams syndrome, neurofibromatosis). There should be a check on vision (Snellen chart) and hearing (clinical screen and audiogram if indicated). The examination should look particularly for any evidence of neurodevelopmental immaturity in gross and fine motor functions and for motor and vocal tics.

Investigations should not be routine but guided by history and physical examination. If there is a history suggestive of seizures, an EEG should be carried out. If there is a developmental delay, then chromosome estimation and a DNA assessment of the Fragile X gene should be done (further gene assessments may be recommended in the near future, but at present the clinical significance of variant alleles is not clear). Audiograms are needed when a clinical evaluation has not ruled out significant hearing loss. Brain scanning and neuropsychological tests are not necessary unless there is particular reason to suspect a structural brain lesion. Functional imagining remains at present a research technique.

Treatment

Psychological interventions, educational change, medication and diet are all used for children with hyperkinetic disorders. They should all be available, and their use should be guided by a treatment plan drawn up for the individual. Most hyperactive children have many problems, and multimodal intervention is usually indicated.

Psychoeducational measures

Education and advice should be the base of any treatment. One should interview parents, child and – ideally – the teacher or nurse, about their health beliefs and causal and control attributions; and inform them all about hyperkinetic disorders – especially symptoms, aetiology, clinical course, prognosis and treatment. Consultation with parents and school, on appropriate class or school placement and management, is nearly always needed. Children who are old enough should be educated about self-observation and self-management.

The therapist should also help parents and teachers to identify specific problem situations and find behaviour management techniques for them. The most widely relevant techniques are paying positive attention to appropriate behaviour and compliance, giving commands more effectively, and using appropriate negative consequences for problem behaviours.

Parent training and behavioural interventions in the family

Parent training and behavioural interventions in the family have been shown to be effective by random allocation trials [112]. There are many approaches, and the following suggestions are made, not to be prescriptive, but to provide a brief framework that commands wide clinical consensus [10, 35].

- Identify specific problem situations, and specific behaviour problems within them, and the immediate precipitants of disruptive behaviour. Monitor the child's progress continuously.
- Analyse positive and negative consequences and contingencies of appropriate and problem behaviours together with the parents. Marked inconsistency in applying negative consequences to problem behaviour, and positive consequences to appropriate behaviours should be identified if it is present.
- If coercive and unpleasant parent-child interactions occur very often, while positive parent-child interactions rarely occur, enhance parental attending skills during supervised playtime sessions.
- Teach the parents effective methods of communicating commands and setting rules (e. g. making eye contact with the child; not giving too many commands at once; framing commands positively) and of paying positive attention to child compliance. Use specific problem situations (e. g. mealtimes) in order to train these skills.
- Use token systems in order to reinforce appropriate behaviour in specific situations. In general, preferred activities (e. g. leisure activity together with parents, special playtime together with parents) should be

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used as backup-reinforcers – rather than material rewards such as candy.
- Develop together with the parents appropriate negative consequences for problem behaviour. These consequences should be closely and consistently linked to the problem behaviour.
- Use response cost systems in order to reduce very frequent problem behaviours (e. g. often leaves seat during mealtime or homework; frequent non-compliant behaviour to different family rules). Teach the parents 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.
- Use 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.
- Integrate the child as an active member in this therapeutic process as far as possible. Use self-management procedures in school-aged children in order to enhance the interventions. Teach self monitoring of problem behaviours in specific situations (e. g. leaving seat during homework). Teach the children to evaluate their own behaviour and to reinforce themselves.
- In adolescence, use contingency contracting rather than token systems or response cost systems and stress self-management procedures. Use problem-solving and communication training as well as cognitive restructuring to reduce parent-adolescent conflicts.

Behavioural interventions in the kindergarten, the preschool or the school

Behavioural interventions in the kindergarten, the preschool or the school are known to be effective in reducing hyperactive behaviour and promoting social adjustment [38]. No one scheme has been shown to be superior to others, and the following outline is an integration of several [10, 40, 35].
- Discuss classroom structure and task demands (e. g. having the child seated close to the teacher, brief academic assignments, interspersing classroom lectures with brief periods of physical exercise).
- Identify specific problem situations and specific behaviour problems (e. g. blurts out answers before questions have been completed; leaves seat in classroom). Monitor the child's progress frequently with a rating scale.
- Analyse positive and negative consequences and contingencies of appropriate and problem behaviours.
- If coercive and unpleasant teacher-child interactions occur very often while positive teacher-child interactions rarely occur, then it may be possible to enhance the differential attending skills of the teacher – for example, during individual feedback after a period of observation. In any event, teachers often appreciate discussion of effective methods of communicating positive commands, setting rules, paying positive attention to child compliance, and developing appropriate negative consequences to problem behaviours.
- Use token systems in order to reinforce appropriate behaviour in specific situations. Back-up reinforcement may be located in the kindergarten or school (e. g. special playtime or lesser homework assignment), at home, or outside (e. g. special playtime with a therapist).
- Response cost systems are useful to reduce very frequent problem behaviours (e. g. often leaves seat, or disrupts others).
- Use brief 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. Make sure, however, that leaving the classroom is not positively reinforcing to the child and that it does not become punitive.
- As considered above, the child needs to be integrated as an active member in this therapeutic process.

Cognitive behaviour therapy of the child

Summer treatment programmes with social skills training and contingency management have been proven to be effective [113]. Isolated self-instructional approaches have not been shown to be effective by controlled trial [1] but experience suggests they may be helpful in individuals in combination with other behavioural approaches. Treatment generalisation is often limited, all the more if the application of the newly acquired skills is not reinforced in the natural environment of the child. They should be used only if the child is able to apply self instruction – in practice from the age of 7 years or greater. Self-instruction is most relevant if the child is motivated and if impairing symptoms of inattention or impulsivity can be observed even under optimal learning conditions, e. g. with reinforcement for attentive and reflective behaviour.
- Teach the child steps of self instruction ("Stop, what is the problem? – Are there possible plans? – What is the best plan? – Do the plan! – Did the plan work?").
- Train self instruction on different materials thus enhancing internalisation of the steps.
- Apply self-instruction procedures to social problem solving if deficits in social problem solving are present.
- Enhance training generalisation by using self moni-

toring and self evaluation of whether procedures have been followed. Teach parents and teachers to help the child to apply self-instruction procedures at home or at school.

Cognitive behaviour therapy (CBT) is essentially a form of self-instructional training, though the term CBT is sometimes used loosely to cover most of the psychological interventions described here. Experimental evidence has supported its ability to alter behaviour in controlled laboratory settings, but has not yet shown a superiority to other approaches in controlled trials [1].

Psychopharmacological treatment

There is a substantial evidence base for the effect of methylphenidate over treatment periods up to a year and in doses up to 60 mg daily. Numerous placebo-controlled randomised control trials confirm the substantial short-term benefit [131, for meta-analysis see 72, for systematic reviews, see 141, 89]. Stimulants markedly and rapidly reduce the overt clinical manifestations of restlessness, inattentiveness and impulsiveness; they improve the quality of social interactions, decrease aggression and increase compliance.

Two other stimulants, dexamfetamine and pemoline, have been shown to be more effective than placebo in a smaller number of short-term trials, conducted some years ago. Methylphenidate and dexamfetamine are licensed for children in most European countries. Where they are not licensed, it is sometimes in the context of legal frameworks to prevent drug abuse, but can have the effect of leading to the use of more toxic drugs to control hyperactivity.

Stimulant medications also have limitations: They are not an acceptable treatment option for some children and families. Many families believe that their child's problems reside in the context of key relationships or in the child's school. Lack of adherence limits the effectiveness of medication, as it does with all medical treatments. Although generally safe, stimulant medication does have side-effects in a proportion of recipients that, in some cases, result in the termination of treatment (see below).

Superiority to placebo in random-allocation, double-blind trials of varying methodology has also been reported for atomoxetine and clonidine; for tricyclic antidepressants such as imipramine and desipramine; and for neuroleptic antidopaminergic drugs (thioridazine, haloperidol).

Indications

Medication should be considered when (i) the patient meets the DSM-IV criteria for the AD/HD syndrome and (ii) psychological treatments are insufficient alone or the criteria for primary use of medication are met (see 'Integration of approaches').

A single drug should be initiated first. If efficacy or tolerability of the given agent should turn out to be unsatisfactory, an alternative monotherapy should usually be initiated, before combined psychopharmacological therapy is introduced (see below).

Details of prescription are generally not based on rigorous evidence, but our consensus recommendation is that initial medication should be as a trial, and *methylphenidate* is usually the first choice. The treatment should be discussed and explained before it is started; and in the early stages of treatment the family (and preferably the teacher) will need a quick and ready access to the prescriber to report progress and any adverse effects.

The effect lasts only for a few hours: Three daily doses are recommended, but practical considerations may dictate a twice daily regime. The dosage should begin at a low level (0.2 mg per kilogram per dose) and be increased in the light of response. The amount should be increased until either a good result is achieved, or adverse effects appear, or a ceiling of 0.7 mg per kilogram per dose is achieved – whichever comes first.

Longer-acting preparations of methylphenidate may also be used from the start of therapy. They are somewhat more expensive, and not available in all countries, but carry many advantages if the effect is long enough to make additional doses at school unnecessary. This makes the treatment more private, avoids stigma at school, and therefore improves compliance. From the school's point of view, it is hard to overstate the advantage that comes if dispensing a controlled medication is no longer on the list of school responsibilities. OROS-methylphenidate (Concerta) is the only such preparation to be widely available outside North America at present; an initial dose of 18 mg daily can be increased at intervals of 1 week up to 54 mg daily. If it is not effective, then immediate-release methylphenidate should be tried in repeated doses, titrated according to the response.

Careful and detailed titration of dosage and timing is likely to improve response. The large North American trial of multimodal treatments [105, 106 described below] compared children with AD/HD who had been randomly assigned to routine community treatment (usually including medication) or to carefully crafted medication, in which varying doses of methylphenidate were given, monitored daily for a month, and the best dose for the child chosen for continuing therapy. This is an expensive process, so it seems logical to reserve en-

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hanced monitoring for those who have not responded to routine therapy.

Adverse effects of stimulant medication

Sleeplessness is a frequent presenting problem. It is clinically important to distinguish those children whose insomnia is an untoward effect of the drug 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 [58].

Nervousness, dysphoria, and appetite reduction are most common at the beginning of treatment. They may be controlled by dose reduction. Uncommon problems include skin rash, nausea, dizziness, headache, weight loss, and changes in blood pressure. Motor tics and mannerisms may emerge at any stage of treatment; if they do, then judgement is needed as to whether they are so severe that the treatment must be stopped, reduced or replaced with another medicine. Overdose produces many harmful effects, including delirium, confusion, tremors, sweating, vomiting and muscle twitching.

Growth can be affected. If there are indications of growth retardation, drug holidays (e. g. during the summer vacation) are recommended [119, 158].

Emotionally unstable adults, or those with a history of substance abuse, may increase a prescribed dose on their own initiative. Chronic abuse of high-dose methylphenidate can lead to tolerance and psychic dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially in response to parenteral abuse.

Epilepsy is not necessarily a contraindication. It is said that methylphenidate may lower the convulsive threshold in animals, but experience suggests that methylphenidate can be safe and effective in most children and adolescents with coexisting seizure disorders and AD/HD [61, 68, 82] – at least if the epilepsy is well controlled. Less is known about those with poorly controlled epilepsy, so frequency of seizures should be carefully monitored, and if their frequency increases, or seizures develop de novo, then methylphenidate should be stopped. Dexamfetamine is then a good substitute.

Precautions and monitoring

We regard all the stimulants as contraindicated in: schizophrenia, hyperthyroidism, cardiac arrhythmias, angina pectoris, and glaucoma; and, of course, when the drug has previously caused hypersensitivity. Caution is needed in the presence of hypertension, depression, tics (or a family history of Tourette's syndrome), pervasive developmental disorders, severe mental retardation, or a history of drug dependence or alcoholism.

Monitoring should include recording blood pressure and pulse (at each adjustment of dose, then every 6 months); height, weight and appetite with maintenance of a growth chart (6 monthly); tics, depression, irritability, lack of spontaneity, withdrawal, and excessive perseveration (at every visit). Manufacturers recommend periodic blood tests to detect any haematological abnormality, but we are aware of no evidence for this practice and think that the remote chance of benefit is usually outweighed by the unpleasantness for the child.

Abuse potential of psychostimulants

Much has been made in the media about the similarities between methylphenidate and cocaine. Both drugs work by blocking the dopamine transporter and indeed methylphenidate is more effective than cocaine in this respect [178]. Detailed studies, however, have demonstrated important pharmacokinetic and pharmacodynamic differences between the two drugs. As a result of these differences methylphenidate, when taken in clinical doses and within a clinical context, appears to be associated with a much lower abuse potential than cocaine [177]. There is some evidence (e. g. from police seizures) to suggest that small quantities of methylphenidate are diverted towards illicit use, but rates of methylphenidate misuse seem to be low and those who do choose to abuse it do so mainly by intravenous injection.

Arguments have been put forward suggesting that exposure to stimulant medications early in life may lead to the development of sensitisation and cross-sensitisation which may render an individual more likely to abuse drugs in later life [122]. The findings from animal studies regarding the development of sensitisation to methylphenidate are contradictory and there have been no well-designed studies to address these issues in human subjects [121]. It is therefore not possible to answer the question, "does early exposure to stimulant medication lead to sensitisation to stimulant or other medications in later life?" with any degree of certainty. The available clinical data suggest that, whether or not sensitisation occurs, the net effect of treating children and young people with AD/HD with stimulant medication is to protect against, rather than lead to, later substance misuse. A meta-analysis of the available literature reported that those treated with stimulants were protected against the development of substance misuse problems by a factor of almost two (Odds Ratio, 1.9), compared with those whose AD/HD was not treated with stimulant medication [184]. Possible mechanisms for this protective effect include a reduction in AD/HD symptoms especially impulsive behaviour, a reduction in conduct disorder and later anti-social personality disorder, im-

proved academic performance and career, or improved peer and family relationships.

Other drugs

Dexamfetamine is also a useful stimulant. The effects are clinically similar to those of methylphenidate; but some patients who do not benefit from methylphenidate respond to dexamfetamine, and vice versa [20]. The dose is half that of methylphenidate.

Pemoline is a longer-acting stimulant, usually considered to have its main actions on the inhibition of dopamine reuptake. For children over 6 years, the starting dose is 2 tablets (of 18.5 or 2 mg) daily; it should be increased by one daily tablet each week; the usual maintenance level is 4 to 6 tablets daily (usually given in two divided doses). Clinical benefit may not be evident until the third or fourth week of therapy. It can induce an elevation of hepatic enzyme levels that is usually minor and can easily be managed by discontinuing the drug. There have, however, been at least two published reports of death due to liver failure [15, 108]. Because of this, the drug is not on the market in most European countries.

There are different non-stimulant drugs in use to treat ADHD [8]. Replicated evidence was shown from multi-centre randomised controlled trials for the efficacy of atomoxetine in AD/HD [96]. Atomoxetine is a specific potent norepinephrine reuptake inhibitor similar in structure to fluoxetine. Data about school and cognitive effects so far are limited. Atomoxetine has been licensed in the USA but no license has been given yet in Europe – though it is under consideration.

Other unlicensed treatments include tricyclic antidepressants, antihypertensives and bupropion; the evidence base derives from small-scale trials with methodology that reviewers have criticised [72]. Their use is essentially in specialist practice where their hazards are understood and monitored.

Desipramine and imipramine are tricyclic antidepressants, with an antihyperactivity action that is probably due to their ability to inhibit norepinephrine uptake. These medications are usually considered when methylphenidate or another stimulant may make tics worse, or has been ineffective, or has exacerbated emotional disturbance. In AD/HD patients with tics, desipramine is more effective than clonidine on the symptoms of AD/HD [146]. Dose should be built up step-wise, over two weeks, to a total of 2.5 mg/kg/day, divided into two or more doses (at morning and evening). Effect evaluation should come after two weeks on a stable dosage.

Adverse effects of desipramine include drowsiness, sleep disturbances, anxiety, headache, dizziness, dry mouth, sweating, constipation, blurred vision, hypotension, tachycardia, weight gain, nausea and allergic skin reactions. The most worrying hazard is on the cardiovascular system with an increase in tachycardias and a possible deterioration of the ECG even two years after the start of the treatment. Most treated children show no ECG change, but a few cases of sudden death, presumably due to cardiac arrhythmia, have been reported in children. The drug has therefore been withdrawn in some countries. Desipramine, like other tricyclics, should be seen as having a cardiotoxic potential that varies greatly between children [180]. When they are prescribed, then children should have pulse, blood pressure and ECG monitoring at baseline, after each dose increase and then every 3 months. Plasma levels should be monitored if anything more than a small dose is given. Female patients seem to reach higher blood levels with the same weight-adjusted dose than male patients, and also show more side-effects [59].

Imipramine may be used instead of desipramine. Children over the age of 6 years should start with 10 mg daily, increase over a period of 10 days to 20 mg (up to the age of 8 years), to 20–50 mg (up to the age of 14 years) and to 50–80 mg (for patients over 14 years). Adults should start with 25 mg and be raised gradually to a maximum of 150 mg daily. For maintenance therapy in adults, 50–150 mg daily is the usual dose range.

Clonidine and guanfacine are alpha-2-noradrenergic drugs which have a presynaptic action to reduce the release of noradrenaline. They may be used when methylphenidate, or another stimulant, and tricyclics have been ineffective or contraindicated. The dosage of clonidine, which should be built up gradually over 2 to 4 weeks, is usually 3–5 µg/kg/day, divided into two doses (at breakfast and bedtime). Effect evaluation is after six weeks on the full dosage. The most common adverse effects are sedation, drowsiness, and depression. Orthostatic hypotension and cardiac arrhythmias are rare but potentially serious; thus the therapist should monitor blood pressure, pulse and electrocardiogram. Contraindications include cardiac arrhythmias (especially sick sinus syndrome) and major depression; special precautions are needed in impaired renal function. The medication should not be stopped abruptly because of the risk of rebound hypertension and tics.

Neuroleptics such as risperidone appear to be less helpful for hyperactive behaviour than stimulants, and they do not reliably produce cognitive improvement. They can be helpful in low daily doses (e. g. risperidone 0.5 to 1.5 mg/day, usually in two doses) when there is comorbid pervasive developmental disorder or when severe aggression or affective instability – especially in those with intellectual disability – requires drug therapy [3]. Potential side-effects that require careful monitoring are weight gain and sedation. The risks usually exceed their possible usefulness in the treatment of uncomplicated AD/HD and would require careful

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consideration before use. Behavioural therapy remains the best evaluated treatment in severely challenging behaviour problems.

Effect evaluation

The items of the Attention Problems and Hyperactivity factor scores of the CBCL, Conners scales and TRF are useful ways of measuring behaviour change [80] and are appropriate for monitoring other drug treatments as well. In addition, before the start of medication parents and teachers may be asked to select (for example) three problem behaviours as targets for the medication effects and to give a mark for each target [2, Checklist of Target Problems, see Appendix]. After one week on a stable dosage both the parents and the teacher are asked to mark again. The effect of the treatment is only considered favourable if the improvement is considerable, and there are no persistent adverse effects. Comparison with a placebo is a powerful way of assessing effect, but it is not needed routinely [see 75].

Duration of treatment

Longer term evidence of efficacy is hard to obtain, but trials are in progress [52]: methylphenidate is still more effective than placebo over periods in excess of a year. In practice, length of treatment is not fixed in advance, and may well need to be for some years. It should be discontinued periodically (e. g. once a year) to assess the child's condition and continuing need for therapy. A common mistake is to stop treatment prematurely.

Treatment will sometimes need to continue into adult life. Some randomised controlled studies have showed that adults are sometimes helped by methylphenidate [62, 179, 159]. Adult patients are variable in their dosage requirement, and up to 1.0 mg/kg/dose has been used [159]; or even 2 mg/kg daily [182]. Tricyclic antidepressants may be considered for nonresponders or adults with concurrent psychiatric disorders.

Combinations of drugs

Stimulants should not be administered with monoamine oxidase inhibitors (MAOIs) or until a period of at least 14 days has elapsed since MAOIs were ingested, to avoid possible hypertensive crises [58].

The blood level of tricyclics is unpredictably increased if methylphenidate is given simultaneously, so the combination should be given, if at all, only with close monitoring of blood level and ECG. The metabolism of coumarin anticoagulants, some anticonvulsants (phenobarbitone, phenytoin, primidone) and phenylbutazone may also be inhibited by methylphenidate, requiring dose reductions.

Clonidine can produce intraventricular conduction delay and T wave abnormalities, so careful ECG-monitoring is recommended if clonidine is used with other drugs affecting the cardiovascular system.

Tricyclic antidepressants in combination with neuroleptics (especially pimozide) can result in an intraventricular conduction delay. The combination is best avoided unless there are very strong clinical reasons for it.

Nutritional approaches

Dietary treatment has a bad name, largely because of some widely promoted claims that dietary salicylates, food colourings and preservatives were the main cause of hyperactivity [48]. These views are now known to be false [95]. Many other diets without the support of clinical trials are promoted from time to time. Popular recent examples include the restriction of sugar, the administration of evening primrose oil, and hyposensitisation to defined allergens; the limited trial evidence indicates that they are of little value and should not be prescribed. Fish oils have been introduced more recently, but there is not enough evidence to recommend one way or the other.

There is limited trial evidence for the value of elimination diets that seek to exclude foods – different for each child – to which intolerance exists [27, 41, 78, 140]. Cows' milk, wheat flour, citrus fruits and food dyes are among the most commonly incriminated foods. On the other hand, a community survey has indicated that the majority of children, whose parents believe them to be food sensitive, are not [189]. The resolution seems to be that at least a few children with hyperactive behaviour are reacting badly to food, but that an elimination diet will help only a minority. The diets are troublesome to apply, and they are often rejected by older children.

We have to conclude that there is not yet enough scientific evidence to establish guidelines for dietary treatment. More research is needed. A food diary approach is a non-intrusive way of establishing whether there is a link between behaviour and food intake; if there is, then a mental health professional can help to monitor behaviour over several weeks while a suitable dietary regime for the individual child is worked out. A dietician should be consulted before any strict elimination approach (such as the "few foods diet") is attempted.

Integration of approaches

European clinicians are often presented with the choice between psychological treatment and medication as the

first specific therapy after diagnosis, education, advice and support. One large-scale trial in the USA – the MTA study – has focused on the comparison of the two kinds of treatment [105, 106]. Children were randomly allocated either to careful medication management, to intensive behaviourally oriented psychosocial therapy, to a combination of the two, or to a simple referral back to community agencies (which usually resulted in medication). The main conclusions were that careful medication is more powerful than behaviour treatment, and considerably more effective than routine medication in the community. There were many advantages in adding medication to behaviour therapy; but relatively few to adding behaviour therapy to medication. The superiority of careful medication to behaviour therapy was all the more striking in that the behaviour therapy provision was more intensive and prolonged than could be achieved by a community service. Combined therapy had some benefits: for example, the control of aggressive behaviour at home, improving the overall sense of satisfaction of parents and achieving "normalisation" (the reduction of problems to a level where none was rated as more than minor). These improvements are real, but would probably not justify the very high costs of the full treatment package in this research-based form.

It does not follow that medication is always the first choice in treatment. Though behavioural therapy may be less effective, it is still helpful for many children and multimodal behavioural interventions with parent training, interventions in school and cognitive behaviour therapy of the child have been shown to be effective in a substantial proportion of patients [162, 36]. The costs of a short course of parent training are comparable to those of medication; the outcome may be somewhat less favourable in terms of symptom reduction, but has the advantage of carrying very little physical hazard.

A reanalysis of the MTA study has assessed whether its conclusions apply to hyperkinetic disorder (Santosh et al., personal communication). The answer is that they do: the superiority of medication to behaviour therapy is greater in hyperkinetic disorder than in other types of AD/HD, and the effects of behaviour therapy appear to be less. Most children whose problems are severe enough to receive a diagnosis of hyperkinetic disorder will need medication. Family attitudes should of course be respected; but if a trial of psychological treatment has not produced substantial improvement within a few weeks, then medication should be advised.

For children at lesser degrees of severity – those who show AD/HD but not hyperkinetic disorder – the choice of initial therapy is more evenly balanced. In these milder cases there are options about which treatment to start with. Decisions will depend on the analysis of the individual child, the strengths and weaknesses of their school and classroom environment, the severity of disturbance of peer relationships, and the preferences of the families. It is quite reasonable to start with either therapy, in the knowledge that one will proceed to the other should the response be suboptimal.

Children who show attention deficit without hyperactivity may also present suitable targets for stimulant medication. Research evidence is rather scanty but tends to favour the idea that stimulants are useful, often in lower doses than are required for the control of overactive and impulsive behaviour. Certainly inattentiveness is improved in children with mixed types of AD/HD, and indeed poor scores on attention tests predict a good response to methylphenidate within mixed groups of children with AD/HD. Care needs to be taken in the inattentive subgroup: first, that the degree of impairment is sufficient to justify the hazards of medication; and, second, that the inattentiveness is indeed a specific problem and not just an expected part of a more global pattern of mental retardation.

The need to have a second line of therapy for some children should particularly be stressed when behaviour therapy has been chosen as the first option. It is not rational to prolong any kind of psychological therapy in the face of suboptimal improvements and there should not be undue delay in proceeding to medication for those children whose behaviour is still holding back their development in school, and their social relationships. Fig. 1 illustrates a treatment algorithm that embodies these principles, while Fig. 2 illustrates a treatment algorithm for ADHD refractory to methylphenidate.

Additional problems are often present, and if so they may need treatment whether or not the core symptoms of hyperactivity have been reduced by specific treatments. *Training of social competence* is often needed. It may help children to make and keep relationships, solve interpersonal problems and provide substitutes for aggressive behaviour to peers. Trials have not yet given clear evidence of the value of any one technique. Group therapy and behavioural instruction in naturalistic settings should be considered. *Individual psychotherapy* may need to be undertaken for poor self-esteem. Again, there is a dearth of experimental evidence; many clinicians favour short-term and cognitively based psychotherapies. *Remedial teaching of academic skills* may be needed for co-existent learning disorders. The curriculum may need to be modified, and individual attention from a teaching aide provided. *Family support* may need to go beyond the provision of advice, guidance and treatment and include the financial help appropriate for a disabled child and the provision of short periods of respite care.

Comorbidity with other psychiatric disorders is common, and poses some problems for the therapist that research has not yet answered. Treatment in these circumstances is guided more by experience than trials, and more trials should be undertaken.

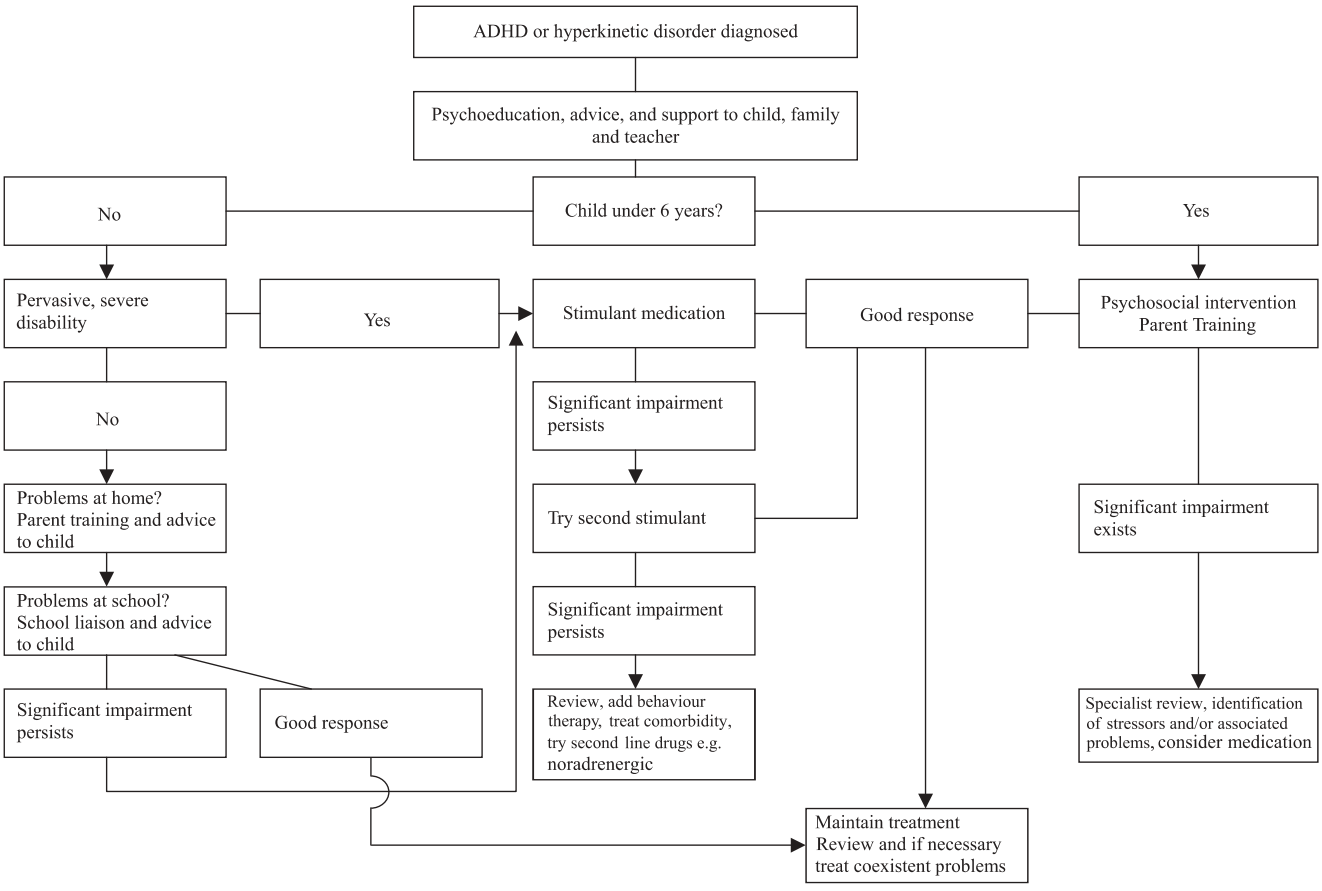

Fig. 1 Initial treatment of children with activity/attention problems

When AD/HD is comorbid with a conduct disorder then we recommend treating the AD/HD first, as above, since the conduct disorder is often secondary. Parent management training and cognitive behavioural therapy can then be provided for the conduct problems, and are often needed [69].

AD/HD with comorbid anxiety disorders is not necessarily refractory to stimulants and anxiety is not a contraindication. However, a further search for psychological stresses on the child is in order, and if they cannot be simply alleviated then psychological treatment may have more to offer than repeated drug trials.

Comorbid tics often present problems because they may be worsened by stimulants. This is not inevitable, and stimulants are sometimes useful even for the hyperactivity seen in Tourette's syndrome. However, there is some evidence that in a few children with AD/HD, tics may be triggered or exacerbated by stimulants. If a dosage reduction of stimulants does not lead to an improvement of the tics, or if the presentation of tics plays an important role concerning psychosocial impairment of the child, the parallel use of stimulants and tic-reducing drugs (e. g. tiapride, risperidone, pimozide, clonidine) seems to be indicated. Coexisting tics and hyperkinetic symptoms can be treated with tiapride only, or a noradrenergic agent, if hyperkinetic symptoms are mild. Behavioural therapy may be added for tics and obsessive symptoms. Careful monitoring is needed and a specialist centre should usually be involved.

When AD/HD is comorbid with a pervasive developmental disorder, then again specialist advice should be sought. There is little trial evidence, but we suggest that even in autism it may be worth a trial of medication for the symptoms of AD/HD. Methylphenidate itself is often the most helpful; clonidine, atomoxetine, and even risperidone may have their place. Behavioural therapy, targeting the AD/HD symptoms, is widely applicable.

For treating individuals with AD/HD and an established comorbid substance misuse disorder, there is little research evidence to guide clinicians. 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 AD/HD symptoms may enhance effective treatment of substance misuse [120]. Pharmacological therapies for AD/HD should be started

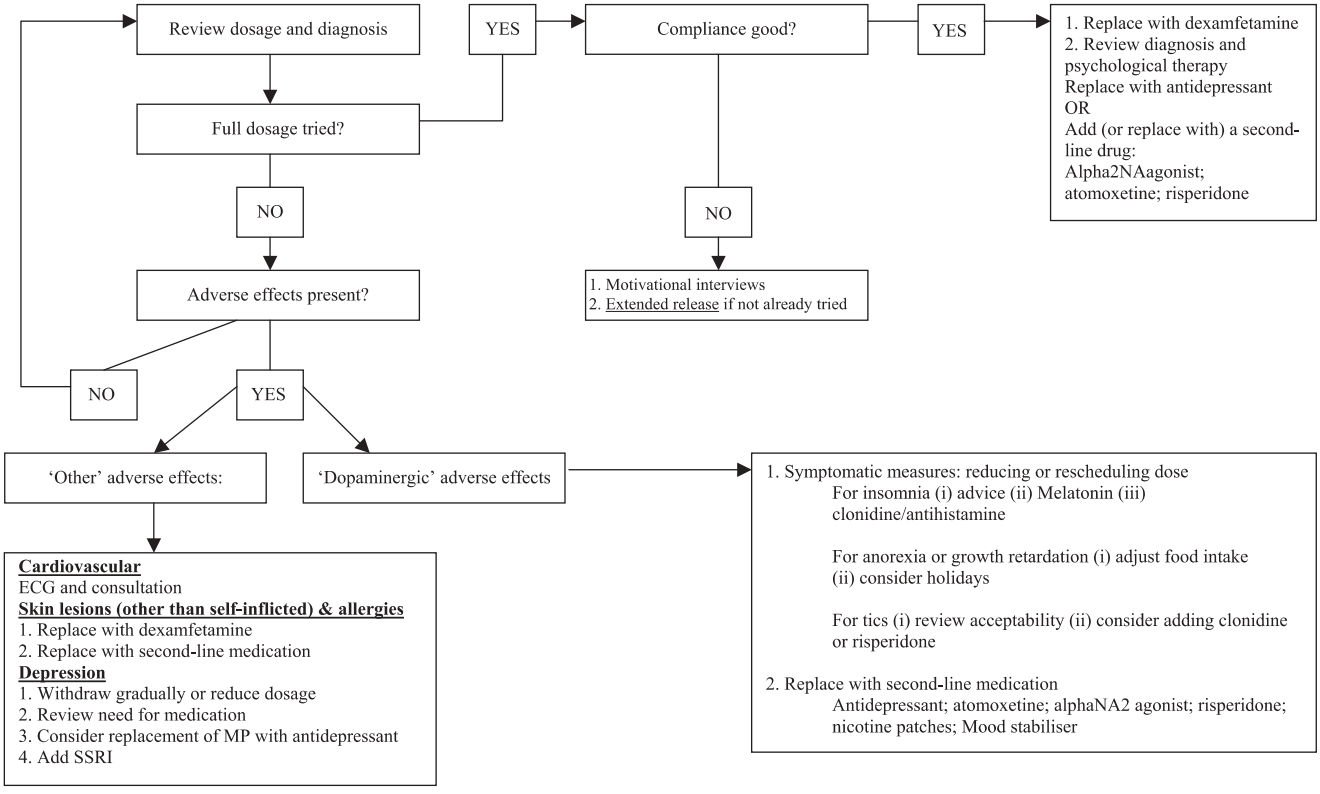

Fig. 2 Treatment for ADHD refractory to methylphenidate

with caution and under close supervision. Medications should be given by a supervising adult and securely stored. Whilst immediate release stimulant preparations are likely to be effective they are potentially more abusable than the extended release preparations. OROS methylphenidate, in particular, is difficult to extract into a form that can be abused. Where stimulant treatment is considered inappropriate non-stimulants may be considered. There are indications that bupropion may be an effective treatment for this group [87, 120] but further controlled studies are required. Where available, atomoxetine is likely to be an attractive effective treatment option for this group.

Diagnosis and management in pre-school

In the USA, but not for the most part in Europe, there has been a dramatic recent increase in the number of children below the age of five who have been treated for AD/HD The literature on this age group remains limited and the recommendations set out here remain tentative [153].

Recent evidence supports the view that pre-school AD/HD, while taking a somewhat different form from school-aged AD/HD, shares many elements with it and has generally similar levels of validity and utility. Symptoms of preschool inattentiveness, impulsiveness and overactivity cluster together [156] and this cluster has largely equivalent associations to those seen with school-aged children in terms of intellectual (e. g. pre-academic skills and developmental delay), behavioural (e. g. ODD and Developmental Co-ordination Disorder) and neuropsychological characteristics (both executive deficits and delay aversion) [39, 50, 154, 160, 181]. There also appear to be continuities between pre-school symptoms and later AD/HD and associated impairments such that pre-school AD/HD is likely to represent a significant barrier to school readiness [93].

Nevertheless, case identification remains uncertain. Future research should introduce new and more age-appropriate diagnostic items, definitions and thresholds. Age-specific criteria for impairment that place special emphasis on non-parental report will be needed, and ways of distinguishing a transitory developmental hiatus from early onset chronic problems will be important.

Management should be correspondingly cautious, especially with regard to drugs. Most of the small number of studies using stimulants with pre-school children report similar levels of short-term symptom control to those with school-aged children. Short-term side-effects may be more marked amongst pre-schoolers and these

may be especially pronounced in children with learning disabilities [64, 104]. The issue of long-term side-effects has not been addressed clinically, but animal models suggest that early administration of methylphenidate has chronic effects on neuro-transmitters in the pre-pubertal rat brain [103]. There is an urgent need for systematic studies.

Psycho-social approaches, by contrast, may be even more valuable in the pre-school than the school years. Two studies have demonstrated that parent training in particular seems to be effective in reducing *both* core symptoms of AD/HD *and* associated oppositional behaviour [19, 115]. These studies give credence to the view that effective early intervention is possible if children can be treated in pre-school before AD/HD behaviours become compounded with factors associated with school failure (e. g. low self esteem; peer relationship problems etc.), hardening of adult attitudes and the deterioration of adult-child interactions. At present there is little evidence that the benefits of PT delivered in the home generalise to nursery-school settings or that the benefits of these approaches are sustained over the longer term.

Delivery of treatments

Most specific treatments will be given in secondary care. A mental health or behavioural paediatric service will probably need to make special arrangements for the children who receive stimulant medication. The need for technically knowledgeable follow-up over long periods is well met by a specialist clinic.

Secondary care should also be able to provide psychological therapy and educational advice and liaison. This will entail building up good working relationships with local agencies. For school interventions, the collaboration of the teacher is prerequisite. Furthermore, successful delivery of behavioural interventions in the classroom will probably need the school system to support it, not just the individual teacher. Long-term liaison with schools can achieve a great deal, both in case-finding and in the development of a whole school response. One member of the staff, for example, may become a resource for training aides and other teachers.

Home interventions, too, require understanding and cooperation from parents and children. This can be impaired by other problems straining family resources – financial, mental health or disturbed relationships. Family meetings with a therapist can be an excellent way of mobilising problem-solving skills. The therapist should remember that most families have a long experience of being blamed, and blaming themselves, for behaviour problems of their children. Guilt and shame may need to be lessened before focussed therapies are feasible. Many parents are exquisitely sensitive to therapist attitudes that can be construed as attributing blame, and need time to build trust.

Complex or refractory cases, often those with severe comorbid problems or failures of care, will need referral to a regional specialist centre that can provide intensive monitoring, detailed psychological and neurological assessment, a range of psychological therapies and expertise in the use of drugs. Day- or in-patient treatment facilities are needed for some cases, for example to allow close monitoring or more intensive work with families. A specialist centre should be linked to a university department and in current touch with the rapidly advancing body of research.

The role of support groups

Support groups in many European countries have ambitious goals, both for the support of individual sufferers and their families, and in public campaigning. At the level of assistance to individuals, they can help greatly in disseminating information about the disorders, developing advocacy work, and providing groups for parents or teenagers or adult sufferers. It is very helpful if such groups can maintain a comprehensive approach. Their credibility, and avoidance of factionalism, are important in persuading society of the importance of recognising and treating the hyperkinetic disorders of childhood.

Appendix

Recommended assessment instruments

Questionnaires

Child Behavior Checklist (CBCL):
Achenbach TM (1991a) Manual for the Child Behavior Checklist/4–18 and 1991 Profile. Burlington, University of Vermont, Department of Psychiatry

Child Communication Checklist
ADHD, Dyslexia, High Functioning Autism
Purvis and Tannock (1997) studied whether the language difficulties of ADHD children could be accounted for by difficulties in the organization and monitoring of their reconstruction of a story, suggesting a pragmatic problem in ADHD children. Dyslexic children had no difficulty in organization or monitoring of their reconstruction but had semantic and receptive language difficulties. ADHD children comorbid for dyslexia had difficulties with both classes of language problems. Geurts et al. (2004) compared HFA and ADHD children on rated language proficiency with the Child Communication Checklist (Bishop 1998). Children with HFA could be reasonably differentiated from children with ADHD in terms of their language deficits. Children with HFA showed more profound language deficits compared to children with ADHD. Luteijn et al. (2000) showed that children with autism have the most profound communication deficits (including pragmatics) compared to other clinical groups, including children with ADHD.

Bishop DVM (1998) Development of the children's communication checklist (CCC): a method for assessing qualitative aspects of communicative impairment in children. J Child Psychol Psychiatry 39:879–891

Bishop DVM, Baird G (2001) Parent and teacher report of pragmatic aspects of communication: Use of the Children's Communication Checklist in a clinical setting. Developmental Med Child Neurol 43:809–818

Geurts HM, Verté S, Oosterlaan J, Roeyers H, Hartman CA., Mulder EJ, van Berckelaer-Onnes, Sergeant JA (2004) Can the Children's Communication Checklist Differentiate between Children with Autism, Children with ADHD, and Normal Controls?

Conners' Parent Rating Scale (CPRS)
Conners CK (1989) Conners' Rating Scales Manual. New York, Multi-Health Systems

Conners' Teacher Rating Scale (CTRS)
Conners CK (1989) Conners' Rating Scales Manual. New York, Multi-Health Systems

Disruptive Behavior Disorder Checklist
Pelham W, Gnagy EM, Greenslade KE, Milich R (1992) Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. Journal of the American Academy of Child and Adolescent Psychiatry 31:210–218

Home Situations Questionnaire
Barkley RA (1991) Attention-deficit hyperactivity disorder. A clinical workbook. New York, Guilford Press

Iowa Conners Teacher Rating Scale
Loney J, Milich R (1982) Advances in Developmental and Behavioral Pediatrics 3:113–147

Revised Behavior Problem Checklist (RBPC)
Quay HC (1983) A dimensional approach to behavior disorder: The Revised Behavior Problem Checklist. School Psychol Rev 12:244–249

Rutter Scales
Rutter M, Tizard J, Whitmore K (eds) (1970) Education, health and behaviour. London, Longmans Green

School Situations Questionnaire (SSQ)
Barkley RA (1991) Attention-deficit hyperactivity disorder. A clinical workbook. New York, Guilford Press

SNAP-IV-Rating Scale
Swanson J (1992) School-based assessments and interventions for ADD students. Irvine, K. C. Publishing

Strength and Difficulties Questionnaire (SDQ) for parents, teachers and youth
Overview in Rothenberger A, Woerner W (eds) (2004) Strenghts and Difficulties Questionnare (SDQ) – Evaluation and Application. Eur Child Adolesc Psychiatry (suppl)

Internet: sdqinfo.com

Teacher's Report Form of the Child Behavior Checklist (TRF)
Achenbach TM (1991b) Manual for the Teacher's Report Form and 1991 Profile. Burlington: University of Vermont, Department of Psychiatry

Youth Self-Report (YSR)
Achenbach TM (1991c) Manual for the Youth Self-Report and 1991 Profile. Burlington: University of Vermont, Department of Psychiatry

Interviews

Diagnostic Interview Schedule for Children – Child & Parent Interviews
Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000) NIMH Diagnostic Interview Schedule for Children version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry 39: 28–38

Parental Account of Children's Symptoms (PACS)
Taylor EA, Schachar R, Thorley G, Wieselberg M (1986) Conduct disorder and hyperactivity: I. Separation of hyperactivity and antisocial conduct in British child psychiatric patients. Br J Psychiatry 149: 760–767

Neuropsychological assessment

Tests of Executive Functioning
Sergeant JA, Geurts H, Oosterlaan J (2002) How specific is a deficit of executive functioning for Attention-Deficit/Hyperactivity Disorder? Behav Brain Res 130:3–28

Continuous performance
The Continuous Performance Test (CPT) has been used in a vast number of studies in both ADHD and autism, as well as other childhood psychopathological conditions. Poorer vigilance (d') has been found in virtually every child disorder compared with controls (see for meta-analysis Losier, McGrath & Klein, 1996). The effect size for the ADHD – control comparison differed slightly for omission errors (E. S. = 0.67) and commission errors (0.73), which are moderate to good effects.

Inhibition
Stop task: a useful task in discriminating children with ADHD from controls (Oosterlaan, Logan & Sergeant, 1998).
Stroop: The Stroop test and its differential diagnostic significance was reviewed by Sergeant, Geurts & Oosterlaan (2002). This headcount indicated that a number of studies (ten) had reported deficits in ADHD and in the related-disorders ODD/CD. An unpulished meta-analysis has subsequently shown that the difference between ADHD and control children is, at best, a weak one (van Mourik et al. under review).

Planning
Planning is the ability to 'look ahead', to construct a plan, and to evaluate and monitor execution of a plan. The attainment of a future goal is reached through a sequence of intermediate steps, which not always directly lead to the future goal. Sergeant et al. (2002) tabulated five studies, which differentiated ADHD from controls and two studies that reported no difference. A recent study compared HFA and ADHD children and found that the execution time of HFA was longer than both ADHD and control children (Geurts et al. 2003). There is some support for the view that HFAs perform poorer than ADHD children in a planning task.

Fluency
In fluency tasks the participant is required to generate sets of appropriate responses to a given set of stimulus conditions. The tasks differ in the responses a subject is required to give. The main conditions are letters, categories, and designs. Cognitive processes involved in fluency include processing speed, size of the vocabulary, semantic memory, working memory, inhibition, and set maintenance.

Six studies contrasted ADHD children with controls on letter fluency and found poorer performance in ADHD compared with controls (see Sergeant et al. 2002).

Set Shifting
WCST: The Wisconsin Card Sorting Test (WCST) is used traditionally as a test to tap set shifting. The WCST differentiates between ADHD children and controls (see Sergeant et al. 2002). The WCST differentiated in 11 studies children with HFA from controls but two did not. Perseveration errors in the WCST have been found to differentiate HFA from ADHD children (Geurts et al. 2003). The WCST can differentiate between ADHD and controls and HFA from ADHD children (Verté et al. under review).

Working memory
Working memory tasks tap several processes: maintenance and manipulation of working memory, inhibitory control, the ability to generate and perform a sequence of responses, phonological and visuospatial abilities and requires an episodic buffer. The Corsi, often considered a working memory task, differentiates High Function Autism (HFA) from controls but not ADHD from controls; the comparison HFA – ADHD did not reach significance (Geurts et al. 2003).

Non-executive functioning tests/tasks

Benton
Geurts et al. (2003) found no difference between HFA and ADHD children.

Delay Aversion
Tasks that investigate delay aversion may be useful in the assessment of ADHD children (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). There is considerable interest in this task since it has been shown to differentiate ADHD from controls but also to do so independently of inhibition deficits (Solanto et al. 2001).

Timing
ADHD children have been demonstrated to have deficits in motor timing, but not in their temporal perception (Rubia et al., 1999b). The deficits observed in motor timing consisted of increased variability of free tapping, synchronizing, and anticipating the motor response to visual stimulation (Rubia et al., 1999b).

Rubia et al. (2003) found that a clinical ADHD group was impaired in time perception, which was spared in a community group of ADHD children. The persistent, but not the acute dose, of methylphenidate reduced the variability of sensori-motor synchronization and anticipation, but had no effect on time perception. This study showed that motor timing functions are impaired in both clinical and community children with ADHD. The study showed the effectiveness of persistent administration of methylphenidate on deficits in motor timing in ADHD children.

Overview of tests

Continuous Performance Tests (CPT)
Conners CK (1985) The computerized Continuous Performance Test. Psychopharmacology Bulletin 21:891–892
Conners CK (1994) The Conners' Continuous Performance Test. Toronto, Canada, Multi-Health Systems

Delayed Response Alternation
Weinberger DR, Berman KF, Gold J, Goldberg T (1994) In: Haith M, Benson JB, Roberts RJ, Pennington BF (eds) The Development of Future-oriented Processes. Chicago, University of Chicago Press

Matching Familiar Figures Test (MFFT)
Cairns E, Cammock T (1978) Development of a more reliable version of the Matching Familiar Figures Test. Developmental Psychology 11: 244–248

Self-ordered Pointing
Petrides M, Milner B (1982) Neuropsychologia 20:249–262
Geurts HM, Verté S, Oosterlaan J, Roeyers R, Sergeant JA (2003) How specific are executive functioning deficits in attention defcit hyperactivity disorder and autism? J Child Psychol Psychiatry 43:1–19

Sequential Memory Test
Gorenstein EE, Mammato CA, Sandy JM (1989) Performance of inattentive-overactive children on selected measures of prefrontal-type function. Journal of Clinical Psychology 45:619–632

Stop Signal Task
Oosterlaan J, Logan GD, Sergeant JA (1998) Response inhibition in AD/HD, CD, comorbid AD/HD+CD, anxious and control children: a meta-analysis of studies with the stop task. J Child Psychol Psychiatry 39:411–426
Scheres A, Oosterlaan J, Swanson J, Morein-Zamir S, Meiran N, Schut H, Vlasveld L, Sergeant JA (2003) The effect of methylphenidate on three forms of response inhibition in boys with AD/HD. J Abn Child Psychol 31:105–120

Stroop
Cohen JD, Servan-Schreiber D (1992) Psychol Rev 99:45–77
Mourik van R, Oosterlaan J, Sergeant JA (under review) The Stroop Revisited: A Meta-Analysis of Interference Control in AD/HD

Timing
Rubia K, Taylor AM, Taylor E, Sergeant JA (1999) Synchronization, anticipation, and consistency in motor timing of children with dimensionally defined attention deficit hyperactivity behaviour. Perceptual and Motor Skills 89:1237–1258
Rubia K, Noorlos J, Smith A, Gunning B, Sergeant J (2003) Motor timing deficits in community and clinical boys with hyperactive behavior: The effect of methylphenidate on motor timing. J Abn Child Psychol 31:301–313

Tower of Hanoi
Welsh MC, Pennington Ozonoff S, Rouse B, McCabe ERB (1990) Neuropsychology of early-treated phenylketonuria: Specific executive function deficits. Child Development 61:1697–1713

Tower of London
Shallice T (1982) Specific impairments of planning. Philosphical Transactions, Royal Society London. Biology 298:199–209
Nigg JT, Blaskey LB, Huang-Pollock C, Rappley MD (2002) Neuropsychological executive-functions and DSM-IV ADHD subtypes. Journal of the American Academy of Child and Adolescent Psychiatry 41: 59–66

Trail Making, Part B
Reitan RM (1958) Validity of the Trail Making Test as an indicator of organic brain damage. Perceptual and Motor Skills 8:271–276
Nigg JT, Blaskey LB, Huang-Pollock C, Rappley MD (2002) Neuropsychological executive-functions and DSM-IV ADHD subtypes. J Am Acad Child Adolesc Psychiatry 41:59–66

Wisconsin Card Sort Test (WCST)
Grant D, Berg E (1948) The Wisconsin Card Sort Test: Directions for administration and scoring. Odessa, Psychological Assessment Resources

WISC-R: Vocabulary, Arithmetic, Block Design and Picture Arrangement
Groth-Marnat G (1990) Handbook of Psychological Assessment 2nd edn. New York, Wiley

Acknowledgements The development of this consensus was greatly aided by the conferences and seminars made possible by the European Network for Hyperkinetic Disorders. We should like to express our appreciation to all participants for their valuable advice. Commercial firms and governmental organisations did not play a role in, or fund, the development of these guidelines.

References

1. Abikoff H (1991) Cognitive training in ADHD children: less to it than meets the eye. J Learning Disabil 24:205–209
2. Aman MG, Turbott SH (1991) Prediction of clinical response in children taking methylphenidate. J Autism Devel Disord 21:211–228
3. Aman MG, De Smedt G, Derivan A, Lyons B, Findling RL; Risperidone Disruptive Behavior Study Group (2002) Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. Am J Psychiatry 159:1337–1346
4. Arnsten AFT (2001) Dopaminergic and noradrenergic influences on cognitive functions mediated by prefrontal cortex. In: Solanto MV, Arnsten AFT, Castellanos FX (eds) Stimulant Drugs and ADHD. Basic and Clinical Neuroscience. New York, NY, Oxford University Press, pp 185–208

5. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH (1995) Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochemistry 65:1157–1165
6. Bakker SC, van der Meulen EM, Buitelaar JK, Sandkuijl LA, Pauls DL, Monsuur AJ, van 't Slot R, Minderaa RB, Gunning WB, Pearson PL, Sinke RJ (2003) A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. Am JHuman Gen 72: 1251–1260
7. Banaschewski T, Brandeis D, Heinrich H, Albrecht B, Brunner E, Rothenberger A (2003) Questioning inhibitory control as the specific deficit of ADHD – evidence from brain electrical activity. J Neural Transm (2004) 111(7):841–864 Epub 2003 Oct 24
8. Banaschewski T, Roessner V, Dittmann RW, Santosh PJ, Rothenberger A (2004) Non-stimulant medications in the treatment of ADHD. Eur Child Adolesc Psychiatry 13(Suppl 1):I102–I116
9. Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 121:65–94
10. Barkley RA (1988) The effects of methylphenidate on the interactions of preschool ADHD children with their mothers. J Am Acad Child Adolesc Psychiatry 27:336–341
11. Barkley RA (ed) (1998) Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment 2nd edn. New York, Guilford Press
12. Barr CL, Feng Y, Wigg K, Bloom S, Roberts W, Malone M, Schachar R, Tannock R, Kennedy JL (2000) Identification of DNA variants in the SNAP-25 gene and linkage study of these polymorphisms and attention-deficit hyperactivity disorder. Molecular Psychiatry 54:405–409
13. Barry RJ, Johnstone SJ, Clarke AR (2003) A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. Clin Neurophysiol 114:184–198
14. Berger A, Posner MI (2000) Pathologies of brain attentional networks. Neurosci Biobehav Rev 24:3–5
15. Berkovitch M, Pope E, Phillips J, Koren G (1995) Pemoline-associated fulminant liver failure: testing the evidence for causation. Clin Pharmacol Therapy 57:696–698
16. Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, Sprich-Buckminster S, Ugaglia K, Jellinek MS, Steingard R, et al. (1992) Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. Arch Gen Psychiatry 49:728–738
17. Biederman J, Milberger S, Faraone SV, Kiely K, Guite J, Mick E, Ablon S, Warburton R, Reed E (1995) Family-environment risk factors for attention-deficit hyperactivity disorder. A test of Rutter's indicators of adversity. Arch Gen Psychiatry 52:464–470
18. Blanz B, Lehmkuhl G, Poustka F, Remschmidt H, Schmidt M, Warnke A (1999) Guidelines for diagnosis and therapy. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie 27:91–92
19. Bor W, Sanders MS, Markie-Dadds C (2002) The effects of the tripe P-Positve Parenting Program on preschool children with co-occurring disruptive behavior and attentional/hyperactive difficulties. J Abnorm Child Psychol 30: 571–589
20. Borcherding BG, Keysor CS, Rapoport JL, Elia J, Amass (1990) Motor/vocal tics and compulsive behaviors on stimulant drugs: is there a common vulnerability? Psychiatry Res 33:83–94
21. Boyle MH, Offord DR, Hoffmann HG, Catlin GP, Byles JA, Cadman DT, Crawford JW, Links PS, Rae-Grant NI Szatmari P (1987) Ontario Child Health Study: I Methodology; II. Six-month prevalence of disorder and rates of service utilisation. Arch Gen Psychiatry 44: 826–836
22. Bramble D (2003) Annotation: The use of psychotropic medications in children: a British view. J Child Psychol Psychiatry 44:169–179
23. Brandeis D, Banaschewski T, Baving L, Georgiewa P, Blanz B, Warnke A, Steinhausen HC, Rothenberger A, Scheuerpflug P (2002) Multicenter P300 brain mapping of impaired attention to cues in hyperkinetic children. J Am Acad Child Adolesc Psychiatry 41: 990–998
24. Breslau N, Brown GG, DelDotto JE, Kumar S, Ezhuthachan S, Andreski P, Hufnagle KG (1996) Psychiatric sequelae of low birth weight at 6 years of age. J Abnorm Child Psychol 24:385–400
25. Buitelaar JK, Kooij JJS (2000) Aandachtstekort/hyperactiviteitsstoornis – ADHD. Achtergronden, diagnostiek en behandeling. Nederlands Tijdschrift voor Geneeskunde 144:1716–1723
26. Buitelaar JK (2002) Epidemiology of Attention-deficit/Hyperactivity Disorder: what have we learned over the last decade? In: Sandberg S (ed) Hyperactivity Disorders. Cambridge, Cambridge University Press, pp 30–63
27. Carter CM, Urbanowicz M, Hemsley R, Mantilla L, Strobel S, Graham PJ, Taylor E (1993) Effects of a few food diet in attention deficit disorder. Arch Dis Childhood 69:564–568
28. Castellanos FX (2001) Neuroimaging studies of ADHD. In: Solanto MV, Arnsten AFT, Castellanos FX (eds) Stimulant Drugs and ADHD. Basic and Clinical Neuroscience. New York, NY, Oxford University Press, pp 243–258
29. Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL (2002) Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. J Am Med Assoc 288:1740–1748
30. Curran S, Mill J, Tahir E, Kent L, Richards S, Gould A, Huckett L, Sharp J, Batten C, Fernando S, Ozbay F, Yazgan Y, Simonoff E, Thompson M, Taylor E, Asherson P (2001) Association study of a dopamine transporter polymorphism and attention deficit hyperactivity disorder in UK and Turkish samples. Molecular Psychiatry 6:425–428
31. Daly G, Hawi Z, Fitzgerald M, Gill M (1999) Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. Molecular Psychiatry 4: 192–196
32. Döpfner M (1996) Hyperkinetische Stoerungen. In: Petermann F (ed) Lehrbuch der Klinischen Kinderpsychologie 2nd edn. Goettingen, Hogrefe
33. Döpfner M, Lehmkuhl G (2003) Hyperkinetische Störungen (F90). In: Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie, Berufsverband der Ärzte für Kinder- und Jugendpsychiatrie und Psychotherapie in Deutschland, Bundesarbeitsgemeinschaft der leitenden Klinikärzte für Kinder- und Jugendpsychiatrie und Psychotherapie (eds) Leitlinien zur Diagnostik und Therapie von psychischen Störungen im Säuglings-, Kindes- und Jugendalter 2nd edn. Köln, Deutscher Ärzte Verlag, pp 237–249
34. Döpfner M, Schmeck K, Poustka F, Berner W, Lehmkuhl G, Verhulst F (1996) Verhaltensauffaelligkeiten von Kindern und Jugendlichen in Deutschland, den Niederlanden und den U.S.A., Eine kulturvergleichende Studie mit der Child Behavior Checklist. Nervenarzt 67:960–967

35. Döpfner M, Frölich J, Lehmkuhl G (2000) Hyperkinetische Störungen. Leitfaden Kinder- und Jugendpsychotherapie Vol 1. Göttingen, Hogrefe
36. Döpfner M, Breuer D, Schürmann S, Wolff Metternich T, Rademacher C, Lehmkuhl G (2004) Effectiveness of an individually tailored multimodal treatment in children with Attention Deficit Hyperactivity Disorder – global outcome. Eur Child Adolesc Psychiatry 13(Suppl 1):I117–I129
37. Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ (1999) Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 354:2132–2133
38. DuPaul G J, Eckert TL (1997) The effects of school-based interventions for Attention Deficit Hyperactivity Disorder: A meta-analysis. School Psychol Rev 23: 5–27
39. DuPaul G, McGoey K, EcKert T, VanBrackle J (2001) Preschool children with attention-deficit/hyperactivity disorder: Impairments in behavioral, social, and school functioning. J Am AcadChild Adolesc Psychiatry 40: 508–515
40. DuPaul GJ, Stoner G (1994) ADHD in the Schools. Assessment and Intervention Strategies. New York, Guilford
41. Egger J, Carter CM, Graham PJ, Gumley D, Soothill JF (1985) Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome. Lancet i:540–545
42. Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM (1998) DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. J Neurosci 18: 5901–5907
43. Ernst M, Zametkin AJ, Matochik JA, Pascualvaca D, Jons PH, Cohen RM (1999) High midbrain [18F]DOPA accumulation in children with attention deficit hyperactivity disorder. Am J Psychiatry 156:1209–1215
44. Ernst M, Liebenauer LL, Tebeka D, Jons PH, Eisenhofer G, Murphy DL, Zametkin AJ (1997) Selegiline in ADHD adults: plasma monoamines and monoamine metabolites. Neuropsychopharmacology 16:276–284
45. Faraone SV, Biederman J (1994) Is attention deficit hyperactivity disorder familial? Harvard Rev Psychiatry 1: 271–287
46. Faraone SV, Doyle AE, Mick E, Biederman J (2001) Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. Am J Psychiatry 158:1052–1057
47. Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J (1997) Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 48: 589–601
48. Feingold BF (1975) Hyperkinesis and learning disabilities linked to artificial food flavors and colors. Am J Nursing 75:797–803
49. Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S (2001) The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. Pharmacogenomics 1:152–156
50. Gadow K, Nolan E (2002) Differences between preschool children with ODD, ADHD, and ODD & ADHD symptoms. J Child Psychol Psychiatry 43:191–201
51. Gillberg C, Carlstrom G, Rasmussen P (1983) Hyperkinetic disorders in children with perceptual, motor and attentional deficits. J Child Psychol Psychiatry 24:233–246
52. Gillberg C, Melander H, von Knorring A.-L, Janols L-O, Thernlund G, Haeggloef B, Eideval-Wallin L, Gustaffson P, Kopp S (1997) Long-term stimulant treatment of children with Attention-Deficit Hyperactivity Disorder symptoms: A randomized, double-blind, placebo-controlled trial. Arch Gen Psychiatry 54:857–864
53. Gillberg C (2003) Deficits in attention, motor control, and perception: a brief review. Arch Dis Childhood 88:904–910
54. Gillberg C, Gillberg IC, Rasmussen P, Kadesjö B, Söderström H, Råstam M, Johnson M, Rothenberger A, Niklasson L (2004) Co-existing disorders in ADHD – implications for diagnosis and intervention. Eur Child Adolesc Psychiatry 13(Suppl 1):I80–I92
55. Gjone H, Stevenson J, Sundet JM (1996) Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample. J Am Acad Child Adolesc Psychiatry 35:588–598
56. Glow RA (1981) Cross-validity and normative data on the Conners' Parent and Teacher Rating Scales. In: Gadow KD, Loney J (eds) The Psychosocial Aspects of Drug Treatment for Hyperactivity. Boulder, CO, Westview Press, pp 107–150
57. Goodman R, Stevenson J (1989) A twin study of hyperactivity: I An examination of hyperactivity scores and categories derived from Rutter Teacher and Parent Questionnaires. II. The aetiological role of genes, family relationships, and perinatal adversity. J Child Psychol Psychiatry 30:671–710
58. Green WH (1991) Child and Adolescent Clinical Psychopharmacology. Baltimore,Williams & Wilkins
59. Greenhill LL, Setterberg S (1993) Pharmacotherapy of disorders of adolescents. Psychiatry Clinics of North America 16:793–814
60. Gross MD (1995) Buspirone in ADHD with ODD. J Am Acad Child Adolesc Psychiatry 34:1260
61. Gross-Tsur V, Manor O, v. d. Meere J, Josphe A, Shalev RS (1997) Epilepsy and attention deficit hyperactivity disorder: Is methylphenidate safe and effective? J Pediatr 130:670–674
62. Gualtieri CT, Ondrusek MG, Finley C (1985) Attention deficit disorder in adults. Clin Neuropharmacol 8:343–356
63. Halperin JM, Newcorn JH, Schwartz ST, Sharma V, Siever LJ, Koda VH, Gabriel S (1997) Age-related changes in the association between serotonergic function and aggression in boys with ADHD. Biol Psychiatry 41:682–689
64. Handen BL, Feldman HM, Lurier A, Murray PJH (2000) Efficacy of methylphenidate among preschool children with developmental disabilities and ADHD. J Am Acad Child Adolesc Psychiatry 38:805–812
65. Harrington R, Myatt T (2003) Is preadolescent mania the same condition as adult mania? A British perspective. Biol Psychiatry 53:961–969
66. Hawi Z, Dring M, Kirley A, Foley D, Kent L, Craddock N, Asherson P, Curran S, Gould A, Richards S, Lawson D, Pay H, Turic D, Langley K, Owen M, O'Donovan M, Thapar A, Fitzgerald M, Gill M (2002) Serotonergic system and attention deficit hyperactivity disorder (ADHD): a potential susceptibility locus at the 5-HT(1B) receptor gene in 273 nuclear families from a multi-centre sample. Molecular Psychiatry 7: 718–725
67. Hazell PL, Carr V, Lewin TJ, Sly K (2003) Manic symptoms in young males with ADHD predict functioning but not diagnosis after 6 years. J Am Acad Child Adolesc Psychiatry 42:552–560
68. Hemmer SA, Pasternak JF, Zecker SG, Trommer BL (2001) Stimulant therapy and seizure risk in children with ADHD. Pediatr Neurol 24:99–102
69. Herbert M (1994) Behavioural methods. In: Rutter M, Hersov L, Taylor E (eds) Child and Adolescent Psychiatry: Modern Approaches 3rd edn. Oxford, Blackwell Scientific Publications, pp 858–879
70. Hill P, Taylor E (2001) An auditable protocol for the medical management of ADHD or hyperkinetic disorder Arch Dis Childhood 84:404–409
71. Huss M, Lehmkuhl U (2002) Methylphenidate and substance abuse: a review of pharmacology, animal, and clinical studies. J Attention Disord 6 (Suppl 1):S65–S71

72. Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R (1998) The treatment of attention-deficit/hyperactivity disorder: an evidence report. Agency for Healthcare Research and Quality, US Department of Health and Human Services, Rockville, MD
73. Jadad AR, Booker L, Gauld M, Kakuma R, Boyle M, Cunningham CE, Kim M, Schachar R (1999) The treatment of attention-deficit hyperactivity disorder: an annotated bibliography and critical appraisal of published systematic reviews and meta-analysis. Can J Psychiatry 44:1025–1035
74. James A, Taylor EA (1990) Sex differences in the hyperkinetic syndrome of childhood. J Child Psychol Psychiatry 31:437–446
75. Johnston C, Fine S (1993) Methods of evaluating methylphenidate in children with attention deficit hyperactivity disorder: acceptability, satisfaction, and compliance. J Pediatr Psychol 18: 717–730
76. Kadesjö B, Gillberg C (2001) The comorbidity of ADHD in the general population of Swedish school-age children. J Child Psychol Psychiatry 42:487–492
77. Kahn RS, Khoury J, Nichols WC, Lanphear BP (2003) Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. J Pediatr 143:104–110
78. Kaplan BJ, McNicol J, Conte RA, Moghadam HK (1989) Dietary replacement in preschool-aged hyperactive boys. Pediatrics 83:7–17
79. Kent L, Craddock N (2003) Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? J Affective Disord 73:211–221
80. Klein RG, Wender P (1995) The role of methylphenidate in psychiatry. Arch Gen Psychiatry 52:429–433
81. Köster I, Schubert I, Doepfner M, Adam C, Ihle P, Lehmkuhl G (2004) Hyperkinetische Störungen bei Kindern und Jugendlichen: Zur Häufigkeit des Behandlungsanlasses in der ambulanten Versorgung nach den Daten der Versichertenstichprobe AOK Hessen/KV Hessen (1998–2001). Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie (in press)
82. Krause KH, Krause J (2000) Ist Methylphenidat bei Komorbidität von Epilepsie und Aufmerksamkeitsdefizit, – hyperaktivitätsstörungen kontraindiziert oder nicht? Aktuelle Neurologie 27:72–76
83. Kuntsi J, Oosterlaan J, Stevenson J (2001) Psychological mechanisms in hyperactivity: I Response inhibition deficit, working memory impairment, delay aversion, or something else? J Child Psychol Psychiatry 42:199–210
84. Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K (2000) Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neuroscience Letters 285:107–110
85. Lahey BB, Applegate B, McBurnett K, Biederman J, Greenhill L, Hynd GW, Barkley RA, Newcorn J, Jensen P, Richters J et al. (1994) DSM-IV field trials for attention deficit hyperactivity disorder in children and adolescents. Am J Psychiatry 151:1673–1685
86. LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, Kennedy JL (1996) Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Molecular Psychiatry 1:121–124
87. Levin FR, Evans SM, McDowell DM, Brooks DJ, Nunes E (2002) Bupropion treatment for cocaine abuse and adult attention-deficit/hyperactivity disorder. J Addictive Dis 21:1–16
88. Leung PWL, Luk SL, Ho TP, Taylor E, Mak FL, Bacon-Shone J (1996) The diagnosis and prevalence of hyperactivity in Chinese schoolboys. Br J Psychiatry 168:486–496
89. Lord J, Paisley S (2000) The Clinical Effectiveness and Cost-Effectiveness of Methylphenidate for Hyperactivity in Childhood. Version 2. London: National Institute for Clinical Excellence
90. Lynskey MT, Hall W (2001) Attention deficit hyperactivity disorder and substance use disorders: Is there a causal link? Addiction 96:815–822
91. McGee R, Share DL (1988) Attention deficit disorder-hyperactivity and academic failure: which comes first and what should be treated? J Am Acad Child Adolesc Psychiatry 27:318–325
92. McGee R, Williams S, Silva PA (1987) A comparison of girls and boys with teacher-identified problems of attention. J Am Acad Child Adolesc Psychiatry 26:711–717
93. Mariani MA, Barkley RA (1997) Neuropsychological and academic functioning in preschool boys with attention deficit/hyperactivity disorder. Devel Neuropsychol 13:111–129
94. Maher BS, Marazita ML, Ferrell RE, Vanyukov MM (2002) Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. Psychiatr Gen 12:207–215
95. Mattes JA, Gittelman R (1981) Effects of artificial food colorings in children with hyperactive symptoms. Arch Gen Psychiatry 38:714–718
96. Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, Spencer (2001) Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Pediatrics 108:E83
97. Mick E, Biederman J, Faraone SV (1996) Is season of birth a risk factor for attention-deficit hyperactivity disorder? J Am Acad Child Adolesc Psychiatry 35:1470–1476
98. Milberger S, Biederman J, Faraone SV, Guite J, Tsuang MT (1997) Pregnancy, delivery and infancy complications and attention deficit hyperactivity disorder: issues of gene-environment interaction. Biol Psychiatry 41:65–75
99. Mill J, Asherson P, Browes C, D'Souza U, Craig I (2002a) Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. Am J Med Gen 114:975–979
100. Mill J, Curran S, Kent L, Gould A, Huckett L, Richards S, Taylor E, Asherson P (2002b) Association study of a SNAP-25 microsatellite and attention deficit hyperactivity disorder. Am J Med Gen 114:269–271
101. Misener VL, Luca P, Azeke O, Crosbie J, Waldman I, Tannock R, Roberts W, Malone M, Schachar R, Ickowicz A, Kennedy JL, Barr CL (2004) Linkage of the dopamine receptor D1 gene to attention-deficit/hyperactivity disorder. Molecular Psychiatry 9:500–509
102. Moll GH, Heinrich H, Trott G, Wirth S, Rothenberger A (2000) Deficient intracortical inhibition in drug-naive children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. Neuroscience Letters 284:121–125
103. Moll GH, Rothenberger A, Ruether E, Huether G (2002) Developmental psychopharmacology in child and adolescent psychiatry: results of experimental animal studies with fluoextine and methylphenidate in rats. Psychopharmakotherapy 9:19–24
104. Monteiro-Musten L, Firestone P, Pisterman S, Bennett S, Mercer J (1997) Effects of methylphenidate on preschool children with ADHD: Cognitive and behavioral functions. J Am Acad Child Adolesc Psychiatry 36: 1407–1415
105. MTA Cooperative Group (1999a) A 14-month randomised clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 56:1073–1086

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106. MTA Cooperative Group (1999b) Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 56:1088–1096
107. Nadder TS, Rutter M, Silberg JL, Maes HH, Eaves LJ (2002) Genetic effects on the variation and covariation of attention deficit-hyperactivity disorder (ADHD) and oppositional-defiant disorder/conduct disorder (Odd/CD) symptomatologies across informant and occasion of measurement. Psychol Med 32:39–53
108. Nehra A, Mullick F, Ishak KG, Zimmerman HJ (1990) Pemoline-associated hepatic injury. Gastroenterology 99: 1517–1519
109. Neligan GA, Kolvin I, Scott DMcL, Garside RF (1976) Born Too Soon or Born Too Small. Clinics in Developmental Medicine No. 61. London, S. I. M. P./Heinemann
110. Nichols P, Chen T-C (1981) Minimal Brain Dysfunction: A Prospective Study. Hillsdale, NJ, Erlbaum
111. Oades RD (1998) Frontal, temporal and lateralized brain function in children with attention-deficit hyperactivity disorder: a psychophysiological and neuropsychological viewpoint on development. Behav Brain Res 94: 83–95
112. Pelham WE, Wheeler T, Chronis A (1998) Empirically supported psychosocial treatments for attention deficit hyperactivity disorder. J Clin Child Psychol 27:190–205
113. Pelham W, Waschbusch DA (1999) Behavioral intervention in attention-deficit/hyperactivity disorder. In: Quay H, Hogan AE (eds) Handbook of disruptive disorders. New York, Kluwer Academic/Plenum, pp 255–278
114. Pennington BF, Ozonoff S (1996) Executive functions and developmental psychopathology. J Child Psychol Psychiatry 37:51–87
115. Pennington BF, Groisser D, Welsh MC (1993) Contrasting cognitive deficits in attention deficit hyperactivity disorder versus reading disability. Devel Psychol 29:511–523
116. Pliszka SR (1989) Effect of anxiety on cognition, behavior, and stimulant response in ADHD. J Acad Child Adolesc Psychiatry 28:882–887
117. Prendergast M, Taylor E, Rapoport JL, Bartko J, Donnelly M, Zametkin A, Ahearn MB, Dunn G, Wieselberg HM (1988) The diagnosis of childhood hyperactivity: A U. S.-UK cross-national study of DSM-III and ICD-9. J Child Psychol Psychiatry 29:289–300
118. Quist JF, Barr CL, Schachar R, Roberts W, Malone M, Tannock R, Basile VS, Beitchman J, Kennedy JL (2003) The serotonin 5-HT1B receptor gene and attention deficit hyperactivity disorder. Molecular Psychiatry 8:98–102
119. Reeve E, Garfinkel B (1991) Neuroendocrine and growth regulation: the role of sympathicomimetic medication. In: Greenhill L, Osman BB (eds) Ritalin: Theory and Management. New York, Liebert, pp 289–300
120. Riggs PD, Leon SL, Mikulich SK, Pottle LC (1998) An open trial of bupropion for AD/HD in adolescents with substance use disorders and conduct disorder. J Am Acad Child Adolesc Psychiatry 37:1271–1278
121. Robbins TW (2002) AD/HD and addiction. Nature Medicine 8:24–25
122. Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 18:247–291
123. Ross DM, Ross SA (1982) Hyperactivity: Current Issues. Research and Theory. New York, Wiley
124. Rothenberger A, Banaschewski T (2004) Tic-Disorders. In: Gillberg C, Harrington R, Steinhausen HC (eds) A Clinician's Handbook of Child and Adolescent Psychiatry. Cambridge, Cambridge University Press (in press)
125. Rothenberger A, Banaschewski T, Heinrich H, Moll GH, Schmidt MH, van't Klooster B (2000) Comorbidity in ADHD-children: effects of coexisting conduct disorder or tic disorder on event-related brain potentials in an auditory selective-attention task. Eur Arch Psychiatry Clin Neurosci 250: 101–110
126. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Bullmore ET (1999) Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry 156:891–896
127. Rutter M, Roy P, Kreppner J (2002) Institutional care as a risk factor for inattention/overactivity. In: Sandberg S (ed) Hyperactivity and Attention Disorders of Childhood 2nd edn. Cambridge, Cambridge University Press, pp 417–434
128. Sagvolden T (2000) Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). Neurosci Biobehav Rev 24:31–39
129. Sagvolden T, Sergeant JA (1998) Attention deficit/hyperactivity disorder – from brain dysfunctions to behaviour. Behav Brain Res 94:1–10
130. Sandberg S (2002) Psychosocial contributions. In: Sandberg S (ed) Hyperactivity and Attention Disorder of Childhood, 2nd edn. Cambridge, Cambridge University Press, pp 367–416
131. Santosh PJ, Taylor E (2000) Stimulant drugs. Eur Child Adolesc Psychiatry 9 (Suppl 1):I27–I43
132. Schachar RJ, Rutter M, Smith A (1981) The characteristics of situationally and pervasively hyperactive children: implications for syndrome definition. J Child Psychol Psychiatry 22:375–392
133. Schachar R, Tannock R, Cunningham C (1996) Treatment. In: Sandberg S (ed) Hyperactivity Disorders of Childhood. Cambridge, Cambridge University Press, pp 433–476
134. Schachar R, Tannock R (2002) Syndromes of Hyperactivity and Attention Deficit. Child and Adolescent Psychiatry: Modern Approaches 4th edn. Blackwell Publishing, pp 399–418
135. Scheres A, Oosterlaan J, Sergeant JA (2001) Response execution and inhibition in children with AD/HD and other disruptive disorders: the role of behavioural activation. J Child Psychol Psychiatry 42:347–357
136. Schleifer M, Weiss G, Cohen N, Elman M, Cvejic H, Kruger E (1975). Hyperactivity in pre-schoolers and the effect of methylphenidate. Am J Orthopsychiatry 45:38–50
137. Schmidt JK, Plück J, v. Gontard A (2002) Verzicht auf eine EEG-Diagnostik vor Beginn und unter einer Therapie mit Methylpenidat: gefährlich oder gerechtfertigt? Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie 30:295–302
138. Schneider JS, Roeltgen DP (1993) Delayed matching-to-sample, object retrieval, and discrimination reversal deficits in chronic low dose MPTP-treated monkeys. Brain Research 615: 351–354
139. Schubert I, Lehmkuhl G, Spengler A, Doepfner M, von Ferber L (2001) Methylphenidat bei hyperkinetischen Störungen. Deutsches Ärzteblatt 98: A541–A544
140. Schulte-Koerne G, Deimel W, Gutenbrunner C, Hennighausen K, Blank R, Rieger C, Remschmidt H (1996) Effect of an oligo-antigen diet on the behaviour of hyperkinetic children. Zeitschrift fuer Kinder- und Jugendpsychiatrie 24:176–183
141. Scottish Intercollegiate Guidelines Network (2001) Attention Deficit and Hyperactivity Disorders in Children and Young People. A National Clinical Guideline. Edinburgh, SIGN

142. Sergeant JA, Geurts H, Oosterlaan J (2002) How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? Behav Brain Res 130:3–28
143. Sergeant J, Steinhausen H-C (1992) European perspectives on hyperkinetic disorder. Eur J Child Psychiatry 1:34–41
144. Shaffer D, Gould M S, Brasic J et al. (1983). A children's global assessment scale (CGAS). Arch Gen Psychiatry 40: 1228–1231
145. Silberg J, Rutter M, Meyer J, Maes H, Hewitt J, Simonoff E, Pickles A, Loeber R, Eaves L (1996) Genetic and environmental influences of the covariation between hyperactivity and conduct disturbance in juvenile twins. J Child Psychol Psychiatry 37:803–816
146. Singer HS, Brown J, Quaskey S, Rosenberg LA, Mellits ED, Denckla MB (1995) The treatment of Attention Deficit-Hyperactivity Disorder in Tourette's syndrome: A double-blind placebo-controlled study with clonidine and desipramine. Pediatrics 95: 74–81
147. Smalley SL, Kustanovich V, Minassian SL, Stone JL, Ogdie MN, McGough JJ, McCracken JT, MacPhie IL, Francks C, Fisher SE, Cantor RM, Monaco AP, Nelson SF (2002) Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. Am J Human Gen 71:959–963
148. Smith KM, Daly M, Fischer M, Yiannoutsos CT, Bauer L, Barkley R, Navia BA (2003) Association of the dopamine beta hydroxylase gene with attention deficit hyperactivity disorder: genetic analysis of the Milwaukee longitudinal study. Am J Med Gen 15; 119B(1):77–85
149. Smith A, Taylor E, Rogers JW, Newman S, Rubia K (2002) Evidence for a pure time perception deficit in children with ADHD. J Child Psychol Psychiatry 43:529–542
150. Solanto MV, Abikoff H, Sonuga-Barke E, Schachar R, Logan GD, Wigal T, Hechtman L, Hinshaw S, Turkel E (2001) The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. J Abnorm Child Psychol 29:215–228
151. Sonuga-Barke E (2003) The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. Neurosci & Biobehav Rev 27: 593–604
152. Sonuga-Barke EJ (2002) Psychological heterogeneity in AD/HD – a dual pathway model of behaviour and cognition. Behav Brain Res 130:29–36
153. Sonuga-Barke EJS, Daley D, Thompson M, Swanson J (2003) The management of preschool AD/HD; Addressing uncertainties about syndrome validity, diagnostic utility and treatment safety. Expert Reviews in Neurotherapeutics 3:89–100
154. Sonuga-Barke EJS, Dalen L, Remington RE (2003) Do delay aversion and inhibitory deficits make distinct contributions to pre-school AD/HD. J Am Acad Child Adolesc Psychiatry 42: 1335–1342
155. Sonuga-Barke EJS, Daley D, Thompson M, Laver-Bradbury C, Weekes A (2001) Parent-based therapies for preschool attention-deficit/hyperactivity disorder: A randomized, controlled trial with a community sample. J Am Acad Child Adolesc Psychiatry 40:402–408
156. Sonuga-Barke EJS, Thompson M, Stevenson J, Viney D (1997) Patterns of behaviour problems among preschool children. Psychol Med 27: 909–918
157. Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS (2003) Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. Lancet 362(9397):1699–1707
158. Spencer T, Biederman J, Harding M, O'Donnell D, Faraone SV, Wilens TE (1996) Growth deficits in ADHD children revisited: Evidence for disorder-associated growth delays? J Am Acad Child Adolesc Psychiatry 35: 1460–1469
159. Spencer T, Wilens T, Biederman J, Faraone SV, Ablon JS, Lapey K (1995) A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood onset attention deficit hyperactivity disorder. Arch Gen Psychiatry 52:434–443
160. Sprafkin J, Gadow KD, Nolan EE (2001) The utility of a DSM-IV-referenced screening instrument for attention deficit/hyperactivity disorder. J Emotion Behav Disord 9:182–191
161. Steinhausen H-C (1987) Global Assessment of Child Psychopathology. J Am Acad Child Adolesc Psychiatry 26:203–206
162. Swanson JM, Kraemer HC, Hinshaw S P, Arnold LE, Conners CK, Abikoff H B, Clevenger W, Davies M, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Jensen PS, March JS, Newcorn JH, Owens EB, Pelham WE, Schiller E, Severe JB, Simpson S, Vitiello B, Wells K, Wigal T, Wu M (2001) Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 40:168–179
163. Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke EJS, Jensen PJ, Cantwell DP (1998) Attention-deficit hyperactivity disorder and hyperkinetic disorder. The Lancet 351:9100:429–433
164. Taylor E, Chadwick O, Heptinstall E, Danckaerts M (1996) Hyperactivity and conduct problems as risk factors for adolescent development. J Am Acad Child Adolesc Psychiatry 35: 1213–1226
165. Taylor E, Sandberg ST (1984) Hyperactive behavior in English schoolchildren: A questionnaire survey. J Abnorm Child Psychol 12:143–156
166. Taylor E, Sandberg S, Thorley G, Giles S (1991) The Epidemiology of Childhood Hyperactivity. Maudsley Monographs 33. Oxford, Oxford University Press
167. Taylor E, Schachar R, Thorle, G, Wieselberg M (1986) Conduct disorder and hyperactivity. Br J Psychiatry 149:760–767
168. Taylor E, Schachar R, Thorley G, Wieselberg HM, Everit B, Rutter M (1987) Which boys respond to stimulant medication? A controlled trial of methylphenidate in boys with disruptive behaviour. Psychol Med 17: 121–143
169. Taylor E, Sergeant J, Döpfner M, Gunning B, Overmeyer S, Mobius HJ, Eisert H-G (1998) Clinical guidelines for hyperkinetic disorder. Eur Child Adolesc Psychiatry 7:184–200
170. Taylor E (1994) Syndromes of attention deficit and overactivity. In: Rutter M, Taylor E, Hersov L (eds) Child and Adolescent Psychiatry: Modern Approaches. Oxford, Blackwell Scientific Publications, pp 285–307
171. Thapar A, Fowler T, Rice F, Scourfield J, van den Bree M, Thomas H, Harold G, Hay D (2003) Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. Am J Psychiatry 160: 1985–1989
172. Thapar A, Hervas A, McGuffin P (1995) Childhood hyperactivity scores are highly heritable and show sibling competition effects: twin study evidence. Behavior Gen 25:537–544
173. Thapar A, Holmes J, Poulton K, Harrington R (1999) Genetic basis of attention deficit and hyperactivity. Br J Psychiatry 174:105–111
174. Toplak ME, Rucklidge JJ, Hetherington R, John SC, Tannock R (2003) Time perception deficits in attention-deficit/hyperactivity disorder and comorbid reading difficulties in child and adolescent samples. J Child Psychol Psychiatry 44:888–903

European Child & Adolescent Psychiatry, Vol. 13, Supplement 1 (2004)

175. Todd RD, Rasmussen ER, Neuman RJ, Reich W, Hudziak JJ, Bucholz KK, Madden PA, Heath A (2001) Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. Am J Psychiatry 158: 1891–1898
176. van Leeuwen TH, Steinhausen HC, Overtoom CC, Pascual-Marqui RD, van't Klooster B, Rothenberger A, Sergeant JA, Brandeis D (1998) The continuous performance test revisited with neuroelectric mapping: impaired orienting in children with attention deficits. Behav Brain Res 94:97–110
177. Volkow ND, Swanson JM (2003) Variables that affect the clinical use and abuse of methylphenidate in the treatment of AD/HD. Am J Psychiatry 160: 1909–1918
178. Volkow ND, Wang GJ, Fowler JS, Fischman M, Foltin R, Abumrad NN, Gatley SJ, Logan J, Wong C, Gifford A, Ding YS, Hitzemann R, Pappas N (1999) Methylphenidate and cocaine have a similar in vivo potency to block dopamine transporters in the human brain. Life Sciences 65:L7–L12
179. Wender PH, Wood DR, Reimherr FW (1985) Pharmacological treatment of attention deficit disorder, residual type. Psychopharmacol Bull 21: 222–231
180. Wilens TE, Biederman J, Baldessarini RJ, Geller B, Schleifer D, Spencer TJ, Birmaher B, Goldblatt A (1996) Cardiovascular effets of therapeutic doses of tricyclic antidepressants in children and adolescents. J Am Acad Child Adolesc Psychiatry 35:1491–1501
181. Wilens TE, Biederman J, Brown S, Tanguay S, Monuteaux MC, Blake C, Spencer TJ (2002) Psychiatric comorbidity and functioning in clinically referred preschool children and school-age youths with ADHD. J Am Acad Child Adolesc Psychiatry 41:262–268
182. Wilens TE, Biederman J (1992) The stimulants. In: Shafer D (ed) Psychiatric Clinics of North America. Philadelphia, Pa., WB, Saunders, pp 191–222
183. Wilens TE, Biederman J, Mick E, Faraone SV, SpencerT (1997) Attention deficit hyperactivity disorder (AD/HD) is associated with early onset substance use disorders. J Nerv Mental Dis 185:475–482
184. Wilens TE, Faraone SV, Biederman J, Gunawardene S (2003) Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 111:179–185
185. Willcutt EG, Pennington BF, Smith SD, Cardon LR, Gayan J, Knopik VS, Olson RK, DeFries JC (2002) Quantitative trait locus for reading disability on chromosome 6p is pleiotropic for attention-deficit/hyperactivity disorder. Am J Med Gen 114:260–268
186. Willcutt EG, Pennington BF, DeFries JC (2000) Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. Am J Med Gen 96:293–301
187. World Health Organization (1996) Multiaxial classification of child and adolescent psychiatric disorders. The ICD-10 classification of mental and behavioral disorders in children and adolescents. Cambridge, Cambridge University Press
188. Yordanova J, Banaschewski T, Kolev V, Woerner W, Rothenberger A (2001) Abnormal early stages of task stimulus processing in children with attention-deficit hyperactivity disorder – evidence from event-related gamma oscillations. Clin Neurophysiol 112: 1096–1108
189. Young E, Patel S, Stoneham M, Rona R, Wilkinson JD (1987) The prevalence of reaction to food additives in a survey population. Journal of the Royal College of Physicians of London 21: 241–247
190. Zametkin AJ, Liebenauer LL, Fitzgerald GA, King AC, Minkunas DV, Herscovitch P, Yamada EM, Cohen RM (1993) Brain metabolism in teenagers with attention-deficit hyperactivity disorder. Arch Gen Psychiatry 50: 333–340