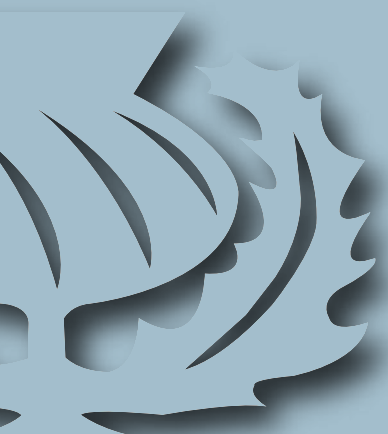




**Management of attention deficit
and hyperkinetic disorders
in children and young people**

A national clinical guideline



October 2009

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review, or RCT rated as 1⁺⁺, and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

- Recommended best practice based on the clinical experience of the guideline development group.

NHS Quality Improvement Scotland (NHS QIS) is committed to equality and diversity and assesses all its publications for likely impact on the six equality groups defined by age, disability, gender, race, religion/belief and sexual orientation.

SIGN guidelines are produced using a standard methodology that has been **equality impact assessed** to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk/guidelines/fulltext/50/index.html The EQIA assessment of the manual can be seen at www.sign.ac.uk/pdf/sign50eqia.pdf The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our web site www.sign.ac.uk

Scottish Intercollegiate Guidelines Network

**Management of attention deficit
and hyperkinetic disorders
in children and young people**

A national clinical guideline



October 2009

ISBN 978 1 905813 53 7

Published October 2009

SIGN consents to the photocopying of this guideline for the
purpose of implementation in NHSScotland

**Scottish Intercollegiate Guidelines Network
Elliott House, 8 -10 Hillside Crescent
Edinburgh EH7 5EA**

www.sign.ac.uk

Contents

1	Introduction	1
1.1	Background.....	1
1.2	The need for a guideline	1
1.3	Aim of the guideline.....	1
1.4	Statement of intent	2
2	Key recommendations	4
2.1	Principles of intervention	4
2.2	Psychological interventions.....	4
2.3	Treatment selection.....	4
3	Definitions and concepts.....	5
3.1	Definition.....	5
3.2	Diagnostic criteria.....	5
3.3	Prevalence	6
3.4	Comorbidity.....	6
3.5	Outcome.....	6
4	Assessment	7
4.1	Initial assessment	7
4.2	Specialist assessment.....	7
4.3	Parent/carer interview	7
4.4	Child/young person interview	8
4.5	Laboratory measures and questionnaires	9
4.6	Psychoeducational assessment	9
4.7	Clinical examination	9
4.8	Ancillary assessments.....	10
5	Principles of intervention	11
6	Psychological interventions.....	12
6.1	Introduction	12
6.2	Pre-school children	12
6.3	Pre-adolescents	13
6.4	Adolescents.....	13
6.5	School-based interventions.....	13
7	Pharmacological therapy.....	14
7.1	Introduction	14
7.2	Psychostimulants.....	14
7.3	Atomoxetine	18
7.4	Unlicensed medications.....	20

8	Nutrition and complementary and alternative therapies	23
8.1	Nutrition	23
8.2	Complementary and alternative therapies.....	24
9	Treatment selection.....	25
9.1	Pre-school children	25
9.2	School-aged children and young people.....	25
10	Provision of information.....	28
11	Implementing the guideline.....	31
11.1	Potential resource implications.....	31
11.2	Auditing current practice	32
11.3	Additional advice to NHSScotland from NHS Quality Improvement Scotland and the Scottish Medicines Consortium.....	32
12	The evidence base	33
12.1	Systematic literature review.....	33
12.2	Recommendations for research	33
12.3	Review and updating	33
13	Development of the guideline	34
13.1	Introduction	34
13.2	The guideline development group.....	34
13.3	Acknowledgements.....	34
13.4	Consultation and peer review.....	35
	Abbreviations.....	37
	Annexes	38
	References	41

1 Introduction

1.1 BACKGROUND

The constellation of symptoms which make up Attention Deficit Hyperactivity Disorder¹ (ADHD) and Hyperkinetic Disorder² (HKD) are the most widely researched in child and adolescent mental health, but there is continuing development of the definition of these disorders and their management.

The core symptoms of ADHD and HKD have a significant impact on a child's development, including social, emotional and cognitive functioning and they are responsible for considerable morbidity and dysfunction for the child or young person, their peer group and their family. The secondary effects of ADHD and HKD can be extremely damaging. Affected children are often exposed to years of negative feedback about their behaviour and suffer educational and social disadvantage. These disorders are, in many cases, persistent. It is estimated that up to two thirds of children affected by hyperactivity disorders continue to have problems into adulthood.³ Professionals must therefore be concerned with the identification and treatment of ADHD and HKD and their secondary effects.

ADHD and HKD present a challenge to professionals from a variety of backgrounds, including general practitioners, health visitors, teachers, psychologists, psychiatrists, paediatricians and social workers. To date, management has been made more difficult by the various professionals involved working in isolation. Similarly, research into this complex constellation of symptoms has tended to follow single cause models with a resulting lack of integration of themes.

1.2 THE NEED FOR A GUIDELINE

Hyperactivity is represented in the general population as a continuum. The core symptoms of ADHD and HKD can be considered to be an extreme of normal behaviour. In addition, children and young people suffering from several other emotional and behavioural disorders may show symptoms of ADHD and HKD.

Some controversy therefore surrounds the extent of these disorders, for which there are, as yet, no robust diagnostic tests; thus their definition continues to be debated. This in turn has led to wide variation in practice, with some affected children going undiagnosed and untreated and, in other cases, unaffected children being treated needlessly. Issues of comorbidity and potential subtypes further cloud the picture. The available evidence suggests that the constellation of symptoms recognised as ADHD and HKD is valid. Causation remains unclear but the evidence for a biological basis appears to be converging. The evidence for a genetic contribution is strong but other factors are also likely to be important.

There is a lack of consensus about the use of psychostimulants, psychosocial, educational and other interventions or combinations of interventions. However, it is generally recognised that ADHD and HKD have the potential to cause considerable morbidity and should be treated.

1.3 AIM OF THE GUIDELINE

The overall aim of this national guideline update is to provide a framework for evidence based assessment and management of ADHD/HKD, from which multidisciplinary and multiagency approaches can be developed locally.

This guideline updates SIGN 52, first published in June 2001, and reflects the most recent evidence on psychological and pharmacological interventions, as well as introducing sections on nutrition and complementary and alternative therapies. Studies were included when improvement in core ADHD/HKD symptoms was the primary outcome.

The National Institute for Health and Clinical Excellence (NICE) published a comprehensive guideline on ADHD/HKD in 2008 covering all age groups.⁴ NICE evidence tables were examined and updated for this guideline as appropriate.

1.3.1 SUMMARY OF UPDATES TO THE GUIDELINE

Page edge highlights indicate new, updated or revised material. Annex 1 outlines the key questions which were addressed.

1	Introduction	Minor updates
2	Key Recommendations	New
5	Principles of intervention	New
6	Psychological interventions	New (with exception of 6.5)
7	Pharmacological therapy	Completely revised
8	Nutrition and complementary and alternative therapies	New
9	Treatment selection	New
10	Provision of information	New

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.

1.4.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (product licence). This is known as “off label” use. It is not unusual for medicines to be prescribed outwith their product licence and this can be necessary for a variety of reasons.

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.⁵

Medicines may be prescribed outwith their product licence in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose.

‘Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers’ professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.’⁵

Any practitioner following a SIGN recommendation and prescribing a licensed medicine outwith the product licence needs to be aware that they are responsible for this decision, and in the event of adverse outcomes, may be required to justify the actions that they have taken.

Prior to prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).

1.4.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE multiple technology appraisals relevant to this guideline are summarised in the section on implementation.

2 Key recommendations

The following recommendations and good practice points were highlighted by the guideline development group as being clinically very important. They are the key clinical recommendations that should be prioritised for implementation. The clinical importance of these recommendations is not dependent on the strength of the supporting evidence.

2.1 PRINCIPLES OF INTERVENTION

- Parents/carers of children with ADHD/HKD (*and older children with ADHD/HKD*) should be given information about ADHD/HKD and about possible interventions, including their potential risks and benefits.
- There should be regular communication between health and education services to promote understanding of the difficulties of ADHD/HKD, to ensure a consistent approach to the individual across settings and to monitor effectiveness of intervention(s).

2.2 PSYCHOLOGICAL INTERVENTIONS

- B** Behavioural parent training is recommended for parents of pre-school children with symptoms of ADHD/HKD. This should be delivered by trained facilitators.

2.3 TREATMENT SELECTION

- A** For school aged children and young people with hyperkinetic disorder (*severe ADHD*) medication is recommended.
- A** For school aged children and young people with ADHD/HKD and comorbid symptoms of oppositional defiant disorder and/or aggressive behaviour a combination of medication and behavioural treatments is recommended.
- B** For school aged children and young people with ADHD/HKD and comorbid generalised anxiety disorders a combination of medication and behavioural treatments is recommended.
- Where symptoms of ADHD are mild, clinicians should consider behavioural approaches in the first instance.

3 Definitions and concepts

3.1 DEFINITION

ADHD and HKD are amongst the most commonly diagnosed behavioural disorders in children and young people. Core symptoms include developmentally inappropriate levels of activity and impulsivity and an impaired ability to sustain attention. Affected children and young people have difficulty regulating their activities to conform to expected norms and as a result are frequently unpopular with adults and peers. They often fail to achieve their potential and many have comorbid difficulties such as developmental delays, specific learning problems and other emotional and behavioural disorders.⁶ The constellation of symptoms which constitutes ADHD/HKD has been recognised for many years and has been given a variety of labels.

3.2 DIAGNOSTIC CRITERIA

The core symptoms of ADHD and HKD comprise developmentally inappropriate levels of:

- inattention (difficulty in concentrating)
- hyperactivity (disorganised, excessive levels of activity)
- impulsive behaviour.

In order to meet diagnostic criteria it is essential that symptoms:

- have their onset before the age of seven years (ADHD) or six years (HKD)
- have persisted for at least six months
- must be pervasive (present in more than one setting, eg at home, at school, socially)
- have caused significant functional impairment
- are not better accounted for by other mental disorders (eg pervasive developmental disorder, schizophrenia, other psychotic disorders, depression or anxiety).

Associated morbidity includes educational underachievement, antisocial behaviour, delinquency and an increased risk of road traffic accidents in adolescence. In addition, there can be a dramatic effect on family life.

The diagnostic criteria for ADHD and HKD have changed with each revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM)¹ and International Classification of Diseases (ICD) respectively.² It is likely that there will be further revision of the criteria to address outstanding issues such as subtypes of disorder, age of onset and the applicability of the criteria across the life span. Current DSM-IV and ICD-10 diagnostic criteria are similar, with differences relating primarily to symptom severity and pervasiveness.

DSM identifies three subtypes of ADHD: predominantly inattentive type (which features inattention but not hyperactivity/impulsivity); predominantly hyperactive-impulsive type (which features hyperactivity/impulsivity but not inattention) and combined type (which features signs of inattention and hyperactivity/impulsivity).¹

HKD characterises more severe disturbance with significant hyperactivity included as a criterion for diagnosis. DSM and ICD are categorical models and minimum thresholds of presenting symptoms must be present to achieve diagnosis. Children and young people failing to meet the defined criteria of ADHD/HKD may nevertheless be experiencing significant difficulties in day to day life.

Despite the immense literature describing the investigation of ADHD and HKD, their precise definitions continue to be debated and their validity as disorders questioned. This has been addressed in a number of ways and there is substantial evidence in support of the above definitions of ADHD, its subtypes and HKD.⁷⁻⁹ Evidence for the validity of diagnostic criteria for younger children is beginning to emerge, although the applicability of diagnostic criteria across the age range requires further investigation.¹⁰

3.3 PREVALENCE

Prevalence estimates are highly dependent on three main factors: the population sampled, the method of ascertainment and the diagnostic criteria applied. Prevalence estimates are rare in the published literature, especially in relation to DSM-IV and ICD-10 criteria. The reported prevalence of ADHD in school-age children varies from 1.7% to 17.8% depending on the criteria used.¹¹ Most estimates lie between 5% and 10%.¹² US estimates have historically been higher than UK estimates, owing presumably to the application of narrower diagnostic criteria by UK authors.¹³ Three studies of English populations have shown a prevalence rate of between 2% and 5%, depending on whether DSM-IV or ICD-10 criteria were applied.^{12,14} A large sample of school children (n = 22,044) screened using DSM-IV teacher rating scales showed a similar prevalence at school entry.¹⁵ The male to female ratio in ADHD prevalence (but not necessarily within all dimensions of the disorder) is at least 4 to 1.¹⁶

In a survey of health service providers across Scotland in 2007, approximately 0.6% of children in the population had a diagnosis of ADHD/HKD and were known to services. This was far below the expected prevalence.¹⁷

3.4 COMORBIDITY

Comorbidity is common and variable. Academic and school failure has also been shown consistently in ADHD children.^{15,18,19} In children diagnosed with ADHD, oppositional defiant disorder (ODD) or conduct disorder (CD) is present in 25-50% of cases; 25% have coexistent anxiety disorder; 20% have mood disorder; and 20% have specific developmental disorders, including specific learning difficulties, language based difficulties and motor coordination difficulties.^{20,21} Many children with Tourette's syndrome fulfil ADHD criteria.^{6,22}

3.5 OUTCOME

There are no good quality prevalence or outcome data for ADHD/HKD in Scotland. However, the observed rate of ADHD diminishes in adolescence^{9,23} and further reductions have been seen in studies which have followed children into adulthood.²⁴⁻²⁶ Rates of persistence of ADHD vary between 11%¹⁹ and 68%.²⁷ Predictors of persistence of ADHD and comorbid ODD or CD include maternal depression, marital discord, negative parent-child interaction,^{12,28} family disadvantage and family history of disorder.^{18,29} The NICE guideline includes evidence on the management of ADHD in adults.⁴ Current service provision for adults is limited.

Many follow-up studies have shown considerable excess of conduct disorder, antisocial personality disorder, substance abuse, and criminality (often clustered in the same individuals) in adults with ADHD/HKD compared with controls.^{3,19,24,26} Early comorbidity with CD and ODD has the most adverse outcome.^{18,28-30}

4 Assessment

4.1 INITIAL ASSESSMENT

The initial presentation will usually be to general practitioners, or to other primary care, education and social work professionals. Important information can be obtained at this stage which will suggest the need for specialist investigation. Those involved in carrying out the initial assessment must be aware of the prevalence and core features of ADHD/HKD as well as some of the difficulties encountered in making the diagnosis, including issues of comorbidity and the impact of situation/environment on presentation.

Key areas to explore at this stage include:

- The nature of the problem: are the presenting problems of the type represented by the diagnostic criteria for ADHD/HKD? (see section 3.2)
- The severity of the problem (dysfunction in a number of domains, including family, education and social).

- If, on the basis of preliminary assessment, it is suspected that a child or young person has ADHD/HKD associated with significant impairment, referral for specialist assessment by a child and adolescent mental health clinician or paediatrician with a specialist interest in this field is recommended.

4.2 SPECIALIST ASSESSMENT

The overall aim of assessment is to obtain information to allow diagnosis and the formulation of a management plan detailing further assessments, leading to the development of an appropriate programme of intervention. Such assessment is necessarily extensive and time consuming. The diagnosis of ADHD/HKD cannot be achieved in a brief consultation.

The important components of assessment for ADHD/HKD include the parent/carer interview, the child/young person interview, questionnaires, psychoeducational assessment, clinical examination and ancillary (physical, psychiatric and psychological) assessments.

4.3 PARENT/CARER INTERVIEW

The interview with the parent(s) or carer(s) of the child or young person with ADHD/HKD is the foundation of assessment.³¹ The purpose is to obtain information relating to the child's presentation in order to inform diagnosis and the formulation of a treatment plan.

4.3.1 HISTORY OF PRESENTING COMPLAINT

Parents/carers should be asked details of the history of the child's current problems, the nature of the symptoms (frequency, duration, situational variation) and any associated behaviours. Emphasis should be on diagnostic criteria for ADHD/HKD and associated disorders.

- Information about performance in the school/nursery setting, including details of academic achievement as well as social functioning in relation to other children and staff, should be reviewed and permission sought to contact the school.
- The clinician should determine what treatment (if any) the child/young person has received in the past.
- It should be noted that although sleep disorders may be reported in up to 50% of children with ADHD their presence is not a criterion for diagnosis.³²

Parental reports of current child psychopathology have been shown to provide an accurate means of assessment.^{33,34} Most studies have examined maternal reports and, whilst there is some conflict, in general parents are accurate reporters of children's behaviour.³⁵ However, maternal psychopathology, especially maternal depression and marital dysfunction/adjustment, are known to influence parental reporting of child behaviour.³⁶⁻³⁸

3

D Parental report of their children’s symptoms is an essential component of the diagnostic assessment.

4.3.2 OBSTETRIC AND PERINATAL HISTORY

Certain complications including pre-term delivery and maternal cigarette, drug and alcohol abuse are known to be associated with ADHD/HKD.³⁹⁻⁴³ | 3

D A history should be obtained of obstetric and perinatal complications

4.3.3 DEVELOPMENTAL HISTORY

Details of the acquisition of developmental milestones and related information about ADHD/HKD and associated problems will allow the development of a chronological picture of a child or young person’s difficulties.⁴⁰ | 2+

C A developmental history should be obtained to show a chronological development of difficulties.

4.3.4 FAMILY HISTORY

Details of the child’s immediate and extended family should be obtained, including a history of ADHD/HKD and psychiatric illness of any kind. There is evidence from various lines of research, including twin and adoption studies, pedigree studies and molecular genetic studies, which clearly demonstrates the contribution of genetic factors to ADHD/HKD.^{33,44-49} | 3

In families with a history of thyroid dysfunction, generalised resistance to thyroid hormone (GRTH) may be present. GRTH is a rare cause of ADHD/HKD and screening need not be routine.⁵⁰

4.3.5 FAMILY FUNCTIONING

An assessment of family functioning including relationships within the family, communication patterns, parental management styles and the presence of marital conflict or stress should be explored.⁵¹

4.4 CHILD/YOUNG PERSON INTERVIEW

Whilst children and young people may not always be reliable in reporting externalising behaviour, they are more reliable than their parents at reporting internalising symptoms such as anxiety and depression, which are important in the diagnosis of comorbid conditions.⁵² The focus of the interview should be on the child’s own perception of the problem including attributional style and attitude to treatment. | 4

The child or young person should be engaged in the therapeutic process with an understanding of their perception of their difficulties, the possibilities of treatment and their responsibility in the management of the disorder.

4.5 LABORATORY MEASURES AND QUESTIONNAIRES

There is extensive research literature examining individual and groups of laboratory assessment measures (eg Matching Familiar Figures Test, Continuous Performance Test, Actometers). In general these measures do not distinguish children and young people with ADHD/HKD from psychiatric controls or normal peers.⁵³

2+

Observation of behaviour in the clinic, whilst important, may be deceptive and clinicians should avoid basing diagnostic conclusions on evidence of behaviour in the clinic. Standardised observational schedules for use in the home, school and laboratory setting are available; however, some practitioners find these time consuming and difficult to use. In addition, children tend to respond well in novel situations, eg a visit to the clinic or the clinician's visit to the home or school setting, and the results therefore may not provide an accurate picture of the child's behaviour.⁵⁴

2+

A detailed analysis of the various rating scales and laboratory assessment measures is beyond the remit of this guideline. Useful reviews of the various assessment instruments have been published.^{53,55}

Self report questionnaires provide a mechanism for obtaining standardised information about parents' and teachers' perceptions of a child's problems. The instruments providing the most useful information are normatively based and structured to allow analysis of independent factors. Questionnaire results should be interpreted with caution where normative data have been derived from populations other than the UK.⁵⁶

4

C Laboratory assessments should not be used routinely.

- Questionnaires are useful in assessment when used in association with information derived from other sources. They can be used as part of the initial assessment as well as for evaluating treatment response.

4.6 PSYCHOEDUCATIONAL ASSESSMENT

Children who have ADHD/HKD may experience educational difficulties. ADHD/HKD is not a learning disability per se, in that it does not impact on the brain's ability to learn, but it can interfere with the individual's availability for learning.⁵⁷ This may affect educational attainment and thereby long term prognosis. There are high levels of comorbidity and many children have learning disabilities in addition to ADHD/HKD.²⁰

4

D An assessment of the child's presentation in their educational placement is important for confirming diagnosis and identifying educational underachievement.

Psychoeducational assessment involves testing the child's level of attainment in basic skill areas such as reading, spelling and number work, and evaluating whether the child is achieving appropriately in terms of age and ability. Qualitative information about the child's learning style, attention skills, speed of working, impulsivity and self confidence can be obtained from discussions with teachers.

4.7 CLINICAL EXAMINATION

Physical evaluation serves a number of purposes, including:

- assessment of underlying medical problems contributing to presentation
- assessment for potential contraindications to pharmacological intervention.

Neurological signs and minor physical anomalies cannot independently exclude or confirm a diagnosis of ADHD/HKD. Although many studies have shown a slight increase in the number of neurological signs in hyperactive children, the usefulness of this association has yet to be demonstrated.^{58,59} Similarly, the presence or absence of minor physical anomalies cannot be used as a diagnostic predictor.⁶⁰ Screening for neurological signs and minor physical anomalies is part of an overall physical evaluation. Standardised assessment schedules are available.

- Clinical examination of children and young people presenting with ADHD/HKD should include a systems inquiry, details of previous health problems, current drug treatment, and physical examination. Vision and hearing should be assessed and formally tested if indicated.

4.8 ANCILLARY ASSESSMENTS

Other physical investigations should be carried out when they are thought to be important in the determination of an underlying medical problem. Such investigations might include:

- blood analyses (lead, chromosomes, Fragile X)
- electrophysiological studies (electroencephalography)
- computed tomography (magnetic resonance imaging (MRI) for neurological disorders/ space occupying lesions).

However, neuroradiological, neurophysiological, neurochemical and chromosomal investigations are as yet unproven in the diagnosis of ADHD/HKD.⁶¹

The history and examination, bearing in mind the prevalence of comorbid conditions, may suggest the need for further assessment in order to exclude other diagnoses or elucidate comorbid disorders. In this context, detailed psychiatric, neurological, psychological, psycho-educational, speech and language, occupational therapy and other assessments should be sought from appropriate specialists.

4.8.1 PSYCHIATRIC ASSESSMENT

- Whilst the core assessment for ADHD/HKD can be undertaken by experienced specialists from a variety of backgrounds, assessment by a child and adolescent mental health professional is essential if there is difficulty in differential diagnosis or concern about the existence of comorbid psychiatric disorders.

4.8.2 PSYCHOLOGICAL ASSESSMENT

The value of psychological tests lies less in the diagnosis of ADHD/HKD than in the exclusion of comorbid conditions and the identification of specific areas of difficulty for individual children which might impede educational and social integration. There is no psychological test which decisively characterises ADHD/HKD.

- Psychological tests should not be regarded as a routine part of the diagnostic process. Use of these tests should be on the basis of a specific hypothesis in a specific case.

Children with ADHD/HKD do not differ from the normal population on the majority of traditionally administered psychological tasks. Neuropsychological measures of attention and concentration (eg continuous performance tasks) do not reliably differentiate ADHD/HKD from other clinical conditions or controls.^{62,63}

Executive functions, that is the management and integration of complex information and behaviour, are impaired in children with ADHD/HKD.⁶⁴ However, tests of executive function have not yet been demonstrated to differentiate reliably children suffering from ADHD/HKD. There is some support for the notion that a failure in behavioural inhibition, and the resulting impulsivity, represents the underlying deficit in ADHD/HKD.⁶⁵ An alternative hypothesis, that an intolerance of delay underpins these children's difficulties, has also received some experimental support.⁶⁶

3

5 Principles of intervention

The focus of this guideline is on interventions to improve core symptoms of ADHD/HKD rather than secondary outcomes (such as low self esteem or poor peer relationships) or treatment of comorbid conditions (such as conduct or anxiety disorder). These are reported only when they have arisen as key points within major intervention studies.

ADHD/HKD can impact on many areas of a child's life. This results in the need for provision of a comprehensive package of care for children with ADHD/HKD and their families, involving education services, in particular, as well as health. The following principles of good practice with respect to intervention were identified by the guideline development group:

- Parents/carers of children with ADHD/HKD (*and older children with ADHD/HKD*) should be given information about ADHD/HKD and about possible interventions, including their potential risks and benefits.
- Consent should be obtained from parents/carers to allow information sharing between all agencies working with children and young people with ADHD/HKD.
- There should be regular communication between health and education services to promote understanding of the difficulties of ADHD/HKD, to ensure a consistent approach to the individual across settings and to monitor effectiveness of intervention(s).
- Practitioners should be aware of legislation relevant to children with ADHD/HKD including the Education (Additional Support for Learning) (Scotland) Act, 2004, and the Disability Discrimination Act, 2005.
- Parents/carers should be informed about potential sources of financial help including Disability Living Allowance.

6 Psychological interventions

6.1 INTRODUCTION

There is a relative lack of randomised trials of psychological and other non-pharmacological interventions for core ADHD symptoms. As well as the lack of funding sources, this is due in part to methodological challenges of study in this area.

The most commonly evaluated psychological intervention is behavioural parent training. This is a treatment method which teaches parents how to apply child management strategies, improve their parenting skills and help them deal with specific problem behaviours. Most programmes incorporate the following aspects:

- assisting parents to understand the way in which specific behaviours can be changed and how to monitor the changes as they take place
- teaching of strategies for the management of misbehaviour:
 - setting clear rules with consequences
 - use of boundaries, routine, countdowns, reminders and limit-setting
 - assisting parents to be firm without being coercive
 - use of quiet time, planned ignoring and timeout
 - importance of consistency and control and a calm emotional environment
- encouraging parents to praise, show physical affection, provide rewards and incentives for appropriate behaviour
- promoting positive parental experience through engagement in play and child-centred activities
- providing feedback using direct observation of interactions between child and parent(s).

6.2 PRE-SCHOOL CHILDREN

Evidence for psychological interventions for ADHD symptoms in the pre-school years is limited to behavioural parent training.

Three RCTs consistently found that behavioural parent training delivered by specialist trained facilitators produced improvement in core ADHD symptoms in children aged three to four years.⁶⁷⁻⁶⁹ A follow-up study found improvement in ADHD symptoms maintained at 12 months post-intervention.⁷⁰ Reliance on parent reports is a likely source of bias in these studies. In a single randomised controlled trial (RCT), delivery of the programme by non-specialist health visitors was not effective when compared with waiting list control.⁷¹

1+

B Behavioural parent training is recommended for parents of pre-school children with symptoms of ADHD/HKD. This should be delivered by trained facilitators.

6.3 PRE-ADOLESCENTS

Behavioural parent training, often as an adjunct to medication, is the most frequently used intervention although some programmes offer group work for children themselves. Interventions tend to be clinic based.

For children aged less than 12 years, behavioural parent training reduces comorbid conduct and internalising problems but does not confer additional benefit to medication or 'routine care' (which, in trials, usually included medication) on core ADHD symptoms.⁷²⁻⁷⁷ In general, improvements in behaviour at home did not transfer to the school context.

1+

The Multimodal Treatment Study of Children with ADHD (MTA) compared 14 month outcomes of children initially aged 7 to 9.9 years in four different treatment groups: strict protocol medical management; manualised intensive behavioural management to parents, child and within the school setting; a combination of medical and behavioural therapy and routine community care which usually included medication. There was significant improvement in core ADHD symptoms in all groups, with the greatest effect in the medical management and combination therapy groups. There were additional benefits on non-core ADHD symptoms (oppositional/aggressive symptoms, internalising symptoms, teacher-rated social skills, parent-child relations and reading achievement) in the combination therapy group.⁷⁸

1+

Details of the MTA study follow up after the 14 month randomised intervention period are outlined in section 9.2.

One RCT in primary school-aged children with predominantly inattentive subtype ADHD found that behavioural intervention for parents, children and teachers led to fewer attention problems and improvement in organisational skills compared to routine 'treatment as usual'.⁷⁹

1+

A In pre-adolescent children with ADHD/HKD and comorbid symptoms of oppositional defiant disorder and/or aggressive behaviour, behavioural programmes are recommended to treat the comorbid problems.

B In pre-adolescent children with ADHD/HKD and comorbid generalised anxiety, behavioural programmes are recommended to treat the comorbid problems.

6.4 ADOLESCENTS

No good quality studies were identified in adolescents; therefore it is not possible to make recommendations for this age group.

6.5 SCHOOL-BASED INTERVENTIONS

Meta-analysis has shown that contingency management strategies and academic interventions are more effective for behaviour change than cognitive behavioural strategies.⁸⁰

1+

A Children with ADHD/HKD require an individualised school intervention programme including behavioural and educational interventions.

The short term effects of behavioural interventions are typically limited to the periods when the programmes are actually in effect. When treatment is withdrawn, children often lose the gains made during treatment. Although in the short term behavioural interventions can improve targeted behaviours, they are less useful in reducing inattention, hyperactivity or impulsivity.⁸¹ Studies of attending have revealed that smaller class size, use of resource rooms versus regular classrooms, direct versus indirect instruction, and entire class engagement have resulted in increased levels of concentration in students with ADHD.⁸²

2+

The class teacher will be the main manager of educational intervention in most cases. Most teachers have only limited knowledge of the condition, and will require, at the very least, information and guidance. They also require collaborative support in evaluating the effectiveness of differing combinations of treatment.

7 Pharmacological therapy

7.1 INTRODUCTION

There are three licensed medicines in the UK for the treatment of ADHD/HKD; methylphenidate hydrochloride, dexamfetamine sulphate and atomoxetine. Methylphenidate and atomoxetine are licensed for use in children aged six years and above, whereas dexamfetamine is licensed for use in children aged three years and above. Medication is not recommended as first line therapy for children of pre-school age (see sections 6.2 and 9.1). For prescribing advice see section 1.4.1 and the British National Formulary.⁵

- The initiation of pharmacological treatment for children with ADHD/HKD should only be undertaken by a specialist, in either child and adolescent psychiatry or paediatrics, who has training in the use and monitoring of psychotropic medications.
- Baseline physical assessment should be undertaken prior to initiation of pharmacological therapy, including, as a minimum, measurement of pulse, blood pressure, weight and height with the appropriate use of centile charts in all measured parameters. Electrocardiography should be considered on an individual case basis.
- Clinicians should provide information about potential benefits and adverse effects of medications.
- The continuing benefit from and need for medication should be assessed at least once per year.
- A shared care protocol should be adopted between primary and secondary care.

Annex 2 provides a sample shared care protocol.

7.2 PSYCHOSTIMULANTS

Methylphenidate and dexamfetamine reduce core ADHD/HKD symptoms and improve quality of life in children diagnosed with ADHD/HKD.⁸³ | 1⁺⁺

Meta-analysis of high quality studies (of at least two weeks duration) using psychostimulant (methylphenidate and dexamfetamine) or non-psychostimulant (atomoxetine) medication concluded that they both have efficacy on ADHD/HKD symptoms, although psychostimulants produced greater effects.⁸⁴ | 1⁺

7.2.1 METHYLPHENIDATE

Two large, high quality studies demonstrate long term efficacy of methylphenidate, over 14 months duration⁷⁸ and over 24 months duration (see section 9).⁷⁴ | 1⁺

Methylphenidate is available in immediate or modified release forms to facilitate medication cover throughout the day. Table 1 outlines the strengths and different formulations available.⁸⁵ Modified release formulations demonstrate extended effects on proxy measures of ADHD/HKD consistent with concomitantly measured drug plasma levels.⁸⁶

Table 1: Characteristics of immediate and modified release forms of methylphenidate

Name	Product details	Strengths	Formulation	Release profile	Administration details
Generic or branded methylphenidate eg: Ritalin [®] Equasym [®] Medikinet [®]	Immediate release 3-4 hours duration	5 mg 10 mg 20 mg	Tablet	Peak plasma concentration in 1-2 hours.	Tablets can be halved.
Concerta XL [®]	Modified release 10-12 hours duration	18 mg 27 mg 36 mg 54 mg Dose equivalent: 18 mg = 5 mg IR tds 36 mg = 10 mg IR tds 54 mg = 15 mg IR tds	Capsule shaped tablet containing two layers of drug separated by semipermeable membrane. Outer layer (overcoat) released first, followed by gradual release of drug from inner core. Empty tablet shell excreted.	22% IR:78% MR Initial peak plasma concentration in 1-2 hours. Second peak at 6-8 hours.	Tablet must be swallowed whole, not chewed, crushed or broken.
Equasym XL [®]	Modified release Up to 8 hours duration	10 mg 20 mg 30 mg	Capsule containing two types of pellets/beads which allow immediate release of drug, followed by gradual release over the day.	30% IR:70% MR Initial peak plasma concentration in 1-2 hours. Second peak at 4.5 hours.	Capsule may be opened and contents mixed with soft foods. (<i>stability unknown</i>) Contents must be swallowed whole, not chewed, crushed or broken.
Medikinet XL [®]	Modified release Up to 8 hours duration	10 mg 20 mg 30 mg 40 mg	Capsule containing two types of pellets/beads allowing immediate release of half the dose, followed by gradual release over the day.	50% IR:50% MR Initial peak plasma concentration in 1-2 hours. Second phase of drug release 3 hours later resulting in a 3-4 hour plateau.	Capsule may be opened and contents mixed with soft foods. (<i>stability unknown</i>) Contents must be swallowed whole, not chewed, crushed or broken. Ingestion with high fat content food delays absorption by approximately 1.5 hours.

IR = Immediate release, MR = Modified release, tds = three times a day

7.2.2 DEXAMFETAMINE

Dexamfetamine is effective in treating core symptoms of ADHD/HKD.⁸³ No contemporary studies on dexamfetamine were identified. Currently only non-proprietary immediate release dexamfetamine (5 mg tablets and 1mg/ml liquid) is available in the UK. 1⁺⁺

A review of four studies compared Adderall (a modified release mixed amphetamine salt) against immediate release methylphenidate or placebo. Adderall showed a small advantage over immediate release methylphenidate and placebo when treatment response was measured by clinician and parent ratings/outcomes.⁸⁷ Adderall is not licensed in the UK. 1⁺

One phase three trial of the dexamfetamine pro-drug, lisdexamfetamine dimesylate showed efficacy over placebo and adverse effects similar to dexamfetamine.⁸⁸ It is not licensed in the UK. 1⁺⁺

7.2.3 DIVERSION/ABUSE OF PSYCHOSTIMULANTS

The potential for diversion ie where legally obtained medicines are traded, sold or offered onwards was not currently considered by the guideline development group to be a major issue in Scotland. This may be because of the strict prescription control models in place within the UK or may reflect a lack of UK based evidence. A systematic review examining diversion in the US described studies reporting from 5% non-prescribed use in younger children, up to 35% in US college students. Use of immediate release formulations, lower academic performance and self reported ADHD/HKD symptoms were among the main risk factors for diversion.⁸⁹

7.2.4 ADVERSE EFFECTS

The adverse effects of psychostimulants include insomnia, reduced appetite, abdominal pain, gastrointestinal disturbance, headache and dizziness and less frequently, anxiety, irritability or tearfulness. Most of the short term adverse effects are dose related and subject to differences between patients. They frequently diminish within 1-2 weeks of starting treatment, and usually disappear when treatment is discontinued, or the dose reduced.^{90,91} Table 2 describes management options for adverse effects.

A systematic review of heterogeneous studies found reduced growth velocity in some children during initial methylphenidate treatment. In some studies there were signs of catch-up growth later in treatment. No good quality evidence was identified to inform risk of long-term harm on growth or on final height.⁹² The 36 month follow up of the MTA trial confirmed the likelihood of an adverse effect on growth related to methylphenidate prescription, but there were no data on effect on adult height.⁹³ 1⁺
2⁺

There remains debate about the association of tics with psychostimulant use. A systematic review⁹⁴ and a review pooling three randomised controlled trials⁹⁵ of modified release methylphenidate suggested no significant induction of tics in children treated with methylphenidate. Analysis was limited by heterogeneity of studies. 1⁻

Concerns have been raised about a small number of sudden deaths attributed to cardiovascular events in children taking psychostimulants including methylphenidate based and dexamfetamine based medications in the US. Some of these cases were found to have pre-existing cardiac risk factors at autopsy, others were coprescribed other treatments. The reported number of cases was extremely low compared with the overall number of prescriptions dispensed.⁹⁶ Psychostimulant medication results in small mean increases in pulse and blood pressure. The potential harm as a result of this is currently being investigated. 3

Table 2: Management of adverse effects of psychostimulant medications

Adverse effects	Management options
Anorexia, nausea, weight loss, growth concerns	Administer medication with food. Consider dose reduction or omission (eg at weekends). Monitor height and weight using centile charts. Provide dietetic advice; caloric augmentation.
Sleep difficulties* (compare against baseline/pre-treatment difficulties)	Give 'sleep hygiene' advice. Reduce evening dose or administer earlier in the afternoon. Consider changing to atomoxetine.
Dizziness, headache	May be temporary. If persisting, monitor symptoms and blood pressure carefully, reduce dose or discontinue.
Involuntary movements or tics	Careful monitoring of pre- and post- treatment tics. Apparent worsening or onset may be temporary. If tics persistent or clearly problematic, change to non-psychostimulant alternative.
Dysphoria, agitation	Reduce dose and monitor effect.
Tachycardia, hypertension	Investigate and consider discontinuation or dose reduction.
Syncope suspected to have cardiac origin	Stop medication immediately and seek specialist advice.

*Melatonin is commonly used for sleep disorders in this population but examination of the evidence on melatonin was beyond the scope of this guideline.

7.2.5 SUMMARY AND RECOMMENDATIONS

In developing the following recommendations the guideline development group considered the immediacy of response, flexibility in initiating and controlling treatment and effect sizes over non-psychostimulants and took account of greater clinical experience with psychostimulants.

- A Psychostimulants are recommended as the first choice medication for the core symptoms of ADHD/HKD in children.**
- Should one psychostimulant fail to be effective, the other should be considered. If one psychostimulant is not tolerated because of adverse effects, atomoxetine should be considered.
- D Psychostimulants should not be first line medication for children with ADHD/HKD where there are known (or where there is a family history of) cardiac abnormalities.**
- Use of modified release formulations or atomoxetine should be considered where there is likelihood of diversion.
 - Psychostimulants are controlled drugs and clinicians should be cognisant with legislation regarding prescribing and dispensing.
 - Clinicians should:
 - follow a structured titration protocol and provide written information on potential adverse effects
 - maintain close contact with patients and carers in the initiation and titration phase so that the optimum dose of medication is established
 - review at least every six months, including assessment of ongoing efficacy and adverse effects and measurement of growth, pulse and blood pressure (*with correct cuff size*) using appropriate centile charts.

- Clinicians should familiarise themselves with the release patterns of the different methylphenidate formulations. It may be necessary to combine immediate and modified release preparations to provide medication cover throughout the day.
- When selecting a formulation, clinicians should consider practical issues of convenience and applicability on an individual case basis.

7.3 ATOMOXETINE

Atomoxetine is a non-psychostimulant medication for the treatment of ADHD/HKD. It is not subject to controlled drug legislation.

Atomoxetine is effective in the treatment of ADHD/HKD in children and young people in both the short and longer term (at least two years) when compared with placebo.^{83-85, 97} 1⁺⁺
1⁻

There is no evidence that atomoxetine is superior to stimulants in the management of core symptoms of ADHD/HKD. A meta-analysis compared atomoxetine and psychostimulants, and found lower effect sizes for atomoxetine.⁸⁴ One systematic review directly comparing psychostimulants and atomoxetine identified five studies, of which four examined methylphenidate. In two studies comparing immediate release methylphenidate with atomoxetine, the two medications were of comparable efficacy. In the two studies comparing modified release methylphenidate with atomoxetine, the methylphenidate preparation was superior.⁹⁸ 1⁺
1⁺

Two trials have been published since this review. One compared twice daily immediate release methylphenidate with atomoxetine, finding atomoxetine to be 'non-inferior' to methylphenidate⁹⁹ and one which found a benefit of modified release methylphenidate over atomoxetine.¹⁰⁰ 1⁺
1⁺

Prescribing of atomoxetine is based upon body weight for individuals under 70 kg. Atomoxetine should be commenced at a low starter dose of 0.5 mg/kg daily for at least seven days before being increased to a maintenance dose of 1.2 mg/kg daily. The manufacturer does not recommend the opening of capsules.

The effects of atomoxetine may not become apparent for four or more weeks. Once treatment is established, efficacy is described as being present over the 24 hour period, with possible greater effect over the 12 hours following administration. Short term initial combination with psychostimulant medication may be necessary during the transition phase.

In one small pilot study (n = 62), subjects were given their full dose of psychostimulant, plus a starting dose of atomoxetine (0.5 mg/kg/day) in week one. In the second week they were given half their usual psychostimulant dose and 1.2 mg/kg/day of atomoxetine. The psychostimulant was stopped at the end of the second week. Atomoxetine was given on its own (1.2 mg/kg/day) for the remaining five weeks of the study. The switch to atomoxetine was well tolerated but mild increases in diastolic pressure and heart rate were observed during the cross over phase.¹⁰¹ 3

A separate issue is the augmentation of atomoxetine with psychostimulant as reported in a pilot study (n = 25). Methylphenidate or placebo was added to atomoxetine for a six week period. The addition of methylphenidate was not found to enhance response, although the combination did appear to be safe. The authors note that the conclusions were limited due to the small sample size.¹⁰² 3

There is insufficient evidence on which to base a recommendation for concomitant use of atomoxetine and psychostimulants.

7.3.1 ADVERSE EFFECTS

Adverse effects of atomoxetine include nausea and appetite reduction, dry mouth, insomnia, constipation and mood swings. These adverse effects are similar to those seen with psychostimulants and diminish over the first few months of treatment.⁸⁵ Unlike psychostimulants, somnolence is commonly seen with atomoxetine.⁸⁵ Atomoxetine is suggested to be less likely to cause sleep problems in comparison to psychostimulants,¹⁰³ but there are no data delineating this from the somnolent adverse effect of the medication. Table 3 describes management options for adverse effects.

1+
1-

In one non-controlled, open label study atomoxetine did not cause growth restriction at two years despite initial reductions in growth velocity.¹⁰⁴

3

Disturbance of hepatobiliary function has been reported in adults and children treated with atomoxetine with a very small number of the hepatic events directly attributable to the medication.¹⁰⁵

3

Small but significant heart rate and blood pressure increases were found in RCTs.¹⁰⁶ These changes were greater in individuals identified as being poor metabolisers of atomoxetine, as are some other adverse effects (decreased appetite, reduced weight gain).¹⁰⁷ Post-marketing reports included several cases of prolonged QT interval and described concern about atomoxetine and risk of seizures.¹⁰⁸

1-
3

Isolated cases of sudden death have been reported in individuals taking atomoxetine treatment at usual doses. These individuals were described as having structural cardiac abnormalities or other serious heart problems.¹⁰⁹

Suicidal ideation was significantly more frequent in paediatric ADHD/HKD patients treated with atomoxetine compared to those treated with placebo in a meta-analysis conducted by the manufacturer.¹¹⁰ There have been no suicides attributed to atomoxetine treatment.

1-

Table 3: Management of adverse effects of atomoxetine

Side effects	Management options
Anorexia, nausea, weight loss, growth concerns	Gastrointestinal effects may be temporary during first few days of treatment. Administer medication with food. Consider dose reduction. Monitor height and weight using centile charts. Provide dietetic advice; caloric augmentation.
Jaundice, signs of liver disease or biliary obstruction	Stop medication immediately and seek specialist help.
Self harm or suicidal ideation	Monitor for suicidal ideation, clinical worsening of mood and unusual changes in behaviour. New onset of suicidal behaviour should prompt discontinuation of medication pending further assessment.
Somnolence	Administer at a different time of day or reduce dose.
Dysphoria, agitation	Reduce dose and monitor effect.
Tachycardia, hypertension	Investigate and consider discontinuation or dose reduction.
Syncope suspected to have cardiac origin	Stop medication immediately and seek specialist advice.

7.3.2 SUMMARY AND RECOMMENDATIONS

In developing the following recommendations the guideline development group considered both the effectiveness of atomoxetine and potential adverse effects.

A **Atomoxetine is recommended as treatment for the core symptoms of ADHD/HKD in children where psychostimulant medication is not appropriate, not tolerated or is ineffective.**

- Where atomoxetine is prescribed, clinicians should review at least six monthly, including assessment of ongoing efficacy and adverse effects and measurement of growth, pulse and blood pressure (*with correct cuff size*) using appropriate centile charts. Additional monitoring is advised for those at increased cardiovascular risk, hepatobiliary risk, seizure risk and potential suicidal ideation.

7.4 UNLICENSED MEDICATIONS

The following medications are not licensed in the UK for treatment of ADHD/HKD and should only be considered when licensed medications have failed. The risk-benefit balance of their use should be considered with particular care (*see section 1.4.1*).

- Considerable experience in treatment of ADHD/HKD is required prior to the consideration of unlicensed medications in children and young people. The decision should be carefully discussed with the child and their family and documented accordingly.

7.4.1 ALPHA-2-AGONISTS

Clonidine

Clonidine is an alpha-2 adrenergic agonist, best known as an antihypertensive. Two RCTs found that clonidine reduced ADHD/HKD symptoms, and that this reduction was greater when clonidine was taken in combination with methylphenidate than when taken on its own.^{111,112} Clonidine was either given three times a day up to a maximum dose of 0.6 mg daily depending on response and adverse effects,¹¹² or twice a day at total dose of 0.10 to 0.20 mg/day.¹¹¹ In one study individuals who had received clonidine had a greater reduction in systolic blood pressure measured standing than controls, and had transient sedation and dizziness.¹¹¹

1+
1-

C **Clonidine can be considered in children unresponsive to or unable to tolerate treatment with psychostimulants or atomoxetine. It may be used on its own or in combination with methylphenidate on an individual case basis.**

- Clinicians should monitor pulse and blood pressure, and check for signs of over-sedation in patients prescribed clonidine.
- Clonidine discontinuation should be carried out gradually to avoid the risk of rebound hypertension.

Guanfacine

A review of guanfacine use in children with ADHD notes that early industry trials suggest efficacy in treatment of symptoms. The major adverse effects were sedation and fatigue. Dry mouth, headache and sleep disturbance were also common. As the dose of guanfacine increases, blood pressure and pulse may be lowered.¹¹³

1+

There is insufficient evidence on which to base a recommendation for guanfacine.

7.4.2 ANTIDEPRESSANTS

Tricyclic antidepressants

The evidence for tricyclic antidepressants (TCAs) is largely from the 1980s and early 1990s and is mainly based on imipramine/desipramine. The TCAs are more effective in addressing the behavioural symptoms (as measured by Conners Teachers Rating Scale) than attention/concentration deficits.¹¹⁴⁻¹¹⁶ | 1++

When considering recommendations for TCAs the guideline development group took account of the availability of licensed and less toxic treatments for ADHD/HKD.

B Tricyclic antidepressants should not be routinely used in treatment of ADHD/HKD in children and should only be considered where children have not responded to licensed medications.

Where tricyclic antidepressants are used, electrocardiographic monitoring should be conducted before and during treatment. Caution is warranted in patients with a personal or family history of cardiac problems.

Reboxetine

Four small open label studies of effectiveness of reboxetine report improvements in symptoms of ADHD/HKD.¹¹⁷⁻¹²⁰ | 2-

One double blind trial comparing reboxetine and methylphenidate demonstrated similar efficacy using parent and teacher ratings. There was no placebo group.¹²¹ | 1-

There is insufficient evidence on which to base a recommendation for reboxetine.

Selegiline

Two trials compared selegiline with methylphenidate and found similar efficacy in improving ADHD/HKD symptoms. Neither study had placebo comparison groups.^{122,123} | 1-

One RCT compared selegiline with placebo, and found improvements in inattention and hyperactivity but not impulsivity.¹²⁴ | 1-

There is insufficient evidence on which to base a recommendation for selegiline.

Bupropion

No contemporary evidence was identified on the use of bupropion in ADHD/HKD. Two older studies compared bupropion with placebo¹²⁵ and with methylphenidate.¹²⁶ The latter suggested symptom reduction comparable with methylphenidate using several measures. | 1-

7.4.3 ANTIPSYCHOTICS

No evidence was identified that reported on the effects of antipsychotics on core ADHD/HKD symptoms.

7.4.4 MODAFINIL

Modafinil is used to promote wakefulness in disorders such as narcolepsy.

A systematic review of four RCTs examining use of modafinil in ADHD/HKD concluded that there was evidence for efficacy of modafinil over placebo, but that the studies relating to children were of low power.¹²⁷ | 1+

Three subsequent RCTs all show benefit for modafinil in reduction of ADHD/HKD symptoms in the short term and report similar adverse effects in trials that extended to a maximum of three months. Adverse effects included insomnia, headache, loss of appetite and loss of weight.¹²⁸⁻¹³⁰ | 1+

Dermatological reactions were amongst the rare adverse effects reported. Since some of these included a possible Stevens Johnson type reaction, which is a rare but potentially severe/life threatening idiosyncratic reaction, the US Food and Drug Administration (FDA) has not approved modafinil for use in children with ADHD/HKD.¹³¹ | 1+

The limitations on the use of modafinil due to adverse effects and the lack of clinical experience prohibit a recommendation for use.

7.4.5 NICOTINE

Two pilot studies (n ≤ 10) found that transdermal nicotine has a positive effect on inattention and impulse control in young people with ADHD/HKD.^{132,133} | 1+

There is insufficient evidence on which to base a recommendation for nicotine.

8 Nutrition and complementary and alternative therapies

8.1 NUTRITION

This section examines the evidence base for dietary manipulation and supplementation as an alternative or complementary intervention in the treatment of core ADHD/HKD symptoms. Investigation of the role of dietary factors in the causation of ADHD/HKD was outside the guideline remit.

8.1.1 FOOD ADDITIVES

There is evidence from well controlled studies that some food colourants and preservatives can have adverse behavioural effects on children both in the general population and in those diagnosed with ADHD/HKD.^{134,135}

1-
1+

In two studies in non-clinical populations of children aged three years and eight/nine years, mixed artificial colourants (sunset yellow, tartrazine, carmoisine and ponceau 4R) or the preservative sodium benzoate, or both, exacerbated hyperactive behaviours as rated by parents. The nature of the response is individual and appears to have a pharmacological rather than an allergic mechanism.^{136,137}

1-
1++

A meta-analysis of additive-free diets followed by food challenges in children with hyperactive disorders showed that pathological responses to foods were multiple and idiosyncratic although the most common responses were to the artificial colourant tartrazine and the preservative sodium benzoate.¹³⁸

1++

Avoiding foods and drinks that contain certain artificial colours and/or preservatives may help some children with ADHD/HKD. Parents should be advised to take reasonable steps to limit the number and variety of these in their children's diets, excluding any item that seems to provoke an extreme physical or behavioural reaction.

8.1.2 OMEGA-3 AND OMEGA-6 FATTY ACID SUPPLEMENTATION

Three systematic reviews of studies of the effectiveness of fatty acid supplementation in children with ADHD/HKD reported a range of methodological difficulties in the trials included.^{134,138,139} No consistent evidence was identified and meta-analysis of study results was not possible.

1+
1++

8.1.3 IRON SUPPLEMENTATION

In a small (n = 23) well conducted, placebo controlled RCT of ferrous sulphate supplementation in French schoolchildren with ADHD/HKD who had low ferritin stores but were not clinically anaemic, there were significant decreases in symptom scores over 12 weeks (ADHD/HKD Rating Scale, $p < 0.008$; Clinical Global Impression Scale, $p < 0.01$).¹⁴⁰

1++

Clinicians should consider iron status when taking a history, with measurement of serum iron and ferritin, and treatment, where appropriate.

8.1.4 ZINC SUPPLEMENTATION

A single RCT on zinc sulphate monotherapy as a treatment for ADHD/HKD found a significant therapeutic response but the validity of these findings was compromised by a high drop-out rate.¹⁴¹

1-

A small study (n = 44) examining the effect of zinc supplementation on the response to methylphenidate in medication-naive children with ADHD/HKD, found that the group taking methylphenidate and zinc improved significantly more than those on methylphenidate and placebo as judged by Du Paul scale parent ratings ($p < 0.048$) and teacher ratings ($p = 0.04$).¹⁴²

1+

There is insufficient evidence on which to base a recommendation.

8.1.5 ANTIOXIDANTS

One controlled study was identified using the antioxidant Pycnogenol®, derived from maritime pine bark, in children diagnosed with a hyperkinetic disorder or attention deficit disorder. A significant effect on hyperactivity scores compared with the baseline and a placebo was seen after one month on treatment. The effects disappeared after a further month without treatment.¹⁴³ This trial has not been replicated.

1⁺

8.2 COMPLEMENTARY AND ALTERNATIVE THERAPIES

There is insufficient evidence on which to base any recommendations for complementary or alternative therapies in the treatment of ADHD.

8.2.1 BACH FLOWER REMEDIES

One small placebo controlled RCT found no effect for Bach flower remedies (five flower essences) in the treatment of children with ADHD/HKD.¹⁴⁴

1⁺

8.2.2 HOMEOPATHY

A well conducted Cochrane meta-analysis identified four small trials of homeopathic treatments. The study concluded that there is little evidence of efficacy.¹⁴⁵

1⁺⁺

8.2.3 MASSAGE THERAPY

One small, short term RCT study found that twice weekly massage therapy improved short term mood state and classroom behaviour in young people with ADHD/HKD.¹⁴⁶

1⁺

8.2.4 NEUROFEEDBACK

Neurofeedback is presently considered to be an experimental intervention in children and young people with ADHD/HKD. There are no standardised interventions.^{147,148}

9 Treatment selection

Annex 3 summarises the treatment selection recommendations.

9.1 PRE-SCHOOL CHILDREN

Although the evidence base for the effectiveness of psychostimulant medication is robust (at least in the short term) in children of pre-school age, there is caution regarding the use of medication as a first line intervention due to the lack of knowledge of the longer term effects on the developing brain and the apparent increased rate of adverse effects in this age group.¹⁴⁹ In addition, in Scotland most clinicians would seldom confirm a diagnosis of ADHD/HKD in this age group.

Behavioural treatment recommendations for pre-school children are given in section 6.

9.2 SCHOOL-AGED CHILDREN AND YOUNG PEOPLE

9.2.1 COMPARING MEDICATION AND BEHAVIOURAL TREATMENTS

All studies comparing medication with behavioural treatments for ADHD/HKD used psychostimulant medication, in most cases methylphenidate, for which there is good quality RCT evidence for efficacy up to 24 months.⁷³

1+

The NIMH Collaborative Multisite Multimodal Treatment Study of Children with ADHD/HKD (MTA) (n = 579) was designed to answer three questions: how do long term medication and behavioural treatments compare with one another? Are there additional benefits when they are used together? What is the effectiveness of systematic, carefully delivered treatments versus routine community care? Participants were randomly assigned to one of three intervention groups or community treatment as usual.⁷⁸

On completion of a 14 month RCT, decisions about treatment reverted to the families, young people and the treating team outwith research protocols, hence all subsequent reports came from naturalistic observations. Results are published from assessments at 24 months (when groups of matched non-ADHD/HKD controls were added) 36 months, and also from 72 and 96 month reports (six and eight years). Outcome measures chosen describe children's functioning for seven domains: ADHD/HKD symptoms, functional impairment, oppositional/aggressive symptoms, internalising symptoms (anxiety and depression), teacher rated social skills, parent-child relations and reading achievement.^{78,93,150,151}

1+
2+

At 14 months there were clinically significant improvements across all four treatment groups with differences in the degree of improvement. Children who received the multimodal combination therapy or medication management alone had similar degrees of symptom improvement and showed significantly greater improvements than those from the group receiving behaviour therapy alone. The community treatment as usual group improved least. Children from the combined treatment group were on lower doses of medication than those taking medication alone.⁷⁸ The study concluded that medication is the most powerful treatment for core ADHD/HKD symptoms and that improvement in core and non-core symptom improvement can be achieved with lower doses of medication if intensive behaviour therapy is also provided.

1+

At 24 months, children from all four study groups continued to show improvement. Those in the combined treatment and medication management groups showed persisting superiority over the behavioural management only group, as well as those receiving community treatment for ADHD/HKD symptoms. However additional benefits were small, less than half that at the 14 month reports. All children were impaired in comparison with the classroom controls.¹⁵⁰ This superiority was not apparent at 36 months follow up, and this equifinality of outcomes was maintained at the eight year follow-up reports.¹⁵¹

2-

	<p>Use of medication during the naturalistic follow-up period was examined to see if changes had confounded the group results. Those children who had received medication during the study were still taking more medication than those from the behaviour therapy and community care groups. The loss of superior outcomes from the end of the RCT to 36 months was not entirely explained by changes in dose and patterns of medication use and may have been affected by the reduced intensity of monitoring and reduced contact with the clinical team outside the RCT period.¹⁵²</p>	2-
	<p>A further analysis examined factors at baseline associated with patterns of response to treatment, the statistical latent class. This described all the children in the study receiving any of the four study interventions during the RCT, and analysed the pattern of symptoms displayed through the naturalistic follow-up phase of the study through 24 and 36 months reports up to and including the six and eight year reports. This data analysis showed three patterns of symptom change during the study period, defined as latent classes 1, 2 and 3: one third (34%) of the total sample showed a gradual improvement maintained over time, the second group of children (52%) had an excellent response in the first 14 months and that continued after the end of the RCT. There was a third group of children (14%) who also had an excellent response in the first 14 months, but this deteriorated during the follow-up naturalistic treatment conditions. The most favourable pattern of response (latent class 2) was associated with children with fewer and less impairing symptoms of ADHD/HKD at baseline, without comorbid mental health problems and of high IQ. Their parents had high educational levels and the majority of them (>60%) had received the MTA medication intervention for the first 14 months. The children with the third response pattern (latent class 3) were those with more severe ADHD/HKD, multiple comorbidities and more often living in families dependent on welfare.¹⁵¹</p>	2-
	<p>Results of the MTA study, both RCT and naturalistic follow up, are consistent with those of recent European research. A small observational study found that children receiving medication as part of the initial intervention showed greater improvement than those without medication, but that this difference was lost at later follow-up points.¹⁵³</p>	3
9.2.2	SEVERITY OF CONDITION	
	<p>In a re-analysis of the 14 month MTA RCT data children whose diagnosis could be classified as severe (HKD by ICD-10 classification) had a larger beneficial response to medication in terms of relief of core symptoms than those with less severe ADHD as classified by DSM-IV.¹⁵⁴</p>	1+
	<p>The findings from the naturalistic follow up of the MTA concur with those from the European observational study which indicate that some children with ADHD (but not HKD by ICD-10 classification) can benefit from behavioural interventions alone. However, the extent of benefit is less than with medication alone and results are based on very intensive behavioural programmes. Outcomes from the eight year MTA study infer that treatment response in the early phase of intervention is the best predictor of adolescent outcomes, irrespective of the intervention delivered in childhood.^{78,93,150,151,153}</p>	3 2-
9.2.3	COMORBIDITY	
	<i>Oppositional defiant disorder/aggression</i>	
	<p>The MTA study found that children with ADHD/HKD and comorbid oppositional defiant disorder achieved better outcomes with combined medication and behavioural therapies at 14, 24 and 36 months.^{78,93} Children with comorbid behaviour problems at the start of the study developed fewer new onsets of oppositional defiant disorder if they had received the combined treatment intervention initially than those receiving any of the other three treatment strategies. This suggests that secondary prevention of more serious externalising behaviour problems can best be achieved by using a combination of medication and behavioural therapy from the start.¹⁵⁵ The MTA reports from six and eight years follow up did not show this protective effect on delinquent behaviours in mid-adolescence eg substance misuse, but there was a high rate of stopping medication, and further research is required to understand adolescent behavioural motivators.¹⁵¹</p>	1+ 2-

Generalised anxiety disorder

In the MTA study children with comorbid anxiety disorders had modest additional benefit in their internalising symptoms at the end of the 14 month RCT if they had received the combined treatment strategy rather than any other treatment. Benefit was maintained at 24 and 36 months follow up.^{78,93,150}

1+
2-

9.2.4 FAMILY CIRCUMSTANCES

Children with ADHD/HKD living in adverse socioeconomic circumstances tend to be more impaired and have comorbid mental health disorders. Children with these risk factors for poor long term outcomes benefit most when treatment addresses both core ADHD/HKD symptoms and comorbid aggressive/oppositional behaviour problems by a combination of psychostimulant medication and behavioural treatments.^{74,93,153}

2-

9.2.5 SUMMARY AND RECOMMENDATIONS

The selection of the most effective intervention for symptom management in school-age children with ADHD/HKD should consider the severity of ADHD/HKD symptoms, the presence of comorbidities and the socioeconomic circumstances. For treatment of the core symptoms of ADHD/HKD medium term outcomes for medication are generally superior to behavioural interventions.

- Parents' views about medication should be explored and taken into account prior to initiating treatment.
- A** For school aged children and young people with hyperkinetic disorder (*severe ADHD*) medication is recommended.
- A** For school aged children and young people with ADHD/HKD and comorbid symptoms of oppositional defiant disorder and/or aggressive behaviour a combination of medication and behavioural treatments is recommended.
- B** For school aged children and young people with ADHD/HKD and comorbid generalised anxiety disorders a combination of medication and behavioural treatments is recommended.
- Where symptoms of ADHD are mild, clinicians should consider behavioural approaches in the first instance.

10 Provision of information

This information leaflet was produced by the guideline development group in collaboration with the SIGN patient network and may be freely copied for distribution to families.

Information about attention deficit hyperactivity disorder (ADHD)
for parents and carers

What is ADHD?

ADHD is a common condition. It affects around 5% of children. In the UK, severe ADHD is sometimes also known as hyperkinetic disorder (HKD). Here we will use the most common term, ADHD. Around 1% to 2% of school-aged children will have the most severe form of ADHD. ADHD is more common in boys than in girls.

The symptoms of ADHD can vary but will include high levels of activity and impulsive behaviour and problems with poor concentration. These symptoms affect all parts of your child's life, for example how they cope at home, at school and in other social settings. They will have caused significant problems for more than six months.

Children with ADHD often have extra problems with:

- learning
- managing their emotions
- sleep and
- co-ordination.

Children with ADHD can have problems at school and with getting on with other people.

What causes ADHD?

The exact cause of ADHD is not clear. There are probably many causes of ADHD. ADHD is not generally caused by poor parenting or diet. It can run in families.

Where can I get help?

You may have your own worries about your child's behaviour, or school staff or others involved in helping your child may have pointed out problems. If you think your child may have ADHD, you should discuss your worries with your GP.

If your GP thinks your child has ADHD, they will refer them for specialist advice. They will usually refer your child to a mental health professional (such as a psychiatrist) or a paediatrician (a doctor who specialises in the care of children). In some areas of Scotland, your child can be referred to these specialists by their head teacher, an educational psychologist or another professional involved in caring for your child.

Who are the specialists and what will they do?

The specialist you are referred to is likely to be a mental health professional working within your local Child and Adolescent Mental Health Service ('CAMHS'), or a paediatrician.

You, your child and often the whole family may be invited to the first appointment. The health professional will talk to you about your child's problems and about other things, such as what your child does well. They will usually ask permission to contact your child's teachers, to find out more about how your child copes at school. They will often ask you and staff at your child's school to fill in questionnaires so they can get more information.

It is important for the health professional to find out whether your child has ADHD and if there are any other difficulties.

Because the health professional needs a lot of information, the assessment process and diagnosis may take several months.

What is the treatment for ADHD?

The treatment recommended for your child will depend on how severe the problems are and how much they are interfering with your child's life at school and at home. The health professional should involve you and your child in planning treatment. The treatment plan will be most effective if everyone who is involved with your child supports the plan.

Treatment and support may include the following:

- Medication
 - Psychostimulants such as methylphenidate and dexamfetamine are most commonly used. They are called 'stimulants' because they stimulate the parts of the brain affected by ADHD.
 - There are many different types of methylphenidate tablets and capsules. Some tablets, known as immediate-release tablets are effective straight away, but only last for a few hours. Other tablets or capsules are made so that the medicine is released slowly and continually throughout the day. If your child is prescribed slow-release tablets, such as Concerta XL, Medikinet XL or Equasym XL, they may only need to take one dose of medicine a day (usually in the morning).
 - The dose of medicine will be tailored to your child's needs and depends on their response and any side effects.
 - Stimulant medicines may cause side effects, but most are not serious. Some common side effects include:
 - often feeling a lot less hungry
 - stomach ache
 - feeling sick
 - headaches and
 - trouble sleeping.
 - Some children's growth may be affected while they are taking psychostimulant medication.
 - Psychostimulants and other medicines used to treat ADHD do not cause a 'high'.
 - ADHD symptoms might come back when your child's medication wears off, but there are no 'withdrawal symptoms' or any evidence that people start to depend on the medication.

- Your child's doctor will monitor their medication carefully. If psychostimulant medicine is not successful, a different type of medicine may be used. This is most likely to be a medicine called atomoxetine. It is not a 'stimulant' and its helpful effects may not be seen for several weeks. It has similar side effects to the psychostimulants.
- Training sessions for parents on how to manage their child's behaviour. Children with ADHD can be difficult to manage at home, and many parents find these sessions very helpful.
- Working with your child's school, class teacher and educational psychologist on consistent ways to manage their behaviour.
- Extra support for your child's learning at school.

What about diet and other therapies?

There is currently no good scientific evidence to suggest that any particular diets or other therapies are effective in treating ADHD. However, it is important that your child has a healthy and balanced diet, and if your child seems to have a bad reaction to a specific food or ingredient, you should avoid it.

Will my child grow out of ADHD?

The symptoms of ADHD reduce in some children as they get older. About two thirds of children with ADHD continue to have problems as teenagers and some of them continue to have problems and to need treatment when they are adults.

Useful contacts

ADD Information Service (ADDISS)

PO Box 340
Edgware
Middlesex, HA8 9HL
Phone: 020 8952 2800 • Fax: 020 8952 2909
Email: info@addiss.co.uk

Disability Living Allowance

Phone: 0800 88 22 00 • Textphone: 0800 24 33 55
Website: www.dwp.gov.uk/eservice

MIND (National Association for Mental Health)

Website: www.mind.org.uk/Information/BookletsUnderstanding/Understanding+ADHD.htm

Royal College of Psychiatrists

Website: www.rcpsych.ac.uk/mentalhealthinfo/mentalhealthandgrowingup/5adhdhyperkineticdisorder.aspx

The Young Minds Parents' Information Service

102-108 Clerkenwell Road
London, EC1M 5SA
Phone: 0800 018 2138



11 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

11.1 POTENTIAL RESOURCE IMPLICATIONS

This section is based on discussions with the guideline development group regarding current resource use in Scotland and the likely impact of implementing the recommendations made in the guideline. Where current practice will not change as a result of the recommendations it is unlikely there will be resource implications.

Table 4 outlines recommendations that will have additional resource implications for NHSScotland.

Table 4: Recommendations and likely resource implications

Recommendation	Section	Likely resource implication
D An assessment of the child's presentation in their educational placement is important for confirming diagnosis and identifying educational underachievement.	4.6	Staff and training resource across education and health.
B Behavioural parent training is recommended for parents of pre-school children with symptoms of ADHD/HKD. This should be delivered by trained facilitators.	6.2	Staff, training and interagency service development across Health, Local Authority and voluntary sector.
A In pre-adolescent children with ADHD/HKD and comorbid symptoms of oppositional defiant disorder and/or aggressive behaviour, behavioural programmes are recommended to treat the comorbid problems.	6.3	
B In pre-adolescent children with ADHD/HKD and comorbid generalised anxiety, behavioural programmes are recommended to treat the comorbid problems.		
<input checked="" type="checkbox"/> The initiation of pharmacological treatment for children with ADHD/HKD should only be undertaken by a specialist, in either child and adolescent psychiatry or paediatrics, who has training in the use and monitoring of psychotropic medications.	7.1	Increase in numbers of specialists in child and adolescent psychiatry or paediatrics.

11.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

Following the development of locally appropriate pathways or guidelines, prospective audit should be undertaken. Service providers should implement systems to ensure that the outcomes for children and young people with ADHD are routinely evaluated.

Firm outcome measures in the assessment and management of ADHD/HKD are difficult to characterise, although the use of standardised assessment measures in day to day clinical practice would be appropriate. Key areas for audit include:

- assessment of core symptoms
- assessment of comorbidity
- assessment of psychosocial functioning
- assessment of family functioning
- number and nature of interventions undertaken
- number of professionals and specialties involved in management
- number of contacts with service
- assessment of patient and family satisfaction with the service.

Development of a national audit of the assessment and management of patients with ADHD/HKD should be considered.

11.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS Quality Improvement Scotland advises that NICE Technology Appraisal Guidance No 98 - Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents (including a review of guidance No 13) supersedes the recommendations issued by the Scottish Medicines Consortium on the use of methylphenidate (Concerta XL) (5 July 2002), atomoxetine (Strattera) (11 July 2005) and methylphenidate (Equasym XL) (11 April 2005).

Methylphenidate prolonged-release capsule (Medikinet XL[®]) is accepted for restricted use within NHSScotland as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in children over six years of age when remedial measures alone prove insufficient. July 2007. www.scottishmedicines.org.uk/smc/5266.html

12 The evidence base

12.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, CINAHL, PsychInfo, ERIC and the Cochrane Library. The year range covered was 2004-2009, although searches for certain questions went back as far as 1990. The main searches were supplemented by material identified by individual members of the guideline development group. All selected papers were evaluated using standard methodological checklists. The Medline version of the main search strategies can be found on the SIGN website.

12.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research have been identified:

- effectiveness of behavioural interventions for ADHD/HKD in both children and adolescents
- methods of delivery of behavioural interventions for ADHD/HKD
- relationship between sleep disorders and ADHD/HKD
- safety of coprescription of atomoxetine with psychostimulants
- safety and timing of treatment discontinuation
- dietary supplementation in ADHD/HKD
- neurofeedback techniques in treatment of ADHD/HKD.

In general there is a lack of research on long term outcomes. Girls, pre-schoolers, adolescents and adults are under-represented in the literature.

12.3 REVIEW AND UPDATING

This guideline was issued in 2009 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

13 Development of the guideline

13.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

13.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Fiona Forbes (Chair)	<i>Consultant Child and Adolescent Psychiatrist, Royal Edinburgh Hospital and Clinical Advisor, NHS Quality Improvement Scotland</i>
Dr Dawn Adams	<i>Chartered Clinical Psychologist, Royal Aberdeen Children’s Hospital</i>
Ms Gazala Akram	<i>Lecturer, University of Strathclyde and Honorary Pharmacist, NHS Greater Glasgow and Clyde</i>
Ms Juliet Brown	<i>Information Officer, SIGN</i>
Dr Jackie Crum	<i>Consultant Paediatrician, Royal Aberdeen Children’s Hospital</i>
Dr Johnny Graham	<i>Clinical Lecturer in Child and Adolescent Psychiatry, Ninewells Hospital, Dundee</i>
Dr Eleanor Kerr	<i>Consultant Child and Adolescent Psychiatrist, North Glasgow Child and Adolescent Mental Health Service</i>
Dr Rachel Oglethorpe	<i>Child and Adolescent Psychiatrist, Glasgow</i>
Ms Sue Reynolds	<i>Area Principal Psychologist, Glasgow Psychological Service</i>
Dr Lorna Thompson	<i>Programme Manager, SIGN</i>
Ms Ruth Thomson	<i>Parent/Carer Representative, Falkirk</i>
Ms Fiona Thomson	<i>Parent/Carer Representative, Ayrshire</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

13.3 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 52 Attention Deficit and Hyperkinetic Disorders in Children and Young People, on which this guideline is based.

SIGN is grateful to the following former member of the guideline development group who has contributed to the development of the guideline.

Mr Gordon Brown	<i>Child and Adolescent Mental Health Practitioner, NHS Forth Valley</i>
-----------------	--

13.4 CONSULTATION AND PEER REVIEW

13.4.1 SPECIALIST REVIEW

This guideline was reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Ama S Addo	<i>Consultant in Child and Adolescent and Learning Disability Psychiatry, NHS Greater Glasgow and Clyde</i>
Dr Lila Agrawal	<i>Consultant Paediatrician, Wishaw General Hospital</i>
Dr Maha Basha	<i>Staff Grade Paediatrician, NHS Tayside Child and Adolescent Mental Health Service, Dundee</i>
Dr Marianne Cochrane	<i>Specialist Registrar, Community Child Health, Royal Aberdeen Children's Hospital</i>
Dr David Coghill	<i>Senior Lecturer in Child and Adolescent Psychiatry, University of Dundee Centre for Child Health</i>
Dr Catherine Cougan	<i>Staff Grade Doctor, Community Child Health, Royal Aberdeen Children's Hospital</i>
Dr Graham Foster	<i>Child Health Commissioner, NHS Forth Valley</i>
Ms Karen Fraser	<i>Principal Pharmacist - Mental Health, Ailsa Hospital, Ayr</i>
Dr Paul Gringras	<i>Paediatric Neurologist, Evelina Children's Hospital, London</i>
Professor Peter Hill	<i>Consultant in Child and Adolescent Psychiatry, Great Ormond Street Hospital for Children, London</i>
Dr Geoff Kewley	<i>Consultant Paediatrician, Learning Assessment and Neurocare Centre, Horsham, West Sussex</i>
Ms Cathy Laver-Bradbury	<i>Consultant Nurse ADHD, School of Health Science, University of Southampton</i>
Professor Thomas MacKay	<i>Consultant Psychologist, Psychology Consultancy Services, Cardross, Dumbartonshire</i>
Dr Graham Mackenzie	<i>Consultant in Public Health Medicine, NHS Lothian</i>
Ms Tracey McPherson	<i>Vice-Chair, ADD It Up Support Group, North Ayrshire</i>
Ms Caroline Parker	<i>Consultant Pharmacist, St Charles Hospital, London</i>
Mr David Rex	<i>Lead Dietitian Child Health, NHS Highland, Inverness</i>
Dr Chris Steer	<i>Consultant Paediatrician, Victoria Hospital, Kirkcaldy</i>
Dr Sami Timimi	<i>Consultant Child and Adolescent Psychiatrist, Lincolnshire Partnership NHS Trust</i>
Dr Joy Tomlinson	<i>Consultant in Public Health Medicine, NHS Ayrshire and Arran</i>

The following expert referees commented collectively on behalf of the Royal College of Paediatrics and Child Health.

Professor Gillian Baird	<i>Consultant Paediatrician, Guy's and St Thomas NHS Foundation Trust and British Paediatric Neurology Association</i>
Dr Somnath Banerjee	<i>Associate Specialist in Community Paediatrics, East Kent Hospitals University NHS Trust and Convenor, George Still Forum (National Paediatric ADHD Network Group)</i>
Dr Peter Baxter	<i>Consultant Paediatric Neurologist, Sheffield Children's NHS Trust</i>
Dr Andrew Lloyd Evans	<i>Consultant in Child and Adolescent Neurodisability, Northwick Park Hospital</i>
Professor Brian Neville	<i>Professor of Childhood Epilepsy, Institute of Child Health, University College London</i>
Professor Anne O'Hare	<i>Consultant in Community Child Health, Royal Hospital for Sick Children, Edinburgh</i>
Dr Mike Reynolds	<i>Retired Consultant Paediatrician</i>
Dr Alan Stanton	<i>Consultant Community Paediatrician, Solihull NHS Care Trust</i>

13.4.2 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Dr Keith Brown	<i>Chair of SIGN; Co-Editor</i>
Professor Chris Kelnar	<i>Royal College of Paediatrics and Child Health</i>
Mrs Fiona McMillan	<i>Royal Pharmaceutical Society of Great Britain</i>
Dr Moray Nairn	<i>Programme Manager, SIGN</i>
Dr Safia Qureshi	<i>SIGN Programme Director; Co-Editor</i>

Abbreviations

ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
BNF	British National Formulary
CAMHS	Child and Adolescent Mental Health Services
CD	conduct disorder
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4 th edition
FDA	Food and Drug Administration
GP	General Practitioner
GRTH	generalised resistance to thyroid hormone
HKD	hyperkinetic disorder
ICD	International Classification of Disease
IR	immediate release
IQ	intelligence quotient
MR	modified release
MRI	magnetic resonance imaging
MTA	Multimodal Treatment Study of Children with ADHD
NHS	National Health Service
NHS QIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
ODD	oppositional defiant disorder
RCT	randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
tds	three times a day
TCA	tricyclic antidepressants
UK	United Kingdom
US	United States

Annex 1

Key questions addressed in guideline update

Key question	See guideline section
<p>1. What is the effectiveness of the following medications in treating attention deficit and hyperkinetic disorders in children and young people?</p> <ul style="list-style-type: none"> ▪ methylphenidate ▪ dexamfetamine ▪ atomoxetine ▪ tricyclic (TCAs) and other antidepressants eg selective serotonin reuptake inhibitors ▪ bupropion ▪ nicotine (as skin patches) ▪ clonidine ▪ atypical antipsychotics ▪ modafinil ▪ neuroleptics ▪ guanfacine ▪ venlafaxine ▪ adderall. 	7
<p>2. What is the evidence for the effectiveness of behavioural (psychosocial) interventions in treatment of children and young people with attention deficit and hyperkinetic disorders? Consider:</p> <ul style="list-style-type: none"> ▪ individual ▪ family-based ▪ school-based interventions. 	6
<p>3. What is the effectiveness of omega-3 and omega-6 fatty acid supplementation in treating attention deficit and hyperkinetic disorders in children and young people?</p>	8.1.2
<p>4. What is the effectiveness of mineral supplementation in treating attention deficit and hyperkinetic disorders in children and young people?</p>	8.1.4 – 8.1.6
<p>5. What is the evidence for the influence of artificial food colours and food additives in children and young people with attention deficit and hyperkinetic disorders?</p>	8.1.1
<p>6. What is the evidence for the influence of dietary modification in children and young people with attention deficit and hyperkinetic disorders?</p>	8
<p>7. What is the evidence for alternative and complementary therapies in treatment of children and young people with attention deficit and hyperkinetic disorders?</p>	8.2
<p>8. Which factors should determine the initial treatment modality (pharmacological vs behavioural interventions) in children and young people with attention deficit and hyperkinetic disorders?</p>	9

Annex 2

Sample shared care protocol for the management of children and young people with ADHD/HKD

Aspects of care for which the paediatrician and/or psychiatrist is responsible:

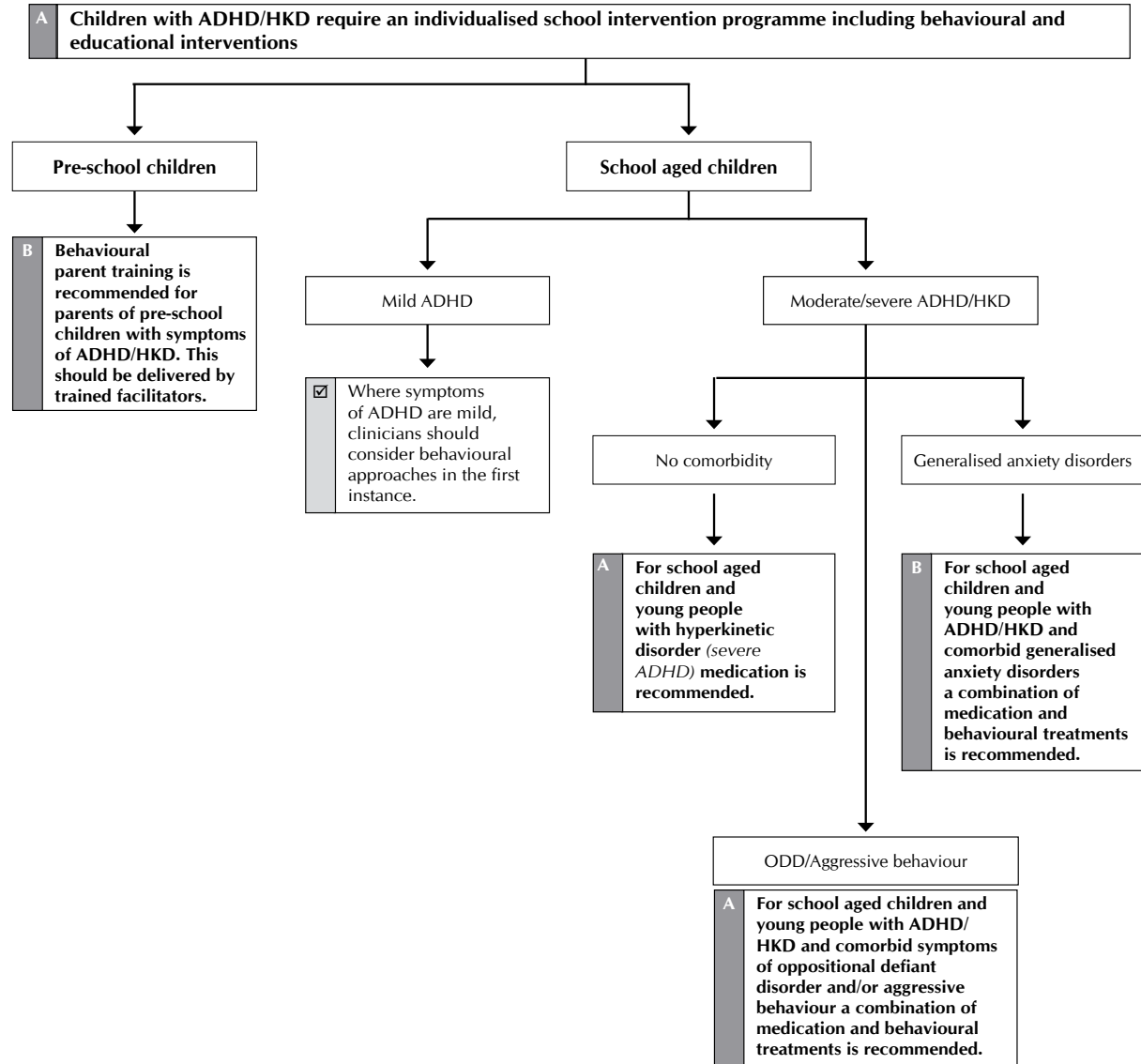
- Assessment and diagnosis of children with ADHD/HKD.
- Initiation of medical therapy and supply of the medicines for one further month after the dose has been stabilised.
- Patient monitoring - initially three monthly, then six monthly in the longer term. This includes height, weight and blood pressure.
- Discontinuation - advising the GP when medication should be discontinued in children receiving long term drug therapy. The specialist will provide necessary supervision and support during the drug discontinuation phase.
- Continuing supply of medication for children under six years.

Aspects of care for which the general practitioner is responsible:

- Prescribing medications once the patient is stabilised.
- Liaising with the paediatrician/psychiatrist regarding any complications in treatment.

Annex 3

Treatment Selection



References

1. Press AP. Diagnostic and statistical manual of mental disorders (DSM-IV). Washington DC: American Psychiatric Press; 1994.
2. WHO. International Classification of Diseases (ICD-10). Geneva: World Health Organization; 1992.
3. Barkley RA. ADHD: Longterm course adult outcome and comorbid disorders. NIH consensus development conference on diagnosis and treatment of attention deficit hyperactivity disorder 1998; 57-60.
4. NICE. Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults. London: NICE; 2008.
5. British Medical Association, Britain RPSoG. British National Formulary 57. London: The Association, The Society; 2009. [cited 29 June 2009]. Available from url: <http://www.bnf.org/bnf/>
6. Hill P. Attention deficit hyperactivity disorder. Archives of Disease in Childhood 1998;79(5):381-4.
7. Faraone SV, Biederman J, Weber W, Russell RL. Psychiatric, neuropsychological, and psychosocial features of DSM-IV subtypes of attention-deficit/hyperactivity disorder: results from a clinically referred sample. Journal of the American Academy of Child & Adolescent Psychiatry 1998;37(2):185-93.
8. Goldman LS, Genel M, Bezman RJ, Slanetz PJ. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Council on Scientific Affairs, American Medical Association. *Jama* 1100;279(14):1100-7.
9. Taylor E, Chadwick O, Heptinstall E, Danckaerts M. Hyperactivity and conduct problems as risk factors for adolescent development. Journal of the American Academy of Child & Adolescent Psychiatry 1996;35(9):1213-26.
10. Lahey BB, Pelham WE, Stein MA, Loney J, Trapani C, Nugent K, et al. Validity of DSM-IV attention-deficit/hyperactivity disorder for younger children.[see comment][erratum appears in *J Am Acad Child Adolesc Psychiatry* 1999 Feb;38(2):222]. *Journal of the American Academy of Child & Adolescent Psychiatry* 1998;37(7):695-702.
11. Elia J, Ambrosini PJ, Rapoport JL. Treatment of attention-deficit-hyperactivity disorder. *New England Journal of Medicine* 1999;340(10):780-8.
12. Taylor E SS, Thorley G, Giles S. The epidemiology of childhood activity. Maudsley Monograph. Oxford University Press; 1991.
13. Prendergast M, Taylor E, Rapoport JL, Bartko J, Donnelly M, Zametkin A, et al. The diagnosis of childhood hyperactivity. A U.S - U.K cross-national study of DSM-III and ICD-9. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1988;29(3):289-300.
14. McArdle P, O'Brien G, Kolvin I. Hyperactivity: prevalence and relationship with conduct disorder. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1995;36(2):279-303.
15. Merrell C, Tymms PB. Inattention, hyperactivity and impulsiveness: their impact on academic achievement and progress. *British Journal of Educational Psychology* 2001;71(Pt 1):43-56.
16. Gaub M, Carlson CL. Gender differences in ADHD: a meta-analysis and critical review.[erratum appears in *J Am Acad Child Adolesc Psychiatry* 1997 Dec;36(12):1783]. *Journal of the American Academy of Child & Adolescent Psychiatry* 1997;36(8):1036-45.
17. QIS. Attention deficit and hyperkinetic disorders Services over Scotland Report of the implementation review exercise. Edinburgh: Quality Improvement Scotland; 2008.
18. Biederman J, Faraone S, Milberger S, Curtis S, Chen L, Marrs A, et al. Predictors of persistence and remission of ADHD into adolescence: results from a four-year prospective follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry* 1996;35(3):343-51.
19. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. *Archives of General Psychiatry* 1993;50(7):565-76.
20. Jensen PS, Martin D, Cantwell DP. Comorbidity in ADHD: implications for research, practice, and DSM-V. *Journal of the American Academy of Child & Adolescent Psychiatry* 1997;36(8):1065-79.
21. Pliszka SRC, C.L. Swanson, J.M. ADHD with co-morbid disorders - clinical assessment and management. New York: Guilford Press; 1999.
22. Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Developmental Medicine & Child Neurology* 2000;42(7):436-47.
23. Cohen P, Cohen J, Kasen S, Velez CN, Hartmark C, Johnson J, et al. An epidemiological study of disorders in late childhood and adolescence--I. Age- and gender-specific prevalence. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1993;34(6):851-67.
24. Gittelman R, Mannuzza S, Shenker R, Bonagura N. Hyperactive boys almost grown up. I. Psychiatric status. *Archives of General Psychiatry* 1985;42(10):937-47.
25. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult psychiatric status of hyperactive boys grown up. *American Journal of Psychiatry* 1998;155(4):493-8.
26. Weiss G, Hechtman L, Milroy T, Perlman T. Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. *Journal of the American Academy of Child Psychiatry* 1985;24(2):211-20.
27. Barkley RA. Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment. 2nd ed. New York: Guilford; 1998.
28. Barkley RA, Fischer M, Edelbrock C, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: III. Mother-child interactions, family conflicts and maternal psychopathology. *Journal of Abnormal Child Psychology* 1991;32(2):233-55.
29. Moffitt TE. Juvenile delinquency and attention deficit disorder: boys' developmental trajectories from age 3 to age 15. *Child Development* 1990;61(3):893-910.
30. Fergusson DM, Horwood LJ, Lynskey MT. The effects of conduct disorder and attention deficit in middle childhood on offending and scholastic ability at age 13. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1993;34(6):899-916.
31. Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. *American Academy of Child and Adolescent Psychiatry. Journal of the American Academy of Child & Adolescent Psychiatry* 1997;36(Suppl 10):855-1215.
32. Corkum P, Tannock R, Moldofsky H. Sleep disturbances in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 1998;37(6):637-46.
33. Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT. Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 1990;29(4):526-33.
34. Faraone SV, Biederman J, Milberger S. How reliable are maternal reports of their children's psychopathology? One-year recall of psychiatric diagnoses of ADHD children. *Journal of the American Academy of Child & Adolescent Psychiatry* 1995;34(8):1001-8.
35. Green SM, Loeber R, Lahey BB. Stability of mothers' recall of the age of onset of their child's attention and hyperactivity problems. *Journal of the American Academy of Child & Adolescent Psychiatry* 1991;30(1):135-7.
36. Sanger MS, MacLean WE, Jr., Van Slyke DA. Relation between maternal characteristics and child behavior ratings. Implications for interpreting behavior checklists. *Clinical Pediatrics* 1992;31(8):461-6.
37. Cohen S, Bromet E. Maternal predictors of behavioral disturbance in preschool children: a research note. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1992;33(5):941-6.
38. Fergusson DM, Lynskey MT. The effects of maternal depression on child conduct disorder and attention deficit behaviours. *Social Psychiatry & Psychiatric Epidemiology* 1993;28(3):116-23.
39. Botting N, Powls A, Cooke RW, Marlow N. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. *J Child Psychol Psychiatry* 1997;38(8):931-41.
40. Hartsough CS, Lambert NM. Medical factors in hyperactive and normal children: prenatal, developmental, and health history findings. *American Journal of Orthopsychiatry* 1985;55(2):190-201.
41. Milberger S, Biederman J, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children?[see comment]. *American Journal of Psychiatry* 1997;153(9):1138-42.
42. Steinhausen HC, Willms J, Spohr HL. Long-term psychopathological and cognitive outcome of children with fetal alcohol syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry* 1993;32(5):990-4.
43. Streissguth AP, Barr HM, Sampson PD, Bookstein FL. Prenatal alcohol and offspring development: the first fourteen years. *Drug & Alcohol Dependence* 1994;36(2):89-99.
44. Alberts-Corush J, Firestone P, Goodman JT. Attention and impulsivity characteristics of the biological and adoptive parents of hyperactive and normal control children. *American Journal of Orthopsychiatry* 1986;56(3):413-23.

45. Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, et al. Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. *Archives of General Psychiatry* 1992;49(9):728-38.
46. Gilger JW, Pennington BF, DeFries JC. A twin study of the etiology of comorbidity: attention-deficit hyperactivity disorder and dyslexia. *Journal of the American Academy of Child & Adolescent Psychiatry* 1992;31(2):343-8.
47. LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, et al. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. [see comment]. *Molecular Psychiatry* 1996;1(2):121-4.
48. Morrison JR, Stewart MA. The psychiatric status of the legal families of adopted hyperactive children. *Archives of General Psychiatry* 1973;28(6):888-91.
49. Smalley SL, Bailey JN, Palmer CG, Cantwell DP, McGough JJ, Del'Homme MA, et al. Evidence that the dopamine D4 receptor is a susceptibility gene in attention deficit hyperactivity disorder. *Molecular Psychiatry* 1998;3(5):427-30.
50. Hauser P, Zametkin AJ, Martinez P, Vitiello B, Matochik JA, Mixson AJ, et al. Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. *New England Journal of Medicine* 1993;328(14):997-1001.
51. Offord DR, Boyle MH, Racine YA, Fleming JE, Cadman DT, Blum HM, et al. Outcome, prognosis, and risk in a longitudinal follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry* 1992;31(5):916-23.
52. Hinshaw SP. *Attention deficits and hyperactivity children*. Thousand Oaks (CA): Sage; 1994.
53. Barkley RA. The ecological validity of laboratory and analogue assessment methods of ADHD symptoms. *Journal of Abnormal Child Psychology* 1991;19(2):149-78.
54. Breen MJ. Cognitive and behavioral differences in ADHD boys and girls. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1989;30(5):711-6.
55. Goldstein S&M, editor. *Managing attention deficit hyperactivity disorder in children: a guide for practitioners*. 2nd ed ed. New York: Wiley; 1998.
56. Achenbach TM. Subtyping ADHD: The request for suggestions about relating empirically derived assessments to DSM-IV. *The ADHD Report*. 1996.
57. Silver LB. Attention deficit-hyperactivity disorder: is it a learning disability or a related disorder? [see comment]. *Journal of Learning Disabilities* 1990;23(7):394-7.
58. Denckla MB. Revised Neurological Examination for Subtle Signs. *Psychopharmacology Bulletin* 1985;21(4):773-800.
59. Reeves JCW, J.S. Soft signs in hyperactivity. In: Tupper DE, editor. *Soft neurological signs*. New York: Grune and Stratton; 1989.
60. Quinn PO, Rapoport JL. Minor physical anomalies and neurologic status in hyperactive boys. *Pediatrics* 1974;53(5):742-7.
61. Tannock R. Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1998;39(1):65-99.
62. Crinella FMT, J.L Wigal, T.L Yu, J. Partitioning neuropsychological deficit in children with attention deficit hyperactivity disorder. *Archives of Clinical Neuropsychology* 1994;9(2):117-8.
63. Katz LW, S. Achenbach T.M. . Utility of current tests in diagnosing ADHD. *Archives of Clinical Neuropsychology* 1994;9(2):146-7.
64. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1996;37(1):51-87.
65. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin* 1997;121(1):65-94.
66. Sonuga-Barke EJ, Williams E, Hall M, Saxton T. Hyperactivity and delay aversion. III: The effect on cognitive style of imposing delay after errors. *Journal of Child Psychology & Psychiatry & Allied Disciplines* 1996;37(2):189-94.
67. Sonuga-Barke EJ, Daley D, Thompson M, Laver-Bradbury C, Weeks A. Parent-based therapies for preschool attention-deficit/hyperactivity disorder: a randomized, controlled trial with a community sample. *J Am Acad Child Adolesc Psychiatry* 2001;40(4):402-8.
68. Bor W, Sanders MR, Markie-Dadds C. The effects of the Triple P-Positive Parenting Program on preschool children with co-occurring disruptive behavior and attentional/hyperactive difficulties. *J Abnorm Child Psychol* 2002;30(6):571-87.
69. Jones K, Daley D, Hutchings J, Bywater T, Eames C. Efficacy of the Incredible Years Basic parent training programme as an early intervention for children with conduct problems and ADHD. *Child: Care, Health and Development* 2007;33(6):749-56.
70. Jones K, Daley D, Hutchings J, Bywater T, Eames C. Efficacy of the Incredible Years Programme as an early intervention for children with conduct problems and ADHD: long-term follow-up. *Child: Care, Health & Development* 2008;34(3):380-90.
71. Sonuga-Barke EJS, Thompson M, Daley D, Laver-Bradbury C. Parent training for Attention Deficit/Hyperactivity Disorder: is it as effective when delivered as routine rather than as specialist care? *British Journal of Clinical Psychology* 2004;43(Part 4):449-57.
72. Arnold LE, Chuang S, Davies M, Abikoff HB, Conners CK, Elliott GR, et al. Nine months of multicomponent behavioral treatment for ADHD and effectiveness of MTA fading procedures. *Journal of Abnormal Child Psychology* 2004;32(1):39-51.
73. Abikoff H, Hechtman L, Klein RG, Weiss G, Fleiss K, Etcovitch J, et al. Symptomatic improvement in children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. *Journal of the American Academy of Child and Adolescent Psychiatry* 2004;43(7):802-11.
74. Abikoff H, Hechtman L, Klein RG, Gallagher R, Fleiss K, Etcovitch J, et al. Social functioning in children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. *Journal of the American Academy of Child and Adolescent Psychiatry* 2004;43(7):820-9.
75. van den Hoofdakker BJ, van der Veen-Mulders L, Sytema S, Emmelkamp PM, Minderaa RB, Nauta MH. Effectiveness of behavioral parent training for children with ADHD in routine clinical practice: a randomized controlled study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2007;46(10):1263-71.
76. Sanders MR, Hoath FE. A Feasibility Study of Enhanced Group Triple P - Positive Parenting Program for Parents of Children with Attention-Deficit/Hyperactivity Disorder. *Behaviour Change* 2002;19(4):191-206.
77. Tutty S, Gephart H, Wurzbacher K. Enhancing behavioral and social skill functioning in children newly diagnosed with attention-deficit hyperactivity disorder in a pediatric setting. *J Dev Behav Pediatr* 2003;24(1):51-7.
78. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry* 1999;56(12):1073-86.
79. Pfiffner LJ, Mikami AY, Huang-Pollock C, Easterlin B, Zalecki C, McBurnett K. A randomized, controlled trial of integrated home-school behavioral treatment for ADHD, predominantly inattentive type. *Journal of the American Academy of Child and Adolescent Psychiatry* 2007;46(8):1041-50.
80. DuPaul GJE, Tanya L. The Effects of School-Based Interventions for Attention Deficit Hyperactivity Disorder: A Meta-Analysis. *School Psychology Review* 1997;26(1):5-27.
81. Abikoff H, Gittelman R. Does behavior therapy normalize the classroom behavior of hyperactive children? *Archives of General Psychiatry* 1984;41(5):449-54.
82. Abramowitz AJ, O'Leary SG. Behavioral interventions for the classroom: Implications for students with ADHD. *School Psychology Review* 1991;20(2):220-34.
83. King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, et al. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. *Health Technology Assessment* 2006;10(23):iii-iv, xiii-146.
84. Faraone SV, Biederman J, Spencer TJ, Alardi M. Comparing the efficacy of medications for ADHD using meta-analysis. *MedGenMed* 2006;8(4):4.
85. Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, et al. Long-acting medications for the hyperkinetic disorders: A systematic review and European treatment guideline. *European Child and Adolescent Psychiatry* 2006;15(8):476-95.
86. Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics* 2004;113(3 Pt 1):e206-16.
87. Faraone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. *Journal of Clinical Psychopharmacology* 2002;22(5):468-73.
88. Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther* 2007;29(3):450-63.

89. Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, et al. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. *J Am Acad Child Adolesc Psychiatry* 2008;47(1):21-31.
90. Musten LM, Firestone P, Pisterman S, Bennett S, Mercer J. Effects of methylphenidate on preschool children with ADHD: cognitive and behavioral functions. *Journal of the American Academy of Child & Adolescent Psychiatry* 1997;36(10):1407-15.
91. Firestone P, Musten LM, Pisterman S, Mercer J, Bennett S. Short-term side effects of stimulant medication are increased in preschool children with attention-deficit/hyperactivity disorder: a double-blind placebo-controlled study. *Journal of Child & Adolescent Psychopharmacology* 1998;8(1):13-25.
92. Poulton A. Growth on stimulant medication; clarifying the confusion: a review. *Archives of Disease in Childhood* 2005;90(8):801-6.
93. Jensen P. Longer term effects of stimulant treatments for Attention-Deficit/Hyperactivity Disorder. *Journal of Attention Disorders* 2002;6(1):51-3.
94. Roessner V, Robatzek M, Knapp G, Banaschewski T, Rothenberger A. First-onset tics in patients with attention-deficit-hyperactivity disorder: impact of stimulants. *Dev Med Child Neurol* 2006;48(7):616-21.
95. Palumbo D, Spencer T, Lynch J, Co-Chien H, Faraone SV. Emergence of tics in children with ADHD: impact of once-daily OROS methylphenidate therapy. *J Child Adolesc Psychopharmacol* 2004;14(2):185-94.
96. FDA. 2006.
97. Buitelaar JK, Michelson D, Danckaerts M, Gillberg C, Spencer TJ, Zuddas A, et al. A randomized, double-blind study of continuation treatment for attention-deficit/hyperactivity disorder after 1 year. *Biol Psychiatry* 2007;61(5):694-9.
98. Gibson AP, Bettinger TL, Patel NC, Crismon ML. Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. *Annals of Pharmacotherapy* 1134;40(6):1134-42.
99. Wang Y, Zheng Y, Du Y, Song DH, Shin YJ, Cho SC, et al. Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. *Aust N Z J Psychiatry* 2007;41(3):222-30.
100. Newcorn JH, Kratochvil CJ, Allen AJ, Casat CD, Ruff DD, Moore RJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. *Am J Psychiatry* 2008;165(6):721-30.
101. Quintana H, Cherlin EA, Duesenberg DA, Bangs ME, Ramsey JL, Feldman PD, et al. Transition from methylphenidate or amphetamine to atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder—a preliminary tolerability and efficacy study. *Clin Ther* 2007;29(6):1168-77.
102. Carlson GA, Dunn D, Kelsey D, Ruff D, Ball S, Ahrbecker L, et al. A pilot study for augmenting atomoxetine with methylphenidate: safety of concomitant therapy in children with attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatry Ment Health* 2007;1(1):10.
103. Sangal RB, Owens J, Allen AJ, Sutton V, Schuh K, Kelsey D. Effects of atomoxetine and methylphenidate on sleep in children with ADHD. *Sleep* 2006;29(12):1573-85.
104. Spencer TJ, Newcorn JH, Kratochvil CJ, Ruff D, Michelson D, Biederman J. Effects of atomoxetine on growth after 2-year treatment among pediatric patients with attention-deficit/hyperactivity disorder. *Pediatrics* 2005;116(1):e74-e80.
105. Bangs ME, Jin L, Zhang S, Desai D, Allen AJ, Read HA, et al. Hepatic events associated with atomoxetine treatment for attention-deficit hyperactivity disorder. *Drug Saf* 2008;31(4):345-54.
106. Wernicke JF, Faries D, Girod D, Brown J, Gao H, Kelsey D, et al. Cardiovascular effects of atomoxetine in children, adolescents, and adults. *Drug Saf* 2003;26(10):729-40.
107. Michelson D, Read HA, Ruff DD, Witcher J, Zhang S, McCracken J. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry* 2007;46(2):242-51.
108. MHRA. Strattera Risk Benefit review. [cited 2/12/08]. Available from url: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2023222>. Accessed 2/12/08.
109. Medication Guide. Strattera. [cited Available from url: <http://pi.lilly.com/us/strattera-ppi.pdf>
110. Bangs ME, Tauscher-Wisniewski S, Polzer J, Zhang S, Acharya N, Desai D, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *J Am Acad Child Adolesc Psychiatry* 2008;47(2):209-18.
111. Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. *Journal of the American Academy of Child & Adolescent Psychiatry* 2003;42(8):886-94.
112. Palumbo DR, Sallee FR, Pelham Jr WE, Bukstein OG, Daviss WB, McDermott MP, et al. Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. *Journal of the American Academy of Child and Adolescent Psychiatry* 2008;47(2):180-8.
113. Strange BC. Once-daily treatment of ADHD with guanfacine: patient implications. *Neuropsychiatr Dis Treat* 2008;4(3):499-506.
114. Rapport MD, Carlson GA, Kelly KL, Pataki C. Methylphenidate and desipramine in hospitalized children: I. Separate and combined effects on cognitive function. *Journal of the American Academy of Child & Adolescent Psychiatry* 1993;32(2):333-42.
115. Garfinkel BD, Wender PH, Sloman L, O'Neill I. Tricyclic antidepressant and methylphenidate treatment of attention deficit disorder in children. *Journal of the American Academy of Child Psychiatry* 1983;22(4):343-8.
116. Biederman J, Baldessarini RJ, Wright V, Knee D, Harmatz JS. A double-blind placebo controlled study of desipramine in the treatment of ADD: I. Efficacy. *Journal of the American Academy of Child & Adolescent Psychiatry* 1989;28(5):777-84.
117. Tehrani-Doost M, Moallemi S, Shahrivar Z. An open-label trial of reboxetine in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2008;18(2):179-84.
118. Mozes T, Meiri G, Ben-Amity G, Sabbagh M, Weizman A. Reboxetine as an optional treatment for hyperkinetic conduct disorder: a prospective open-label trial.[see comment]. *Journal of Child & Adolescent Psychopharmacology* 2005;15(2):259-69.
119. Ratner S, Laor N, Bronstein Y, Weizman A, Toren P. Six-week open-label reboxetine treatment in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2005;44(5):428-33.
120. Toren P, Ratner S, Weizman A, Lask M, Ben-Amity G, Laor N. Reboxetine maintenance treatment in children with attention-deficit/hyperactivity disorder: a long-term follow-up study. *Journal of Child & Adolescent Psychopharmacology* 2007;17(6):803-12.
121. Arabgol F, Panaghi L, Hebrani P. Reboxetine versus methylphenidate in treatment of children and adolescents with attention deficit-hyperactivity disorder. *Eur Child Adolesc Psychiatry* 2008;18(1):53-9.
122. Mohammadi MR, Ghanizadeh A, Alaghband-Rad J, Tehrani-doost M, Mesgarpour B, Soori H. Selegiline in comparison with methylphenidate in attention deficit hyperactivity disorder children and adolescents in a double-blind, randomized clinical trial. *Journal of Child & Adolescent Psychopharmacology* 2004;14(3):418-25.
123. Akhondzadeh S, Tavakolian R, Davari-Ashtiani R, Arabgol F, Amini H. Selegiline in the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27(5):841-5.
124. Rubinstein S, Malone MA, Roberts W, Logan WJ. Placebo-controlled study examining effects of selegiline in children with attention-deficit/hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology* 2006;16(4):404-15.
125. Barrickman LL, Perry PJ, Allen AJ, Kuperman S, Arndt SV, Hermann KJ, et al. Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1995;34(5):649-57.
126. Conners CK, Casat CD, Gualtieri CT, Weller E, Reader M, Reiss A, et al. Bupropion hydrochloride in attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* 1996;35(10):1314-21.
127. Lindsay SE, Gudelsky GA, Heaton PC. Use of modafinil for the treatment of attention deficit/hyperactivity disorder. *Annals of Pharmacotherapy* 2006;40(10):1829-33.
128. Greenhill LL, Biederman J, Boellner SW, Rugino TA, Sangal RB, Earl CQ, et al. A randomized, double-blind, placebo-controlled study of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2006;45(5):503-11.
129. Swanson JM, Greenhill LL, Lopez FA, Sedillo A, Earl CQ, Jiang JG, et al. Modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, fixed-dose study followed by abrupt discontinuation. *J Clin Psychiatry* 2006;67(1):137-47.

130. Wigal SB, Biederman J, Swanson JM, Yang R, Greenhill LL. Efficacy and safety of modafinil film-coated tablets in children and adolescents with or without prior stimulant treatment for attention-deficit/hyperactivity disorder: pooled analysis of 3 randomized, double-blind, placebo-controlled studies. *Prim Care Companion J Clin Psychiatry* 2006;8(6):352-60.
131. FDA. Modafinil Briefing Document for Psychopharmacologic Drugs Advisory Committee Meeting. 2006.
132. Potter AS, Newhouse PA. Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. *Psychopharmacology* 2004;176(2):182-94.
133. Shytle RD, Silver AA, Wilkinson BJ, Sanberg PR. A pilot controlled trial of transdermal nicotine in the treatment of attention deficit hyperactivity disorder. *World Journal of Biological Psychiatry* 2002;3(3):150-5.
134. Rojas NL, Chan E. Old and new controversies in the alternative treatment of attention-deficit hyperactivity disorder. *Mental Retardation & Developmental Disabilities Research Reviews* 2005;11(2):116-30.
135. Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *Journal of Developmental & Behavioral Pediatrics* 2004;25(6):423-34.
136. Bateman B, Warner JO, Hutchinson E, Dean T, Rowlandson P, Grant C, et al. The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. *Archives of Disease in Childhood* 2004;89(6):506-11.
137. McCann D, Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet* 2007;370(9598):1560-7.
138. Benton D. The impact of diet on anti-social, violent and criminal behaviour. *Neuroscience and Biobehavioral Reviews* 2007;31(5):752-74.
139. Clayton EH, Hanstock TL, Garg ML, Hazell PL. Long chain omega-3 polyunsaturated fatty acids in the treatment of psychiatric illnesses in children and adolescents. *Acta Neuropsychiatrica* 2007;19(2):92-103.
140. Konofal E, Lecendreux M, Deron J, Marchand M, Cortese S, Zaim M, et al. Effects of iron supplementation on attention deficit hyperactivity disorder in children. *Pediatr Neurol* 2008;38(1):20-6.
141. Bilici M, Yildirim F, Kandil S, Bekarolu M, Yildirmi S, Deer O, et al. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2004;28(1):181-90.
142. Akhondzadeh S MM, Khademi M. . Zinc sulphate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomised trail. . *BMC Psychiatry* 2004;4:9.
143. Trebaticka J, Kopasova S, Hradecna Z, Cinovsky K, Skodacek J, Suba J, et al. Treatment of ADHD with French maritime pine bark extract, Pycnogenol. *Eur Child Adolesc Psychiatry* 2006;15(6):329-35.
144. Pintov S, Hochman M, Livne A, Heyman E, Lahat E. Bach flower remedies used for attention deficit hyperactivity disorder in children - a prospective double blind controlled study. *European Journal of Paediatric Neurology* 2005;9(6):395-8.
145. Coulter MK, Dean ME. Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. *Cochrane Database of Systematic Reviews*. 2007(4):(CD005648).
146. Khilnani S, Field T, Hernandez-Reif M, Schanberg S. Massage therapy improves mood and behavior of students with attention-deficit/hyperactivity disorder. *Adolescence* 2003;38(152):623-38.
147. Beaugregard M, Levesque J. Functional magnetic resonance imaging investigation of the effects of neurofeedback training on the neural bases of selective attention and response inhibition in children with attention-deficit/hyperactivity disorder. *Applied Psychophysiology & Biofeedback* 2006;31(1):3-20.
148. Baydala L, Wikman E. The efficacy of neurofeedback in the management of children with attention deficit/hyperactivity disorder. *Paediatrics and Child Health* 2001;6(7):451-5.
149. Ghuman JK, Arnold LE, Anthony BJ. Psychopharmacological and other treatments in preschool children with attention-deficit/hyperactivity disorder: current evidence and practice. *J Child Adolesc Psychopharmacol* 2008;18(5):413-47.
150. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. *Pediatrics*. 2004;113(4 Part 1):754-61. .
151. Molina BS. The MTA at 8 Years: Prospective Follow-up of Children Treated for Combined-Type ADHD in a Multisite Study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2009;48(5):461-2.
152. Swanson JM, Hinshaw SP, Arnold LE, Gibbons RD, Marcus S, Hur K, et al. Secondary evaluations of MTA 36-month outcomes: propensity score and growth mixture model analyses. *Journal of the American Academy of Child & Adolescent Psychiatry* 2003;46(8):1003-14.
153. Dopfner M, Breuer D, Schurmann S, Metternich TW, Rademacher C, Lehmkuhl G. Effectiveness of an adaptive multimodal treatment in children with Attention-Deficit Hyperactivity Disorder – global outcome. *European Child & Adolescent Psychiatry* 2004;13(Suppl 1):17-29.
154. Santosh P . ET, J . Swanson , T . Wigal , S . Chuang , M . Davies , L . Greenhill , J . Newcorn , L . Arnold , P . Jensen. Refining the diagnoses of inattention and overactivity syndromes: A reanalysis of the Multimodal Treatment study of attention deficit hyperactivity disorder (ADHD) based on ICD-10 criteria for hyperkinetic disorder *Clinical Neuroscience Research* 2005;5(5-6):307-14.
155. Molina BS, Flory K, Hinshaw SP, Greiner AR, Arnold LE, Swanson JM, et al. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. *Journal of the American Academy of Child & Adolescent Psychiatry* 2008;46(8):1028-40.

ISBN 978 1 905813 53 7

Scottish Intercollegiate Guidelines Network

Elliott House

8 -10 Hillside Crescent

Edinburgh EH7 5EA

www.sign.ac.uk

