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# Attention deficit hyperactivity disorder: guidelines for investigating efficacy of pharmacological intervention

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## 1. Introduction

In March 2001, the European College of Neuropsychopharmacology held a consensus meeting in Nice to address issues in the methodology for investigating pharmacological treatments for Attention Deficit Hyperactivity Disorder. These guidelines have been produced following the discussions.

## 2. Background

### 2.1. Features of ADHD

Attention deficit hyperactivity disorder (ADHD) is characterised by a persistent pattern of overactivity, inattention and impulsivity that is pervasive across social situations and accompanied by substantial social impairments in family and social relationships. It has an early onset and clinical experience suggests that in the majority of the children with ADHD, first onset of symptoms (particularly overactivity and impulsiveness) can occur as young as 2 or 3 years. Prospective studies have shown that clinically referred preschoolers of about 3 years of age who present with severe hyperactivity, irritability, and/or impulsiveness are at high risk to be diagnosed with ADHD or related externalizing disorders at the age of 6 to 9 years (Pierce et al., 1999; Campbell et al., 2000).

### 2.2. Burden of the disorder

ADHD is a relatively common disorder occurring in 5–9% of children between the ages of 5 and 14 years with 2–3 times as many boys affected as girls (Buitelaar, 2001). Estimates of prevalence of ADHD vary according to the strictness of the definition of the syndrome, the source of information about symptoms and impairment (from parents or teachers), and the method used to gather diagnostic information (behaviour checklist, structured interview, etc.). Some symptoms, for example hyperactivity and impulsivity, tend to decline with age, though others, for example inattentive symptoms, are more persistent (Biederman et al., 2000). Predicting outcomes is difficult given the wide variation in developmental differences between juveniles. Very long-term follow-up is made more difficult by the inevitable changes in the sources of information. Complete remission of symptoms and resolution of functional impairment occurs in only 10% of the cases and the prevalence of ADHD in adults, estimated at 2–3%, is not markedly lower than in adolescents at 3–5% (Buitelaar, 2001). There is a considerable need for research into ADHD occurring outside the child to adolescent age range.

Both clinical and epidemiological studies have found that some 50% of all children with ADHD also have comorbid aggressive disorders (oppositional defiant disorder and conduct disorder). The presence of other comorbid conditions is the rule rather than the exception with depressive disorders, anxiety disorders, bipolar disorder, learning disorder, and tic disorder frequently reported (Kadesjo and Gillberg, 2001; Angold et al., 1999). The presence of ADHD in childhood is a major risk factor for the development of aggressive and antisocial behaviour

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(Taylor et al., 1996). The long-term outcome is poor, with an increased risk of social isolation, academic underachievement, substance abuse, and persistent psychopathology in adolescence and adulthood affecting up to 60% of cases (Hansen et al., 1999; Mannuzza et al., 1997, 1998).

### 2.3. Aetiology of ADHD

The precise aetiology of ADHD is not known but a number of approaches to investigating the biological basis of the disorder have provided interesting information. The disorder is known to aggregate within families and first-degree relatives of ADHD patients have a three to five times increased risk of the syndrome, and in second-degree relatives, the relative risk ratio is about 2 (Faraone and Biederman, 1994). Adoption and twin studies consistently support the genetic component with heritability estimates as high as 90% (for review, see Thapar et al., 1999). Involvement of dopaminergic neurotransmission has been proposed and several groups have reported associations between ADHD and the dopamine D4 receptor and the dopamine transporter gene, which are both involved in dopaminergic transmission (Thapar et al., 1999).

Current findings of structural and functional brain imaging indicate there are smaller and less active frontal–basal ganglia neural network areas in patients with ADHD compared to unaffected individuals. MRI studies of brain anatomy have reported rather consistent abnormalities in children with ADHD (Castellanos et al., 1996, 2001, 2002) and a meta-analysis of the findings suggest subjects with a moderate reduction in frontal lobe size, and in the size of the basal ganglia (caudate nucleus and globus pallidus) compared with healthy controls (Swanson et al., 1998). Functional brain imaging studies have found abnormalities in response to stimuli and reduced brain activation in the anterior cingulate (Bush et al., 1999; Rubia et al., 1999; Overtoom et al., 1998; Jonkman et al., 1997; Kemner et al., 1996).

Association with a variety of environmental risks has been noted, the most important being obstetric adversity, and adverse parent–child relationships (Woodward et al., 1998; Taylor et al., 1991; Breslau et al., 1996; Whitaker et al., 1997).

### 2.4. Current treatment

There is some evidence of efficacy for symptoms of hyperactivity, impulsivity and inattentiveness with tricyclic antidepressants, in particular desipramine (Pliszka, 1987; Biederman et al., 1989), and positive placebo controlled trials have been completed with atomoxetine (Michelson et al., 2001, 2002). The psychostimulant methyl phenidate in its various formulations is currently the first choice of treatment. The evidence for their efficacy in the treatment of ADHD in children aged between 5 and 15 years is based on the many controlled trials showing clinically meaningful benefit in about 80% of the patients. Although it has been shown that efficacy persists if treatment is maintained for 1 year or longer (Gillberg et al., 1997), reliable data on eventual outcome from very long-term follow-up are lacking.

There is considerable variation between European countries in the acceptance and place of stimulant medication in the treatment of ADHD. This may be due to concerns about the potential for abuse with psychostimulants and their perceived overprescription. These concerns may have led to a tendency towards the underdiagnosis of ADHD in Europe. In the US, a rigorous treatment programme with medication is the first line of treatment supplemented, or followed by, psychosocial interventions or behavioural modification programmes.

## 3. Diagnostic criteria

Controlled studies to establish efficacy of treatments for ADHD should use internationally recognized diagnostic criteria. The most widely used classification systems, the Diagnostic Statistical Manual of the American Psychiatric Association and the International Classification of Disease of the World Health Organization, both include definitions of hyperactivity disorders, ADHD in DSM-IV and hyperkinetic disorders in ICD-10, which are defined by a very similar list of items (American Psychiatric Association, 1994; World Health Organisation, 1992).

DSM-IV lists 18 symptoms/behaviours (Tables 1 and 2)

Table 1
Symptom domains for ADHD/HKD in DSM-IV and ICD-10

| Inattention | Hyperactivity | Impulsivity |
|---|---|---|
| Fails to attend to details | Fidgets with hands or feet | Talks excessively (ICD-10) |
| Difficulty sustaining attention | Leaves seat in classroom | Blurts out answers to questions |
| Does not seem to listen | Runs about or climbs | Difficulty waiting turn |
| Fails to finish | Difficulty playing quietly | Interrupts or intrudes on others |
| Difficulty organizing tasks | Motor excess/'on the go' | |
| Avoids sustained effort | Talks excessively (DSM-IV) | |
| Loses things | | |
| Distracted by extraneous stimuli | | |
| Forgetful | | |

Table 2
Definition of ADHD in DSM-IV

| | |
|---|---|
| A. | Either six (or more) symptoms of inattention or six (or more) symptoms of hyperactivity/impulsivity that have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level |
| B. | Some inattentive or hyperactive/impulsive symptoms that caused impairment were present before age 7 years |
| C. | Some impairment from the symptoms is present in two or more settings (e.g. at school or work, and at home) |
| D. | There must be clear evidence of clinically significant impairment in social, academic, or occupational functions |
| E. | The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder, and are not better accounted for by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, or a personality disorder) |

covering three dimensions: inattention, hyperactivity, and impulsivity and at least six symptoms are required, either from the inattention, or from the hyperactivity/impulsivity dimensions. Three subtypes of ADHD are recognized: inattentive type having at least six inattention symptoms, hyperactive/impulsive type having at least six hyperactivity and/or impulsivity symptoms, and combined type which meets both sets of criteria. The ADHD symptoms taken together must be impairing, in two or more settings (e.g. at school and at home) and show clinically significant impairment in social academic or occupational functioning. The symptoms must have been present for at least 6 months.

Hyperkinetic Disorder (HKD) in ICD-10 is based on an almost identical list of 18 symptoms as in DSM-IV but the diagnosis differs in requiring the presence of both inattention (at least six out of nine symptoms), hyperactivity (at least three out of five symptoms) and impulsivity (at least one out of four symptoms). The main subdivision is between HKD and Hyperkinetic Conduct Disorder, the latter defining a category of HKD plus conduct disorder.

In population-based studies, the inattentive subtype comprises about 50% of all ADHD cases but in clinically referred children the DSM-IV combined subtype of ADHD is diagnosed more often than the inattentive or hyperactive/impulsive type. ICD-10 HKD can be considered a more strictly defined subset of ADHD combined type with a lower prevalence at school age.

Both DSM-IV and ICD-10 classifications are valid though neither is perfect. The presence of symptoms and behaviours and the impairment is not operationalised, and the definitions which typically apply to 6–12 year olds are not adjusted for developmental stage.

Almost all medication trials using stimulants have included subjects that were diagnosed according to the criteria of DSM-IV or its predecessors DSM-III-R and DSM-III. Since more placebo-controlled studies have been carried out using the DSM criteria on the basis of current knowledge, these criteria may be preferred for clinical trials.

Ideally, patients would be recruited using stratified randomisation by subtypes in order to achieve a trial sample representative of the clinical population. A secondary analysis of stratified subgroups can be planned a priori to investigate, for example, possible differential drug effects, or time of response effects.

## 4. Establishing a diagnosis

The diagnosis of ADHD should be established by an experienced clinician and should be based on a comprehensive evaluation in a clinical interview. This evaluation will also be informed by additional information obtained from external informants, for example the parents or other family members, and teachers.

While the diagnosis may be established by a clinical interview with a flexible approach it is recommended that an internationally recognized, structured or semi-structured interview schedule be used to achieve standardization and a comprehensive coverage of potential comorbid disorders.

Recommended instruments include the Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer et al., 2000) and Diagnostic Interview for Children and Adolescents (DICA) (Reich, 2000). These are respondent-based structured interview schedules that can also be administered by lay interviewers to capture most psychiatric diagnoses occurring in children and adolescents using DSM-IV and ICD-10 criteria though the diagnosis should be established by an experienced clinician. The Schedule for Affective Disorders and Schizophrenia for School-age Children (K-SADS) (Ambrosini, 2000; Kaufman et al., 1997) and Child and Adolescent Psychiatric Assessment (CAPA) (Angold and Costello, 2000) are interviewer-based schedules that should be administered by clinicians who have received specific training.

## 5. Patient sample

### *5.1. Age*

The population to be investigated in efficacy studies

should be precisely defined and full demographics recorded. The diagnosis is difficult to establish in children below the age of 6 years but studies should include the full age range from 6 to 18 years. Over this age span in development, the presentation of the disorder tends to change but there is no current evidence that separate studies in different age groups are necessary. However, the full age range should be included in the study and an analysis stratified by age planned prospectively.

### *5.2. IQ*

Low IQ may increase the likelihood of the diagnosis of ADHD but does not appear to affect the outcome. It is preferable that inclusion criteria allow for a representation of the whole range. It may be difficult to obtain reliable assessments in children with an IQ below 75 and a minimum IQ entry level should therefore be set.

### *5.3. Severity*

In general, in studies of efficacy of treatment of psychiatric disorders, patients included are required to reach a minimum level of severity of the disorder, as it is in this group that differences between placebo and active drug are more readily established. There have been too few studies in ADHD to be able to recommend specific severity criteria and some of those that have been applied in studies lack supportive psychometric data.

A cut-off of one standard deviation above the mean score on the ADHD-DSM-IV symptom rating scale (DuPaul, 1991) has been used to define the minimum entry score in some studies. Other scales that might be considered are the inattention scales of the Child Behavior Checklist (CBCL) and Teacher Report Form (TRF) (Achenbach, 1991a–c) for which norms are available in most countries, and the revised Conners questionnaire (Conners, 1996) for which norms are available only in the USA. A minimum severity level on a disorder specific scale is preferred since a global scale such as a minimum severity defined on the Clinical Global Impression (CGI) (NIMH, 1985) or the Children's General Adaptation Scale (CGAS) (Shaffer et al., 1983) might include the range of psychiatric comorbidity rather than just ADHD.

In efficacy studies in ADHD, the selection of the minimum severity criterion for inclusion in the studies must be justified and defined in advance. It should be a measure of the severity of ADHD rather than related to comorbid disorders. The minimum severity score should be sufficient for it to be likely that a drug placebo difference will be identified. This is normally equivalent to at least moderate severity.

## 6. Comorbidity

ADHD occurs in a pure form in only a minority of cases. Mostly the disorder will be diagnosed in the context of various comorbid psychiatric disorders. Some of the more common comorbidities include depressive disorders, anxiety disorders, oppositional defiant and conduct disorder, bipolar disorder and substance abuse.

The initial studies to test the efficacy of a compound in treating ADHD should preferably be carried out in a population without significant comorbidity. This provides the clearest test of whether a treatment has a specific direct and independent therapeutic effect on the condition. It is particularly important if a potential treatment under investigation for efficacy in ADHD has established efficacy in other disorders such as major depressive disorder or an anxiety disorder. There is sometimes insufficient data concerning the efficacy of particular treatments in childhood or adolescent depressive disorder but studies investigating ADHD that include subjects with marked depressive symptoms, even if stratified in the analysis, belong to a later stage in the trial programme.

Recruitment to studies would be impaired if life time comorbidity were rigidly excluded but excluding current comorbid diagnoses is generally not a practical problem. It is recommended that any subjects with current, or a history in the last 6 months of, major depressive disorder, post traumatic stress disorder, and obsessive compulsive disorder should be excluded from studies. The severity of subsyndromal symptoms of these disorders should be controlled. A history of psychosis or bipolar disorder should also be excluded.

Conduct disorder is a common comorbidity with ADHD but in studies in ADHD, comorbid conduct disorder should be restricted as far as possible in at least one study in order that efficacy in ADHD itself can be established. In study populations that include patients with conduct disorder, strategies will be needed for analysis of efficacy with and without comorbidity.

Generalised anxiety disorder (GAD) is a particular problem. In contrast to adults, the diagnosis of GAD in children can be triggered by a single anxiety symptom. Since the core symptoms of ADHD such as lack of concentration, mind going blank, may be thought of as anxiety symptoms there is the potential for serious confusion. The symptoms that are part of ADHD should not be counted towards the diagnosis of comorbid GAD, which should depend on other anxiety symptoms.

The diagnosis of ADHD is based on information from the child/adolescent, parents, and/or teachers but the diagnosis of comorbid psychiatric disorder should be made by an experienced trained physician.

## 7. Severity scales

Scales that measure symptomatology, scales that measure the global severity, and scales that measure disturbance in function have all been used. Other supportive

criteria may also be useful such as the need for additional therapy, participation in social activities, school performance, family functioning, etc.

Achieving interrater reliability is a problem with scales applied by parents and teachers but a number of severity scales that can be completed by parents and teachers have been used successfully to measure response to stimulant medication in placebo-controlled studies.

These include the ADHD-DSM-IV rating scale which rates the 18 symptoms of the DSM-IV definition of ADHD on a four-point scale from 'never' to 'always', and a number of related scales (DuPaul, 1991). The ADHD-DSM-IV rating scales may also be completed by the investigator on the basis of information provided by parents and teachers. Various forms of the Conners scales (Conners, 1996) have also been used.

The SNAP is a clinician rated scale that is very similar to the DSM-IV rating scale based on the 18 symptoms of the DSM-IV definition of ADHD and integrates information from teacher and/or parent; this scale has been used successfully (The MTA Cooperative Group, 1999).

Global scales such as the CGI-severity and CGI-improvement scales completed by the investigator have been used successfully in efficacy studies (Pliszka et al., 2000). These scales could be used globally in the presence of only limited comorbidity or may be anchored to ADHD.

The scales used to measure the severity of ADHD in efficacy studies need to be internationally recognized, robust, validated to measure the severity, cover the core symptoms, and be sensitive to change with treatment. Where needed, adequate translations should be available and cultural differences addressed. There are insufficient data available to form the basis for a firm recommendation for specific scales. The choice of pivotal scale for assessing efficacy should be justified and identified in advance.

## 8. Dose

The dosage regime recommended for treatment needs to be justified and should be based on demonstrable efficacy of the drug compared with placebo. The methodology for establishing the dose in dose–response studies is well developed. The ideal design is to compare the efficacy of fixed doses of the drug, adjusted for the individual in relation to body weight or similar relevant parameters compared to placebo. An initial blinded fixed titration period, based on the properties of the drug, may be used at the start of the study to avoid an abrupt challenge with a drug with untoward side effects. Pharmacokinetic studies should have been conducted to help identify possible target doses. Data are needed to support the dosage in adolescents and children separately. The few data available suggest that lower weight adjusted doses of medication are needed as children age through adolescence (Findling et al., 2001).

## 9. Choice of control treatment

The best evidence of efficacy is derived from positive results comparing monotherapy with placebo in careful studies using the well established double-blind randomized designs in both short-term and long-term treatment separately. Such designs have been able to establish the efficacy of current treatments of ADHD at least in short-term treatment. Evidence of the efficacy of a potential treatment is normally accepted if there are at least two positive placebo-controlled studies one of which must be in short-term treatment.

The use of a comparator treatment in a placebo-controlled study is useful in that it provides some measure of the clinical relevance of the response seen in the study as well as providing confirmation that the population studied is assay sensitive and the study design used is appropriate. The comparator chosen and the dose employed will need to be justified on the basis of relevant placebo-controlled studies. Confidence in the positive placebo-controlled study will be enhanced using the preferred three-way design where the potential treatment, a comparator treatment and placebo are used. It is recommended that at least one such study should be conducted to establish efficacy. Stimulant medication may be used as an active comparator in a pivotal placebo-controlled study since it is licensed for the treatment of ADHD in several European countries.

## 10. Clinically relevant changes

It is important to establish not merely that the treatment is better than placebo on the pivotal severity scale but also that the change seen is clinically relevant. Several definitions of clinical relevance have been used in studies of other disorders but in ADHD, there is no broadly accepted definition of a clinically relevant response. Remission criteria have also not been established for ADHD and using a normalised population as a reference may not be appropriate.

In other conditions, a reduction of 50% in a pivotal severity scale score has been frequently used as a criterion to define responders. In ADHD, however, a reduction of 30% is likely to equate to a Clinical Global Impression of 1 (very much improved) or 2 (much improved).

Some studies have used a mean score of 2 on the ADHD-DSM-IV rating scale as a definition of responder. A mean score of 2 reflects that symptoms occur on average only 'sometimes'. More research is needed in this area, however.

As with other conditions the definition of responder needs to be specified a priori in the study.

The clinician's global assessment provides a measure of overall response separate from the scale scores but the assessment needs to be specific to the disorder. A CGI improvement measure of 1 ('very much improved') or 2

('much improved') has been used as a clinically relevant measure of response in some studies.

Because the symptoms are related to events seen in daily living and the pivotal scales are related to clinically relevant observed behaviour, the better scales provide a direct measure of clinical relevance. A significant difference between the treatment and placebo provides some evidence that the treatment has a clinically relevant effect.

## 11. Duration of short-term studies

The duration of placebo-controlled studies in ADHD needs to be sufficient to establish clear-cut efficacy but short enough to justify treatment with placebo. The length will be determined by when a significant difference from placebo can be reliably expected, based on placebo-controlled studies in the literature, using the intention to treat analysis. In the studies that investigated stimulant medication, positive results were often seen from 2 weeks onwards. Typically, short-term medication studies in ADHD have had a duration of 4–6 weeks. It is recommended that short-term studies should have a duration of 6 weeks.

## 12. Size of study

The study should be powered at least to establish efficacy compared to placebo on the predefined pivotal scale in an ITT population. Statistical methods for estimating missing values due to dropouts will need to be prespecified. It is also recommended that the study has sufficient power to establish efficacy on the prespecified responder criteria.

## 13. Duration of long-term studies

ADHD is, for most patients, a chronic persisting disorder that predisposes to life-long handicaps in social, adaptive and occupational functioning. In Europe, the Committee for Proprietary Medicinal Products (CPMP) recommends that long-term efficacy be established separately in chronic disorders where treatment is likely to be maintained over many years. In most chronic disorders, demonstration of efficacy is normally required over a 6-month period. Studies will therefore be needed to establish that the treatments are not merely effective in acute treatment but that they continue to be effective in long-term treatment.

Preliminary data indicate that discontinuation of treatment is associated with relapse in 95% of patients over a 2-year period. This suggests that placebo-controlled studies may demonstrate long-term efficacy of treatments for ADHD. The usual design is to take responders to acute treatment and re-randomise soon after response is achieved to drug or placebo and establish a lower relapse rate on drug than placebo. However, this design is compromised if the treatment is associated with discontinuation symptoms which either lead to relapse or are confused with relapse. This risk will need to be quantified.

An alternative design is to investigate treatment in a placebo-controlled study over 6 months, which will establish a different aspect of long-term treatment. There are too few data to be able to recommend specific response and relapse criteria. Recommendations for the length of study can also only be provisional. The exact length of the study and the point of discontinuation would be the choice of the study sponsor and need to be justified but a 6-month placebo-controlled treatment period is recommended.

## 14. Safety

The method of reporting of adverse effects, whether by means of spontaneous or elicited reports, questionnaires or other means, must be clearly stated and be appropriate for the age groups under study. Age appropriate normal laboratory values and clinical measurements should be used in adverse event reporting.

At least some studies should be designed in such a way that discontinuation symptoms and withdrawal events can be assessed in order to establish and quantify the risk and duration of any discontinuation symptoms and withdrawal phenomena after both short- and long-term treatment.

Medication may have effects on physical and cognitive growth and development, and the adverse event profile may differ in children and adolescents compared to adults. The dynamic process of growth and development may not manifest an adverse event acutely but at a later stage of growth and maturation. Preclinical safety data including appropriate neurobiological and behavioural studies relating to development, maturation, and growth in animals should be obtained prior to performing clinical trials in children. Particular clinical or laboratory safety information may be required on the basis of preclinical findings. Postmarketing long-term studies would be helpful in producing the documentation on safety in children that is currently limited.

## 15. Conclusion

There have been sufficient studies carried out in ADHD to establish that the usual placebo-controlled design is able to produce scientifically rigorous evidence of efficacy. Placebo-controlled studies are clearly feasible and necessary to provide acceptable evidence of efficacy.

ADHD is a serious and common disorder where appropriate treatment is able to improve the condition and reduce suffering. These guidelines summarise the available

experience and indicate how studies to establish the efficacy of new treatments may be conducted to document both the efficacy and safety and allow a proper risk benefit assessment of a treatment to be made.

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