National Institute for Clinical Excellence

Health Technology Appraisal

Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents including review of existing guidance number 13 (Guidance on the Use of Methylphenidate [Ritalin, Equasym] for Attention Deficit/Hyperactivity Disorder [ADHD] in childhood)

Scope

**Objective:** To assess the clinical and cost effectiveness of methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents relative to other treatments in the NHS, and to update if and as necessary, guidance on the use of methylphenidate in ADHD issued to the NHS in England and Wales in October 2000.

The Institute issued guidance on the use of methylphenidate in October 2000. The date set for revision of the guidance to the NHS was August 2003. The review date was set on the basis of the Institute’s judgement of the pace of change in the evidence base at the time the original guidance was issued. Since the guidance was issued, new formulations of methylphenidate have been introduced, and other new drugs for the condition are in development. The scope for this appraisal has therefore been broadened to encompass newer products. It will also include dexamfetamine (an older drug licensed for the treatment of ADHD in children aged 3 years or above) so that the clinical and cost effectiveness of the full range of drug treatments for the condition is appraised.

The original guidance will remain in place unless and until any new guidance has been issued.

**Background:** ADHD is defined by the ‘core’ signs of inattention, hyperactivity and impulsiveness. There are three subtypes of ADHD: ‘combined type’ with signs of inattention and hyperactivity/impulsivity; ‘predominantly inattentive type’ with inattention but not hyperactivity/impulsivity; and ‘predominantly hyperactive-impulsive type’ with hyperactivity/impulsivity but not inattention.

Estimates of the prevalence of the disorders vary widely and depend upon a number of factors including the diagnostic criteria used. The estimated prevalence for ADHD school-aged children is between 2% and 5% depending on whether Diagnostic and Statistical Manual (DSM-IV) or International...
Classification of Diseases (ICD-10) criteria are used. The male to female ratio is about 4:1.

The consequences of severe ADHD can be serious for the child, family and society; children can develop poor self-esteem, emotional and social problems and their educational attainment is frequently severely impaired.

**The technologies:** the amphetamines and the related drug methylphenidate are central nervous stimulants (indirectly acting sympathomimetics). They have been used in the treatment of ADHD for many years. Atomoxetine is a newer drug, which acts by selectively inhibiting norepinephrine (noradrenaline) reuptake.

**Methylphenidate hydrochloride** (Concerta XL, Janssen-Cilag; Equasym, Celltech; Ritalin, Cephalon; Tranquilin, Link) is licensed as part of a comprehensive treatment programme for ADHD in children aged six and above, when remedial measures alone prove insufficient. A modified release formulation, for use once a day, was launched in the UK in 2002 (Concerta XL) and another is likely to be launched within the timeframe of this appraisal (Equasym XL).

**Dexamfetamine sulphate** (Dexedrine, Celltech) is licensed for the treatment of children with refractory hyperkinetic states under the supervision of a physician specialising in child psychiatry.

**Atomoxetine** is licensed in the USA for the treatment of ADHD in children over 6, adolescents and adults. This drug has not yet been granted a marketing authorisation in the UK.

| Intervention(s)          | Methylphenidate hydrochloride  
|                         | Dexamfetamine  
|                         | Atomoxetine  
| Population(s)           | Children and adolescents diagnosed with ADHD.  
| Current standard treatments (comparators) | Current standard pharmacological treatments for ADHD are the psychostimulants (methylphenidate and dexamfetamine). These may or may not form part of a multimodal treatment programme involving psychological/behavioural interventions. Relevant comparators in this appraisal are placebo/usual care and either of the psychostimulant drugs licensed for this indication.  
| Other considerations:    | Outcomes should include  
|                         | • incidence and severity of core symptoms  
|                         | • incidence and severity of problem behaviours  

National Institute for Clinical Excellence
Invitation to participate in the appraisal of methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents including review of existing guidance number 13
Issue Date: August 2003
### Educational Performance
- Measures of depression and/or anxiety
- Measures of conduct/oppositional-disorder-related outcomes
- Adverse events
- Quality of life

If the evidence allows, consideration should be given to the following:
- The use of pharmacological treatments in the presence of co-morbid disorders.
- The effect of pharmacological treatments on quality of life of other members of the family.
- The optimal duration of treatment before attempting discontinuation and reassessment.

### Current NICE Guidance (methylphenidate in ADHD)

- Methylphenidate is recommended for use as part of a comprehensive treatment programme for children with a diagnosis of severe Attention Deficit/Hyperactivity Disorder (ADHD). 'Severe ADHD' is broadly similar to a diagnosis of Hyperkinetic Disorder (HKD), although in some cases treatment may be appropriate for children and adolescents who do not fit the diagnostic criteria for HKD but are experiencing severe problems due to inattention or hyperactivity/impulsiveness.
- Methylphenidate is not currently licensed for children under the age of six or for children with marked anxiety, agitation or tension; symptoms or family history of tics or Tourette's syndrome; hyperthyroidism; severe angina or cardiac arrhythmia; glaucoma; or thyrotoxicosis. Caution is required in the prescribing of methylphenidate for children and young people with epilepsy, psychotic disorders, or a history of drug or alcohol dependence.
- Diagnosis should be based on a timely, comprehensive assessment conducted by a child/adolescent psychiatrist or a paediatrician with expertise in ADHD. It should also involve children, parents and carers and the child's school, and take into account cultural factors in the child's environment. Multidisciplinary assessment, which may include educational or clinical psychologists and social workers, is advisable for children who present with indications of significant comorbidity.
- Treatment with methylphenidate should only be initiated by child and adolescent psychiatrists or paediatricians with expertise in ADHD, but continued prescribing and monitoring may be performed by general practitioners, under shared care arrangements with specialists.
- Careful titration is required to determine the optimal dose level and timing. The drug should be...
<table>
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<th>Discontinued if improvement of symptoms is not observed after appropriate dose adjustment.</th>
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<td>• A comprehensive treatment programme should involve advice and support to parents and teachers, and could, but does not need to, include specific psychological treatment (such as behavioural therapy). While this wider service is desirable, any shortfall in its provision should not be used as a reason for delaying the appropriate use of medication.</td>
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<td>• Children on methylphenidate therapy should receive regular monitoring. When improvement has occurred and the child's condition is stable, treatment can be discontinued at intervals, under careful specialist supervision, in order to assess both the child's progress and the need for continuation of therapy.</td>
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<td>• This guidance relates only to children and adolescents with ADHD.</td>
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1 The Department of Health remit to the Institute is “To appraise the clinical and cost effectiveness of methylphenidate, atomoxetine and dexamfetamine for Attention Deficit Hyperactivity Disorder (ADHD), within their licensed indications for children and adolescents. This will include a review of guidance originally issued for methylphenidate only” ( Guidance on the use of Methylphenidate (Ritalin, Equasym) for Attention Deficit/Hyperactivity disorder [ADHD] in childhood [No.13, October 2000]. NICE: London)