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Amfetamine for attention deficit hyperactivity disorder in people with intellectual disabilities (Review)

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[Intervention Review]

Amfetamine for attention deficit hyperactivity disorder in people with intellectual disabilities

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ABSTRACT

Background

Attention-deficit hyperactivity disorder (ADHD) is increasingly recognised as occurring in people with intellectual disability (ID), although treatment of ADHD in this population has not been tested widely. Amfetamine has been used to treat ADHD in people with and without ID, although the evidence for its efficacy in people with ID is unclear.

Objectives

To examine the effectiveness of amfetamine for the treatment of attention deficit hyperactivity disorder in people with intellectual disabilities.

Search methods

MEDLINE, PsycINFO, EMBASE, AMED, ISI Web of Science and WorldCat Dissertations were searched using an extensive list of synonyms for ADHD and ID. CENTRAL, Current Controlled Trials meta-register (mRCT), CenterWatch, NHS National Research Register, clinicaltrials.gov were searched in August 2007. Pharmaceutical companies and experts in the field were contacted. Reference lists of review articles were examined and citation searches were performed in ISI Web of Knowledge.

Selection criteria

All randomised controlled studies, both published and unpublished, in any language, in which children or adults with ADHD and ID were treated with amfetamine.

Data collection and analysis

Data were extracted independently by two reviewers using a standardised extraction sheet. Risk of bias was assessed by two authors using a standardised framework. Meta-analyses were planned but were not performed due to a lack of suitable studies.

Main results

Only one study was suitable for inclusion. This was a cross-over study in 15 children with ADHD, ID and Fragile X syndrome. Duration of treatment was only one week. No significant difference was reported between amfetamine and placebo for any of the ADHD measures, but significantly more side effects were reported while taking amfetamine, mainly mood lability and irritability.

Authors' conclusions

There is very little evidence for the effectiveness of amfetamine for ADHD in people with ID . Prescribing in this population is based on extrapolation of research in people without ID. More research into effectiveness and tolerability is urgently needed.

PLAIN LANGUAGE SUMMARY

Amfetamine for ADHD in people with intellectual disabilities

Some people with intellectual disability (ID; also known as mental retardation) may also have attention-deficit hyperactivity disorder (ADHD). Most of the research into treatment of ADHD with amfetamine has been performed in people who do not have ID. The objective of this review was to assess whether amfetamine is effective in treating ADHD in people who also have an intellectual disability. We found only one study, which examined this question in a small group of participants. This did not find an effect, but we do not think this is enough evidence to draw conclusions about whether or not amfetamine is effective. More research in this area is urgently needed.

BACKGROUND

Description of the condition

Attention-deficit hyperactivity disorder is a developmental disorder usually diagnosed in childhood and characterised by symptoms of inattention, hyperactivity and impulsivity which are present in two or more settings and associated with significant functional impairment (APA 2000APA 2000). It is one of the most common psychiatric disorders in childhood, with an estimated worldwide prevalence of 5.29% in children (Polanczyk 2007). Intellectual disability (ID), also referred to as mental retardation, is defined as subaverage general intellectual functioning (IQ below 70) associated with significant impairment or deficits of adaptive functioning (APA 2000; WHO 1992). ID affects approximately 3% of the general population. Although symptoms of inattention, hyperactivity and impulsivity are frequently observed in children with ID, these have traditionally been considered by clinicians and researchers to be consistent with delayed developmental age. The current diagnostic criteria for ADHD emphasise that symptoms must be inappropriate for the developmental level, which may discourage making the diagnosis in the presence of ID. Nevertheless, there is increasing evidence to support the validity and clinical utility of making a diagnosis of ADHD in people with ID (Antshel 2006; Dekker 2003; Hastings 2005).

Estimates of prevalence of ADHD in populations with ID vary; one US study suggested that, at the very least, 15% of individuals with severe and profound levels of ID may meet diagnostic criteria for ADHD, even when mental age has been taken into account (Fox 1998). Rates of ADHD in children and adults with ID vary from 4- 42% depending on the severity of ID and the context in which each study was conducted. Estimates of prevalence are higher from studies which only measure target symptoms, such as hyperactivity, poor concentration and impulsivity (Dekker 2003Dekker 2003; Fox 1998; Hardan 1997; Kadesjo 2001; Rojan 1993; Strømme 2000).

When compared to peers with ADHD and normal intellectual ability, children with ADHD and ID have similar, if not heightened, risk for persistence of ADHD from childhood into adolescence, are more likely to have comorbid separation anxiety disorder and behavioural disturbance in adolescence, and have more restrictive educational placements (Aman 1993; Aman 2002). ADHD is associated with challenging behaviour in people with ID. A follow-up study of 51 people with ADHD and moderate to borderline ID found that many continued to have behavioural problems and take prescribed medication at 1 to 5 years follow-up (Handen 1997). Bullying and violent behaviour have been found to be associated with hyperactivity in adolescents with ID (Reiter 2007) and a study of medication for disruptive behaviour in children with ID reported high rates of co-morbid ADHD (Aman 2002). Thus, treatment of ADHD may have a role in the management of challenging behaviour in this group. The comorbidities present in people with ID represent a further diagnostic challenge and may influence both the types of treatment offered and its efficacy.

Description of the intervention

Amfetamine is a psychostimulant drug which binds to the dopamine (DA) transporter in the brain, blocking the reuptake of DA, and directly stimulates further DA release. This results in raised resting extracellular DA levels, but reduced pulsatile DA release (Seeman 1998Seeman 1998). It is thought that the behavioural effects result from modulation of DA in the attention and response inhibition circuits of the prefrontal cortex (Arnsten 2006)

Why it is important to do this review

There are reports which suggest that amfetamine may be effective in people with ID and comorbid ADHD (Jou 2004). However, clinical commentators have observed that people with ID and ADHD tend to show a lesser response to stimulant medication and to be more sensitive to its side effects (Aman 1996). Accordingly, guidelines for prescribing in ID suggest a "start low, go slow" approach - i.e. use lower initial doses and increase cautiously (Nutt 2006). It is possibly for these reasons that treatment of ADHD with amfetamine appears to be uncommon in people with ID (Lott 2004). Furthermore, British learning disability psychiatrists report a tendency to prescribe antipsychotics rather than stimulants in this group, in part due to uncertainty about efficacy of amfetamine (Bramble 1999). This review may help examine whether or not such uncertainties are justified.

OBJECTIVES

To examine the effectiveness of amfetamine for the treatment of attention deficit hyperactivity disorder in people with intellectual disabilities.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled studies in which patients with a diagnosis of ID and ADHD are treated with amfetamine were included. Studies which made use of a crossover design were included. Studies which also involved a psychosocial intervention, such as psycho-education or behaviour therapy, were considered for inclusion, provided that any such intervention was identical between the active and placebo medication groups.

Types of participants

Children, adolescents or adults with a diagnosis of Intellectual Disability and Attention Deficit Hyperactivity Disorder. The diagnosis of ID may be made on the basis of psychometric testing or clinical diagnosis. All categories of ID - mild, moderate, severe and profound - were considered. The diagnosis of ADHD must be made according to specified diagnostic criteria, e.g. ICD-10 (WHO 1992), DSM-III (APA 1987), DSM-IV (APA 2000) or equivalent.

Studies in which participants have a comorbid diagnosis of Pervasive Developmental Disorder or Autism, or in which participants have diagnosed congenital syndromes were considered for inclusion. Studies were excluded if participants have uncontrolled epilepsy, comorbid psychotic illness or a history of head injury.

Types of interventions

Trials were included if they investigated treatment with amfetamine - either dexamfetamine or a mixture of enantiomers such as mixed amfetamine salts - compared to medication placebo. Treatment could be delivered in any setting, such as home, hospital or residential care.

Types of outcome measures

Primary outcomes

Change in symptoms of attention deficit and hyperactivity as measured by a validated scale rated by parents, teachers, carers, assessors or clinicians e.g. Revised Conners Parent and Teacher Rating Scales (Goyette 1978) or Barkley Scale (Barkley 1990).

Secondary outcomes

We also planned to consider the following secondary outcomes, if available:

1. Response to treatment as a dichotomous outcome - this may be defined by the study e.g. as a percentage reduction in symptom scale scores, or by a rating of improvement on a Clinical Global Impression (NIMH 1985) scale;

2. Cognitive ability - as measured by standardised psychometric tests of IQ, attention and working memory;

3. General level of impairment -as measured by a scale such as a Karnofsky Scale (Karnofsky 1948), Global Assessment of Functioning (APA 2000), Children's Global Assessment Scale (Shaffer 1983) or Clinical Global Impression (NIMH 1985) scales;

4. General level of functioning -as measured by a standardised activities of daily living scale e.g. Barthel Index (Collin 1988; Mahoney 1965), Functional Status Questionnaire (Cleary 2000; Jette 1986);

5. Challenging behaviour - as measured by a standardised scale such as the Aberrant Behaviour Checklist (Aman 1985) or the Challenging Behaviour Checklist (Harris 1990);

6. Substance abuse, as measured by estimates of frequency and amount of drug or alcohol use;

7. Psychiatric morbidity. Instruments that have been developed to assess different dimensions of psychopathology in ID people, would be preferred if available e.g. the Developmental Behavior Checklist (Einfeld 1995); the Psychiatric Assessment Schedule for Adults with Developmental Disabilities (Moss 1996); or the Psychopathology Instrument for Mentally Retarded Adults (Matson 1984). Other validated rating scales, e.g. the Children's Depression Inventory (CDI, Kovacs 1992), Beck Depression Inventory (Beck 1979), Montgomery-Åsberg Depression Rating Scale (Montgomery 1979), Beck Anxiety Inventory (Beck 1988), Hamilton Depression Rating Scale (Hamilton 1960), Hamilton Anxiety Rating Scale (Hamilton 1959), Brief Psychiatric Rating Scale (Ventura 1993), the Strengths and Difficulties Questionnaire (Goodman 1997), the SCL-90 Symptom Checklist (Derogatis 1973), were considered;

8. Carer burden - as measured by a validated scale e.g. Montgomery Borgotta Caregiver Burden Scale (Montgomery 1985);

9. Side effects - either dichotomous outcomes such as hypertension, growth retardation, tics, seizures, cardiac arrhythmias/ECG abnormalities or as measured using a side effect symptom checklist such as the Barkley Side Effect Scale (Barkley 2006) or the Fawcett side effect scale (Fawcett 1987);

10. Acceptability of the treatment - as rated by patients, parents or carers;

11. Drop-out rates - classified by reasons for withdrawal.

NOTE: A number of instruments have been developed to assess different dimensions of psychopathology in people with ID; however, many psychiatric scales which were not developed for use with people with ID appear in studies undertaken within this population. Where possible, we selected the former for analyses in this review and considered the appropriateness of outcome measures in the context of available research.

Search methods for identification of studies

The search strategy aimed to identify all randomised controlled trials of medication for ADHD in people with ID, from which studies investigating amfetamine were considered for this review.

Electronic searches

All searches were conducted in August 2007.

1) MEDLINE, PsycINFO, EMBASE and AMED were searched using the Cochrane Collaboration Highly Sensitive Search Strategy (Higgins 2006) plus additional terms for ADHD, ID and medication (Table 1);

2) ISI Web of Science and WorldCat Dissertations were searched using the search strategy described in Table 2 and Table 3.

Searching other resources

Trials Registers

CENTRAL, Current Controlled Trials meta-register (mRCT), CenterWatch, NHS National Research Register, clinicaltrials.gov were searched using the search strategies described in Table 4, Table 5 and Table 6.

Pharmaceutical Databases

Pharmaceutical companies were contacted and asked to give details of published and unpublished trials.

Personal Contact

Experts in the field were contacted and asked to identify other published and unpublished trials.

Citations

a) The reference lists of retrieved studies and relevant review articles were inspected to identify any further studies

b) For each included study, a citation search was performed in ISI Web of Knowledge to identify any later studies that may have cited it.

Timeline

This is the first published version of this review. The search will be repeated within three years of publication and the review updated accordingly.

Data collection and analysis

No meta-analysis was possible in this review. Please see Table 7 for plans for analysis for future updates of this review.

Selection of studies

Abstracts of potentially relevant studies were inspected by at least two of the reviewers and full articles requested if they appeared to be relevant. If unpublished trials were identified, the co-ordinators were contacted to request data. Full papers were inspected by at least two reviewers using a standardised assessment sheet to assess whether studies fulfil criteria for inclusion. Any disagreements were resolved by discussion among all the authors.

Data extraction and management

A standardised extraction sheet was designed to extract data from included trials independently by two authors. The study authors were contacted to request missing data or clarifications where necessary.

Assessment of risk of bias in included studies

Risk of bias was assessed independently by two review authors according to criteria specified in the Cochrane Collaboration Handbook (Higgins 2008). Review authors independently assessed the risk of bias within each included study based on the following five domains with ratings of 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias):

Sequence generation
Description: the method used to generate the allocation sequence was examined so as to assess whether it should have produced comparable groups; review authors' judgment: was the randomisation sequence adequately generated?

Allocation concealment
Description: the method used to conceal allocation sequence was examined to assess whether intervention schedules could have been foreseen in advance of, or during, recruitment; review authors' judgment: was allocation adequately concealed?

Blinding
Description: any measures taken to blind participants, personnel and outcome assessors to knowledge of which intervention a given participant might have received; review authors' judgment: was knowledge of the allocated intervention adequately prevented during the study?

Incomplete outcome data
Description: data on attrition and exclusions was extracted, including the numbers involved (compared with total randomized), reasons for attrition/exclusion, and any re-inclusions in analyses performed by review authors; review authors' judgment: were incomplete outcome data adequately addressed?

Selective outcome reporting
Description: attempts were made to assess the possibility of selective outcome reporting by investigators, to include comparing published results to outcomes detailed in the study protocol or published methods, considering whether primary outcomes were stated *a priori* and considering whether or not commonly used outcomes reported in similar studies were reported; review authors' judgment: are reports of the study free of suggestion of selective outcome reporting?

Other sources of bias
Description: other potential sources of bias were considered. These included source of funding, competing interests, adequacy of washout period in cross-over studies and validity/reliability of outcome measures. Review authors' judgment: are reports of the study free of other sources of bias?

For the purposes of sensitivity analysis, studies were described as being overall low, moderate or high risk of bias. Disagreements between authors were resolved by discussion or the use of a third party opinion. Since standardised rating scales for the assessment of methodological quality may be more sensitive to the quality of reporting than validity of study design ((Higgins 2008) such scales were not used. If published articles did not contain sufficient detail to permit full assessment, the authors were contacted and asked to clarify the methods used.

Data synthesis

The data available for this review were not suitable for meta-analysis. The methods as described in the protocol are given in Table 7 and may be used in future updated versions of this review.

RESULTS

Description of studies

Results of the search

The initial search identified over 2,000 references. Forty-one references were considered possibly relevant and the full articles retrieved for consideration. Only one study met inclusion criteria and 40 were excluded.

Included studies

Only one study meeting inclusion criteria was identified (Hagerman 1988). This used a double-blind, randomised cross-over design with one week each of treatment with amfetamine, methylphenidate, and placebo. There were 15 participants, all of whom had fragile X syndrome diagnosed clinically and on the basis of cytogenetic testing. Mean age of participants was 7.9 years, range 3.8-11.8. The mean IQ was 58, range 29-77 with all but 3 participants having IQ<70. ADHD diagnosis was not clearly reported: parents or teachers had reported attentional problems in all participants and they were assessed with the Conners Abbreviated Parent-Teacher Questionnaire (Conners 1973), but no minimum score for inclusion was stated. Mean baseline score was 19, range 11-26. No other inclusion or exclusion criteria were stated.

Interventions were methylphenidate 0.3mg/kg every morning and midday, dextroamfetamine as Dexedrine Spansules 0.2mg/kg every morning plus a placebo capsule at midday (to mimic the methylphenidate condition), and placebo consisting of lactose powder. Each was given for one week. Outcomes were ADHD symptoms; response as judged by parents and teachers; side effects. ADHD symptoms were assessed using the Conners Abbreviated Parent-Teacher Questionnaire the ADD-H: Comprehensive Teacher Rating Scale (ACTeRS) (Ullman 1984) and a 10 minute behavioural observation. Movement was assessed using a Large Scale Integrated Sensor actometer (a device worn on the wrist which records amount of movement). Impulsivity was assessed using the delay task, in which the participant was rewarded for delaying pressing a button. Attentiveness was assessed using the vigilance task, in which the participant was instructed to press a button in response to certain numbers being

presented on a screen (Gordon 1986). Side effects were assessed using the Barkley Side Effect Scale (Barkley 1981). Although pulse and blood pressure were measured, these were not reported in the results.

Excluded studies

Thirty-eight published studies did not meet inclusion criteria. Of these, eight were not controlled (Anton 1969; Burgio 1985; Craft 1959; Geller 1981; Gittelman-Klein 1980; Hagerman 1992; Ounsted 1955; Volkmar 1985), and four were not randomised (Broomand 1967; Eaton 1977; Eisenberg 1963; Payton 1989). Participants in seven studies had neither ADHD nor ID (Barcai 1971; Comly 1971; Conners 1967; Conners 1969; Molitch 1937; Molitch 1937a, Steinberg 1971), in ten studies did not have ADHD (Berkson 1965; Craft 1959; Cutler 1940; Eaton 1977; Fish 1962; Lobb 1968; McConnell 1964; Morris 1955; Sulzbacher 1972; Volkmar 1985), and in four studies not have ID (Denhoff 1971; Faraone 2001; Faraone 2002; Zrull 1963). Two references were case reports (Moskowitz 1941; Sulzbacher 1972). One study included participants with ID and normal IQ, reporting "the Wechsler intelligence quotient ranged from 55 to 85" (Alexandris 1968). However, no median or interquartile range was reported so it was not possible to determine whether or not the majority of participants met criteria for ID. Accordingly a consensus decision was made to exclude this study from the review. Two references to studies of "stimulant medication" were in fact studies of methylphenidate (Schmidt 1982; Swanson 1991).

Two references were excluded because insufficient information was available. One letter in a journal described a series of single-case studies but did not specify which medication was used (Helsel 1989). No further information was found. One reference to a conference presentation was identified (Sprague 1967). The conference organisers were contacted but did not have records of the details.

Risk of bias in included studies

See also 'Risk of bias' table for the one included study (Hagerman 1988).

Allocation

In the one included study (Hagerman 1988) sequence generation and allocation concealment were not described; risk of bias assessed as 'unclear'.

Blinding

Patients and researchers were blind to the medications given, which were presented in identical capsules with the same dosing schedules. Blinding was assessed to be adequate and the risk of bias, low.

Incomplete outcome data

It is not clearly stated whether any patients dropped out of the study, although this appears unlikely given the brief duration of the study. Risk of bias was assessed as low.

Selective reporting

There were some concerns regarding selective outcome reporting. Data were presented only in graphs rather than in tables. Where an outcome measure showed a non-significant difference, results for subscales were presented. Blood pressure and pulse readings were not presented despite being described in the methods section of the paper. Risk of bias was assessed as high.

Other potential sources of bias

There were some concerns regarding the appropriateness of some of the outcome measures in children with ID or to detect change in symptoms. The primary outcome measure was the ACTeRS scale. This has been demonstrated to be reliable in children with ID (Miller 2004), but has poor correlation with behavioural observation in this population (Miller 2004a). Actometer recordings have been shown to be sensitive to medication response (Pfadt 1983) but may correlate poorly with report measures (Barkley 1991). The use of continuous performance tasks may not be sensitive to medication effects (Barkley 1991). It is not clear how these issues may affect the estimate of effect size, and the risk of bias is therefore assessed as unclear. In summary, the study was considered to be at high risk of bias.

Effects of interventions

The one included study only presented graphs of results. No tables or numbers were reported. The investigators were contacted and confirmed that the raw data were no long available. They did report t tests between outcome measures for placebo and amfetamine and we have summarised these results below.

ADHD Symptoms
Although positive trends were identified, no significant differences were reported between amfetamine and placebo for any measures of ADHD symptoms.

Response to treatment
Ten out of 15 participants were considered clinical responders to either methylphenidate or amfetamine, according to teacher and parent reports. The number who responded to amfetamine is not reported, though two participants were continued on amfetamine after the end of the study.

Adverse effects

Mean side effects scores were significantly higher for amfetamine compared to placebo (28.5 and 17.5 respectively; p=0.05). The most frequent complaints were mood lability and irritability.

DISCUSSION

We performed a systematic review to examine the effectiveness of amfetamine for the treatment of attention deficit hyperactivity disorder in people with intellectual disability, based on evidence from randomised controlled trials. We identified and considered 39 published papers for inclusion. Only one study met inclusion criteria.

The one RCT which met inclusion criteria for this review reported that amfetamine had no significant effect on symptoms of ADHD compared to placebo, with increased reporting of adverse effects. One would not want to generalise from a small study in any circumstances, and this particular study may not be generalisable for a number of reasons. The participants studied were children with fragile X syndrome, pathophysiology and response to medication may be different in other causes of intellectual disability. The duration of treatment was only a week, which may have been insuffieient for effects of medication to emerge. Additionally the ability of the ACTeRS scale to accurately measure

ADHD symptoms in a population with ID has been questioned. ACTeRS was found to be negatively correlated with other ADHD teacher rating measures and did not correlate significantly with observation data by teachers or teacher assistants on either the Hyperactivity or the Attention factor (Miller 2004a). Its test-retest reliability was low for the teacher ratings, ranging from r=.55 for the oppositional factor to r=.77 for the hyperactivity factor. The interrater reliability between teachers and teacher assistants was low, while there was no significant correlation for the Hyperactivity factor (Miller 2004).

The current RCT evidence does not allow conclusions to be drawn about the efficacy or the risk-benefit profile of amfetamine for the treatment of ADHD in children or adults with ID. Prescribing amfetamine in this group can be based only on non-RCT studies and extrapolation of research in people without a diagnosis of ID. As with any prescribing in this population it must be borne in mind that a significant proportion of people with ID may lack capacity to give informed consent (Arscott 1999; Wong 2000). In such cases the involvement of family members and carers should be sought in an attempt to maximise the person's capacity and provide ongoing support. Moreover the prescription of amfetamine for adults with ID should be within the framework of person centred planning (Robertson 2007).

Although emphasis is increasingly given to the inclusion of people with ID in mainstream services where appropriate (Fyson 2003), the difficulty of prescribing decisions and lack of research evidence supports the maintenance of specialist psychiatric services for this group. Challenging behaviour in ID is common and its management very resource intensive (RCPsych 2007). From a health economics perspective further research into the use of medication such as amfetamine in adults with ID and ADHD may lead to improvements in the management of a difficult to treat problem, and may influence current prescribing practice.

AUTHORS' CONCLUSIONS

Implications for practice

For patients and their families

Prescribing of amfetamine for ADHD in people with intellectual disability is based only on studies performed in people without intellectual disability. Apart from one small study in people with a genetic syndrome (fragile X), there are no studies which examine whether people with ID respond in the same way to this medication.

For clinicians

ADHD symptoms are not only more common in people with ID but they tend to be more severe and have greater stability over time (Hastings 2005). Furthermore, there is concern that such symptoms may be less responsive to medical treatment and people with ID may be more susceptible to side effects (Aman 1996). Without randomised controlled studies in this population, prescribing decisions can only be based on clinical judgement, non-RCT studies and studies in people without ID. For the reasons outlined above the difficulties in extrapolating from research in the general population are apparent.

For managers

Although service planning should aim to include people with ID in mainstream services where appropriate, managers should consider the need for access to professionals with relevant specialist prescribing experience.

Implications for research

This review has highlighted the absence of randomised controlled trials investigating the efficacy of amfetamine for the treatment of attention deficit hyperactivity disorder in people with intellectual disability. Such trials are needed urgently. In order to ensure validity of future trials, they should use outcome measures which have been specifically validated in people with intellectual disability and clearly measure and report adverse effects.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hagerman 1988

Methods	Double-blind randomised crossover trial Study length: 3 weeks
Participants	15 participants 2 female, 13 male Mean (s.d.) age: 7.9 (2.4) years Age range: 3.8 - 11.8 years Mean (s.d.) IQ: 58 (12.8) IQ range: 29 - 77 (3 have IQ >70)
Interventions	1. Dextroamfetamine as Dexedrine Spansules 0.2mg/kg every morning + placebo capsule at midday (to give same dosing as methylphenidate) 2. Methylphenidate 0.3mg/kg twice daily

Hagerman 1988 *(Continued)*

	3. Placebo (lactose in capsule) twice daily Each intervention lasted one week
Outcomes	Primary outcome not stated. Outcome measures used: Conners Abbreviated Parent-Teacher Questionnaire ADDH: Comprehensive Teacher Rating Scale (ACTeRS) Behavioural observation Large scale integrated sensor actometer Delay task Vigilance task
Notes	Sequence generation unclear Participants, personnel and outcome assessors were blinded Outcome data were complete (i.e. no withdrawals/drop-outs) Possible selective outcome reporting: subscale scores presented where main scale not significant; blood pressure readings not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described. Investigators were contacted, but had no further information.
Allocation concealment?	Unclear risk	Not described. Investigators were contacted, but had no further information.
Blinding? All outcomes	Low risk	Medication and placebo tablets were described as identical.
Incomplete outcome data addressed? All outcomes	Low risk	It is unclear whether any participants dropped out (although this is unlikely given the brevity of the study).
Free of selective reporting?	High risk	Trial protocol unavailable. Where an outcome measure showed a non-significant difference, results for subscales were presented. Blood pressure and pulse readings were not presented despite being described in the Methods section of the paper.
Free of other bias?	Unclear risk	Study was supported by the Children's Hospital of Kempe Research Center, Colorado (USA). No competing interests declared.
Washout	Unclear risk	There was no washout period between treatment and placebo.
Validity/reliability of outcome measures	Unclear risk	The primary outcome measure was the ACTeRS scale. This has been demonstrated to be reliable in children with ID, but has poor correlation with behavioural observation in this population. Actometer recordings may be sensitive to medication response but may correlate poorly with report measures. Use continuous performance tasks may not be sensitive to medication effects.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alexandris 1968	Not all participants have ID:"The Wechsler intelligence quotient ranged from 55 to 85" but no median or interquartile range stated.
Anton 1969	Not randomised or controlled
Barcai 1971	Participants do not have ADHD or ID
Berkson 1965	Participants do not have ADHD
Broomand 1967	Not randomised
Burgio 1985	Not randomised or controlled
Comly 1971	Participants do not have ADHD or ID
Conners 1967	Participants do not have ADHD or ID
Conners 1969	Participants do not have ADHD or ID
Craft 1959	Not randomised or controlled; participants do not have ADHD
Cutler 1940	Participants do not have ADHD
Denhoff 1971	Participants do not have ID
Eaton 1977	Participants do not have ADHD
Eisenberg 1963	Not randomised; participants do not have ADHD or ID
Faraone 2001	Participants do not have ID
Faraone 2002	Participants do not have ID
Fish 1962	Participants do not have ADHD
Geller 1981	Not randomised or controlled
Gittelman-Klein 1980	Not randomised or controlled
Hagerman 1992	Not randomised or controlled
Helsel 1989	Insufficient information - letter describing 13 single-case controlled trials with stimulants. Drug not specified.
Lobb 1968	Participants do not have ADHD
McConnell 1964	Participants do not have ADHD
Molitch 1937	Participants do not have ADHD or ID
Molitch 1937a	Participants do not have ADHD or ID
Morris 1955	Participants do not have ADHD
Moskowitz 1941	Case report

Study	Reason for exclusion
Ounsted 1955	Not randomised or controlled (large case series)
Payton 1989	Single cases. Not randomised
Schmidt 1982	Not randomised or controlled (single case report). Treatment is with methylphenidate not amfetamine.
Sprague 1967	Conference proceedings. Unable to find more information.
Steinberg 1971	Participants do not have ADHD or ID
Sulzbacher 1972	3 case reports. Only one participant with ID. No diagnosis of ADHD
Swanson 1991	Participants do not have ADHD. Treatment is with methylphenidate not amfetamine.
Volkmar 1985	Not randomised or controlled (case series). Participants do not have ADHD.
Zrull 1963	Participants do not have ID

ADDITIONAL TABLES

Table 1. MEDLINE, PsycINFO, EMBASE and AMED search strategy

Search Terms
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomized Controlled Trials/
4. Random Allocation/
5. Double-Blind Method/
6. Single-Blind Method/
7. or/1-6
8. animal/ not human/
9. 7 not 8
10. clinical trial.pt.
11. exp Clinical Trials/
12. (clinic$ adj25 trial$).tw.
13. ((singl$ or double$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
14. Placebos/
15. placebo$.tw.
16. random$.tw.
17. Research Design/
18. or/10-17
19. 18 not 8
20. 19 not 9
21. Comparative Study/
22. exp Evaluation Studies/
23. Follow-Up Studies/
24. Prospective Studies/
25. (control$ or prospectiv$ or volunteer$).tw.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28

Table 1. MEDLINE, PsycINFO, EMBASE and AMED search strategy *(Continued)*

30. exp Attention Deficit Disorder with Hyperactivity/
31. (attention adj5 deficit).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32. (adhd or adhkd or addh or adhs).tw.
33. hyperactiv$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
34. exp Child Behavior Disorders/
35. exp hyperkinesis/
36. hyperkine$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
37. (minimal$ adj brain adj3 disorder$).tw.
38. (minimal$ adj brain adj3 dysfunction).tw.
39. (minimal$ adj brain adj3 damage$).tw.
40. or/30-39
41. exp Learning Disorders/
42. (education$ adj5 subnorm$).tw.
43. (intellect$ adj5 def$).tw.
44. (intellect$ adj5 disab$).tw.
45. (intellect$ adj5 disorder$).tw.
46. (intellect$ adj5 handicap$).tw.
47. (intellect$ adj5 impair$).tw.
48. (intellect$ adj5 subnorm$).tw.
49. (learn$ adj5 difficult$).tw.
50. (learn$ adj5 disab$).tw.
51. (learn$ adj5 disorder$).tw.
52. (mental$ adj5 def$).tw.
53. (mental$ adj5 disab$).tw.
54. (mental$ adj5 handicap$).tw.
55. (mental$ adj5 impair$).tw.
56. exp Mental Retardation/
57. (mental$ adj5 retard$).tw.
58. (mental$ adj5 subnorm$).tw.
59. exp Child Development Disorders, Pervasive/
60. autis$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
61. asperger$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
62. (pervasive adj25 development$ adj25 disorder$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
63. or/41-62
64. 40 and 63
65. 29 and 64
66. exp Central Nervous System Stimulants/
67. exp Phenylacetates/
68. methylphenidate.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
69. exp Amphetamines/
70. (dexamphetamine or dexamfetamine or dextroamphetamine or dextroamfetamine or amphetamine or amfetamine or dexedrine or benzedrine).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
71. adderall.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
72. modafinil.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
73. caffeine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
74. exp Imidazolines/
75. clonidine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
76. guanfacine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
77. exp Guanidines/
78. exp Oxazoles/
79. pemoline.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
80. nicotine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
81. exp Adrenergic Agents/
82. atomoxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
83. exp Antidepressive Agents/
84. amitriptyline.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
85. amoxapine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
86. clomipramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
87. Dosulepin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
88. dothiepin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

Table 1. MEDLINE, PsycINFO, EMBASE and AMED search strategy *(Continued)*

89. Doxepin.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
90. Imipramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
91. Lofepramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
92. Nortriptyline.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
93. Trimipramine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
94. citalopram.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
95. escitalopram.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
96. fluoxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
97. fluvoxamine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
98. paroxetine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
99. sertraline.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
100. venlafaxine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
101. bupropion.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
102. exp Antipsychotic Agents/
103. Benperidol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
104. Chlorpromazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
105. Flupentixol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
106. Flupenthixol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
107. Fluphenazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
108. Haloperidol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
109. Levomepromazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
110. Pericyazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
111. Periciazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
112. Perphenazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
113. Pimozide.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
114. Prochlorperazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
115. Promazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
116. Stelazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
117. Sulpiride.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
118. Thioridazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
119. Trifluoperazine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
120. Zuclopenthixol.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
121. Amisulpiride.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
122. Aripiprazole.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
123. Clozapine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
124. Olanzapine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
125. Quetiapine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
126. Risperidone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
127. Sertindole.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
128. Ziprasidone.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
129. Zotepine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
130. exp Carnitine/
131. acetylcarnitine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
132. exp Fatty Acids, Unsaturated/
133. exp Amantadine/
134. amantadine.mp.
135. exp Naloxone/
136. exp Naltrexone/
137. exp Buspirone/
138. exp Benzodiazepines/
139. diazepam.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
140. exp Anticonvulsants/
141. lamotrigine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
142. carbamazepine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
143. or/66-142
144. 65 and 143

Table 2. ISI Web of Knowledge Search Strategy

Search Terms
1. TS=((attention SAME deficit) OR hyperactiv* OR hyperkine* OR ADHD OR ADHS OR ADDH OR ADHKD OR (minimal* SAME brain SAME disorder*) OR (minimal* SAME brain SAME dysfunction) OR (minimal* SAME brain SAME damage*)) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 2. TS=((education* SAME subnormal) OR (intellect* SAME def*) OR (intellect* SAME dis*) OR (intellect* SAME handicap*) OR (intellect* SAME impair*) OR (intellect* SAME subnorm*) OR (learn* SAME difficult*) OR (learn* SAME dis*) OR (mental* SAME def*) OR (mental* SAME disab*) OR (mental* SAME handicap*) OR (mental* SAME impair*) OR (mental* SAME retard*)) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 3. TS=((pervasive SAME development* SAME dis*) OR autis* OR asperger*) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 4. #2 OR #3 5. #1 AND #4 6. TS=(stimulant* OR methylphenidate OR amphetamine OR amfetamine OR dextroamphetamine OR dextroamfetamine OR dexamphetamine OR dexamfetamine OR dexedrine OR benzedrine OR adderal OR modafinil OR caffeine OR clonidine OR guanfacine OR pemoline OR nicotine OR atomoxetine OR venlafaxine) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007OR 7. TS=(tricyclic OR amitriptyline OR amoxapine OR clomipramine OR dosulepin OR dothiepin OR Doxepin OR Imipramine OR Lofepramine OR Nortriptyline OR Trimipramine OR "serotonin reuptake inhibitor*" OR SSRI* OR citalopram OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR bupropion) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 8. TS=(Antipsychotic* OR neuroleptic OR Benperidol OR Chlorpromazine OR Flupentixol OR Flupenthixol OR Fluphenazine OR Haloperidol OR Levomepromazine OR Pericyazine OR Periciazine OR Perphenazine OR Pimozide OR Prochlorperazine OR Promazine OR Stelazine OR Sulpiride OR Thioridazine OR Trifluoperazine OR Zuclopenthixol OR Amisulpiride OR Aripiprazole OR Clozapine OR Olanzapine OR Quetiapine OR Risperidone OR Sertindole OR Ziprasidone OR Zotepine) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 9. TS=(Carnitine OR acetylcarnitine OR "Fatty Acid*") DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 10. TS=(Amantadine OR Naloxone OR naltrexone OR Buspirone) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 11. TS=(Benzodiazepine* OR diazepam OR Anticonvulsant* OR antiepileptic* OR lamotrigine OR carbamazepine) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 12. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 13. #5 AND #12 14. TS=(random* OR control* OR trial OR placebo* OR prospective OR ((singl* OR doubl* OR trebl* OR tripl*) SAME (mask* OR blind*))) DocType=All document types; Language=All languages; Database=SCI-EXPANDED; Timespan=1900-2007 15. #13 AND #14

Table 3. WorldCat Dissertations Search Strategy

Search Terms
(kw: attention w deficit OR kw: hyperactiv* OR kw: hyperkine* OR kw: ADHD OR kw: ADHS OR kw: ADDH OR kw: ADHKD OR su= "attention-deficit hyperactivity disorder" OR kw: minimal w brain w disorder OR kw: minimal w brain w dysfunction OR kw: minimal w brain w damage OR kw: MBD) and ((kw: education* w subnorm* OR kw: intellect* w def* OR kw: intellect* w disab* OR kw: intellect* w disorder* OR kw: intellect* w handicap* OR kw: intellect* w impair* OR kw: intellect* w subnormal* OR kw: learning w difficult* OR kw: learning w disab* OR kw: learning w disorder* OR kw: mental* w def* OR kw: mental* w disab*OR kw: mental* w handicap* OR kw: mental* w impair* OR kw: mental* w retard* OR su= "mental retardation" OR kw: mental* w subnormal) or (kw: pervasive n5 disorder OR kw: autism OR kw: autistic OR kw: asperger OR su= "autism"))

Table 4. CENTRAL Search Strategy

Search Terms

Table 4. CENTRAL Search Strategy *(Continued)*

#1 MeSH descriptor Attention Deficit and Disruptive Behavior Disorders explode all trees
#2 MeSH descriptor Learning Disorders explode all trees
#3 MeSH descriptor Mental Retardation explode all trees
#4 MeSH descriptor Child Development Disorders, Pervasive explode all trees
#5 (#2 OR #3 OR #4)
#6 (#1 AND #5)

Table 5. mRCT Search Strategy

Search Terms
("attention deficit" OR hyperactiv% OR hyperkine% ADHD OR ADHS OR ADDH OR ADHKD OR "minimal brain dysfunction" OR "minimal brain disorder" OR "minimal brain damage" OR MBD) AND ("education% subnormal" OR "intellectual% def%" OR "intellectual% dis%" OR "intellectual% impair%" OR "intellect% subnorm%" OR "learning difficult%" OR "learning dis%" OR "mental% def%" OR "mental% disab%" OR "mental% handicap%" OR "mental% impair%" OR "mental% retard%" OR "mental% subnormal")

Table 6. National Research Register Search Strategy

Search Terms
#1. ATTENTION DEFICIT AND DISRUPTIVE BEHAVIOR DISORDERS explode tree 1 (MeSH) #2. LEARNING DISORDERS explode all trees (MeSH) #3. CHILD DEVELOPMENT DISORDERS PERVASIVE explode all trees (MeSH) #4. MENTAL RETARDATION explode all trees (MeSH) #5. (#2 or #3 or #4) #6. (#1 and #5)

Table 7. Protocol for meta-analysis

Measures of Treatment Effect
If participants, interventions and outcome measures are sufficiently similar, meta-analyses will be carried out. Data from the extraction sheets will be entered into an Excel spreadsheet and copied into Review Manager version 4.2.8 (RevMan). Data entry will be checked by entering the same data from a different author's extraction sheets into RevMan using the double data entry facility. Dichotomous data will be pooled using odds ratios. Ordinal data from rating scales will be treated as continuous data. Where the same rating scale has been used for all studies, data will be pooled using weighted mean differences; where different rating scales have been used to measure the same outcome, standardised mean differences will be used.

Dichotomous Outcomes
Response to medication (secondary outcome) will be defined as a 25% reduction in scores on a validated ADHD rating scale. Reported response rates will be pooled where they are sufficiently similar, however if this information is not reported, the raw data will be requested from study authors and response rates calculated.

Cross-over Trials
Data from cross-over trials will be pooled according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006b) and by Elbourne et al. (Elbourne 2002). Mean within-participants difference and standard error of the mean difference will be entered into RevMan using the generic inverse outcome type. Where the standard error of the mean difference is not reported, the original data will be requested from study authors or the value will be imputed. Correlation coefficients will be calculated from studies where sufficient data is available and if these values are consistent they will be used to calculate the missing standard errors for other studies.

Table 7. Protocol for meta-analysis *(Continued)*

Dealing with Missing Data
If studies do not report intention-to-treat analyses, attempts will be made to obtain missing data by contacting the study authors. If dichotomous outcome data are not available, values will be imputed by assuming that all participants for whom data is missing did not experience a favourable outcome. If missing continuous data is not forthcoming, an available case analysis will be performed.

Where studies do not report response rates, values will be imputed using the method described by Furukawa et al. (Furukawa 2005). Outcome data will be assumed to be normally distributed. Number of responders (n) will be calculated using the formula in Figure 01, where N is the number of participants at endpoint, x is 75% of the baseline mean score, mu is the endpoint mean score, sigma is the standard deviation of the endpoint mean and phi is the cumulative distribution function. The validity of this method will be checked by applying it to studies which do report response rates and then calculating the correlation coefficient between reported and imputed response rates.

Assessment of Heterogeneity
The chi-squared and I-squared tests will be performed to assess for heterogeneity between studies. Graphical representations will also be inspected. Where significant heterogeneity is suspected ($p > 0.1$, I-squared > 50% or on visual inspection), a random effects meta-analysis will be used. Fixed effects meta-analyses will be used where significant heterogeneity is not suspected.

Subgroup Analysis and Investigation of Heterogeneity
Where heterogeneity is identified, it will be investigated by performing the following subgroup analyses:

1) Subgroups by severity of intellectual disability (mild, moderate, severe or profound);
2) Subgroups by different doses of drug (fixed doses rather than mg/kg as this reflects clinical practice)
3) Subgroups by whether participants have comorbid pervasive developmental disorder or not;
4) Subgroups by age - whether participants are adults (18 years or over) or children (under 18 years old);
5) Subgroups by whether treatment is with dexamfetamine or mixed amfetamine salts, and with sustained release or immediate release preparations.

Sensitivity Analysis
A sensitivity analysis will be performed as follows to explore whether the results of the review are robust.

1) Studies will be grouped qualitatively into low, moderate or high quality and meta-analyses performed by group.
2) Comparisons will be made between studies which use a crossover design and those with a separate control arm.
3) If missing data have been imputed for intention-to-treat analysis with dichotomous outcomes, a "best case/worst case" analysis will be performed. All participants for whom data is missing will be assumed to have had a favourable outcome (response to medication) and the results compared to the original, more conservative, analysis.

These analyses will be compared with the original meta-analysis and any effect on the results noted.

Assessment of Reporting Bias
1) Publication bias will be assessed by constructing funnel plots.
2) If unpublished data is included in the review, a subgroup analysis will be performed to compare published and unpublished data.

WHAT'S NEW

Date	Event	Description
14 April 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 1, 2009

Date	Event	Description
27 October 2008	Amended	Converted to new review format.
15 July 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

SM and EP wrote the "Background" section and were involved with searching, quality assessment, data extraction and writing up.

AT wrote the protocol, developed the search strategies and was involved in searching, quality assessment, data extraction and writing up.

KX reviewed the protocol, oversaw decisions regarding study inclusion and was involved in quality assessment and writing up.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Additions were made to the 'Risk of bias' section to incorporate assessment criteria for selective outcome reporting and other potential sources of biases, including competing interests, adequacy of washout period in crossover studies and validity/reliability of outcome measures. A reference to the most recent version of the Cochrane Handbook (Higgins 2008) has been added.

INDEX TERMS

Medical Subject Headings (MeSH)

Amphetamine [*therapeutic use]; Attention Deficit Disorder with Hyperactivity [*drug therapy]; Central Nervous System Stimulants [*therapeutic use]; Fragile X Syndrome [complications]; Mentally Disabled Persons [*psychology]; Methylphenidate [therapeutic use]

MeSH check words

Child; Child, Preschool; Humans