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Clinical Gains from Including Both Dextroamphetamine and Methylphenidate in Stimulant Trials

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Abstract

Objective: The purpose of this study was to investigate clinical gains from including both dextroamphetamine and methylphenidate in stimulant trials.
Method: Thirty-six medication-naïve children ages 9–14 years diagnosed with attention-deficit/hyperactivity disorder (ADHD) were enrolled for 6 weeks in a crossover trial, with 2 weeks of methylphenidate, dextroamphetamine, and placebo, in a randomly assigned, counterbalanced sequence. Outcome measures constituted a computer-based continuous performance test combined with a motion tracking system (Qb Test) and an ADHD questionnaire rated by parents and teachers.
Results: Group analyses found significant treatment effects of similar size for the two stimulants on both outcome measures. Single-subject analyses revealed that each stimulant produced a favourable response in 26 children; however, an individual child frequently responded qualitatively or quantitatively differently to the two stimulants. By including both stimulants in the trial, the number of favorable responders increased from 26 (72%) to 33 (92%). In children with favorable responses of unequal strength to the two stimulants, a shift from inferior drug to best drug was associated with a 64% mean increase in the overall response strength score, as measured by the ADHD questionnaire.
Conclusions: The likelihood of a favorable response and optimal response strength is increased by including both stimulants in the stimulant trial.
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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a prevalence of ~3–5% in school-aged children (Faraone et al. 2003; Polanczyk and Jensen 2008). Its core behavioral symptoms of inattention, impulsivity, and hyperactivity are associated with impaired academic performance and social functioning and a higher risk of comorbid externalized and internalized psychiatric disorders (Jensen et al. 2001a). Stimulants have been found to be the single most effective short-term treatment of ADHD symptoms (Jensen et al. 2001b). Although long-term effects are less well studied, reduced ADHD symptoms (Charach et al. 2004), improved academic outcome (Powers et al. 2008), improved occupational outcome (Halmoy et al. 2009), and reduced risk of subsequent psychiatric comorbid disorder (Biederman et al. 2009) are reported. Methylphenidate is the drug most frequently prescribed and the drug of first choice in clinical practice (Greenhill et al. 1996; Safer et al. 1996).

Group data show amphetamine products to be at least as potent as methylphenidate in the treatment of ADHD. Two reviews reported no significant differences between these stimulants (Arnold 2000; Brown et al. 2005), whereas a meta-analysis based on 23 double-blind placebo-controlled studies in children and adolescents found the effect size of amphetamine products to be moderately but significantly greater than that of methylphenidate, although the authors noted that comparisons among stimulants are hindered by the absence of direct comparative trials (Faraone and Buitelaar 2010).

Single-subject data differentiate further between stimulants. Some individuals respond well to methylphenidate and not to amphetamine products and vice versa. When both stimulants are included in a clinical trial, the number of favorable responders is reported to increase from the 70–80% range to the 85–95% range (Elia et al. 1991; Arnold 2000). In cases with a favorable response to both stimulants, the responses are still often unequal in strength (Elia et al. 1991; Green 1996). Stimulant trials tend to start with one type of stimulant, creating the risk that if the first stimulant leads to improvement, a second stimulant that could produce a stronger favorable response is not tried, and a suboptimal favorable response is accepted.

Behavioral ratings are generally used as primary outcome measures, and the use of both teacher and parent reports for documenting efficacy in stimulant trials is recommended (Swanson et al. 1999). Because ADHD rating forms are vulnerable to placebo

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(Waschbusch et al. 2009) and source (Gomez et al. 2003) effects, the inclusion of objective test measures in clinical trials has been recommended by several authors (Teicher et al. 2008; Waschbusch et al. 2009; Sumner et al. 2010). Computer-based continuous performance tests (cb-CPT) are a large family of laboratory tests measuring attention; they are administered in a diversity of forms. Cb-CPTs consistently demonstrate responsiveness to the effect of stimulants (Rapport et al. 1987; Pelham et al. 1990; Tabori-Kraft et al. 2007; Teicher et al. 2008; Fernandez-Jaen et al. 2009), and an absence of practice effects is reported (Fernandez-Jaen et al. 2009). Recent studies show that cb-CPTs combined with motion tracking systems (MTS) also serve as responsive measures of attention and motor activity in clinical trials (Tabori-Kraft et al. 2007; Teicher et al. 2008), vulnerability to placebo effects is low (Sumner et al. 2010), and a degree of ecological validity has been demonstrated (Teicher et al. 2008).

Objective

The present study investigated short-term clinical gains from including both dextroamphetamine and methylphenidate in a stimulant trial in children diagnosed with ADHD. No significant difference in treatment effect between the stimulants was expected at the group level; however, it was hypothesized that clinical gains would be demonstrated as an increase in the number of favorable responders and in the possibility of optimal response strength for an individual child.

Methods

Subjects

Subjects were children referred to Østfold Hospital Trust, Neuropsychiatric Unit from four outpatient child and adolescent psychiatric clinics, all under the umbrella of Østfold Hospital Trust. Diagnosis was set by a psychologist, psychiatrist, or pediatrician after a comprehensive psychiatric assessment following formalized guidelines (www.adhd-behandlingslinje.no), and confirmed by a specialist in neuropsychology before enrolment. Thirty-six children were finally included. All children met diagnostic criteria of ADHD according to American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV TR) (American Psychiatric Association 2000) and were rated ≥2 SD above mean on the Conner's Rating Scale DSM-IV Inattention subscale and/or DSM-IV Hyperactivity-Impulsivity subscale. Additional criteria for enrolment in the trial were: 1) Age between 9.0 and 14.0 years at the time of enrolment, 2) no prior treatment with stimulants, and 3) stimulant treatment that has been approved by a pediatrician or psychiatrist. The exclusion criteria were: 1) Moderate to severe mental retardation, 2) psychosis, 3) brain injury, 4) sensory deficits and/or motor impairment that could influence test performance, 5) epilepsy, and 6) factors that would substantially reduce the possibility of obtaining reliable observations from a parent or teacher. The study protocol and informed consent form were approved by the regional committee of medical research ethics prior to the study. Parents or guardians provided written informed consent before the children were enrolled.

Study design

The study was conducted as part of clinical practice in an outpatient psychiatric clinic. The design was a crossover trial in which each child received 2 weeks of methylphenidate, dextroamphetamine, and placebo respectively for a total of 6 weeks, in order to allow direct comparison of the stimulants. Drug order, but not dosage, was counterbalanced. Participants were randomly and evenly assigned to each of six possible drug orders. For each drug, a low dosage was administered in the 1st week and a high dosage in the 2nd week, as a gradual increase is recommended (Greenhill et al. 2002). Fixed doses were prescribed because they reflect typical clinical practice, and because body weight is not a valid predictor of optimal dosage (Rapport and Denney 1997). Immediate-release 10 mg methylphenidate tablets (Novartis), immediate-release 5 mg dextroamphetamine tablets (UCB Pharma Ltd.) and placebo tablets (Krageroe Pharmacy) were administered. The participants were randomly assigned to one of six drug orders:

1. MPH–PLA–DEX
2. PLA–MPH–DEX
3. DEX–PLA–MPH
4. DEX–MPH–PLA
5. PLA–DEX–MPH
6. MPH–DEX–PLA

Observation periods ran from Monday to Friday each week. Saturday and Sunday were used to increase the dosage and to serve as a 48 hour washout period before the subsequent drug was introduced. The morning dose was administered between 07.30 and 08.00, the lunch dose between 11.00 and 11.30, and the afternoon dose between 14.30 and 15.00. Dextroamphetamine was administered only in the morning and afternoon because of its longer serum half-life and duration of action. To ensure an equal number of daily administrations in each drug condition, placebo tablets were administered at lunch during the dextroamphetamine condition. Delivery patterns (Table 1) were selected to reflect common clinical practice.

Pill dispensers were prepared by a psychologist in collaboration with a pediatrician and handed to parents and teachers shortly before the trial began. No information about drug order was given to participants, parents, and teachers. Tablets with similar colors, shapes, and textures were administered, but the drugs were not camouflaged in identical capsules. The parents chosen to administer the medication at home were required to confirm before the

Table 1. Drug Protocol

	Low doses				*High doses*			
Drug	*Morning*	*Lunch*	*Afternoon*	*TDD*	*Morning*	*Lunch*	*Afternoon*	*TDD*
Placebo	1 tbl	1 tbl	1 tbl		2 tbl	2 tbl	2 tbl	
Methylphenidate	10 mg	10 mg	10 mg	30 mg	15 mg	15 mg	10 mg	40 mg
Dextroamphetamine	5 mg	1 tbl[a]	5 mg	10 mg	10 mg	2 tbl[a]	10 mg	20 mg

TDD, total dosage per day.
[a]Placebo tablets.

trial started that they were unfamiliar with stimulants. The test administrator was blind to drug order.

Pretreatment assessment

Intelligence was assessed with the Wechsler Intelligence Scale for Children-Third Edition (Wechsler 1999) or the Wechsler Abbreviated Scale of Intelligence (Brager-Larsen 2001), depending upon the clinic where intelligence quotient (IQ) was being tested. The DSM-IV Inattention and Hyperactive-Impulsive subscales from the Conners' Rating Scale – Revised, Long Version, Parent and Teacher Form (Conners 1997) were used to quantify the level of ADHD symptoms. Internalizing and the Externalizing groupings from the Child Behavior Checklist and the Teacher Rating Form, the Achenbach System of Empirically Based Assessment were used to assess a broader range of psychiatric symptoms (Achenbach and Rescorla 2001). Metacognition Index and Behavioral Regulation Index from the Behavior Rating Inventory of Executive Functions, Parent and Teacher Edition (Gioia and Isquith 2000) were chosen to evaluate executive functions in daily life. All the rating scales used T scores (mean = 50, SD = 10; high scores reflected elevated symptoms or disability).

Outcome measures used in the stimulant trial

A cb-CPT-MTS (Qb Test, provided by Qbtech, Gothenburg, Sweden; www.qbtech.se/products/qbtest) was selected as neuropsychological outcome measure. Participants were instructed to respond by clicking on a handheld button electronically attached to a computer each time a go stimulus (a gray circle) appeared on the screen and to refrain from clicking when a no-go stimulus (a gray circle with a cross) appeared. Both speed and accuracy were emphasized in the instruction video shown prior to testing. Stimulus duration was 100 ms, with an interstimulus interval (ISI) of 1900 ms. Test duration was 15 minutes, and consisted of 450 trials with an equal number of go and no-go stimuli presented in random order. For the MTS, an infrared camera recorded the movements of a marker attached to a headband worn by the participants during the test session. The marker coordinates were sampled 50 times per second, with a spatial resolution of 0.04 mm per camera unit (Bergfalk 2003).

Participants were tested on the cardinal measures of attention (Qb Inattention) and motor activity (Qb Activity) between 1 and 2 hours after drug administration either on a Wednesday, Thursday, or Friday, once in each of three high dosage conditions. Qb Inattention is based on a weighted combination of reaction time, reaction time variability, omission errors, and commission errors, submeasures that load on the same factor (Knagelhjelm and Ulberstad 2010). Qb Activity is based on the number of microevents (a microevent = movements of >1 mm since previous microevent). Test performances were recorded and scored by a computer program using age-adjusted norms developed by Qb Tech with proven reliability and validity (Bergfalk 2003; Brocki et al. 2010), and test results were expressed in *q*-scores (mean = 0, SD = 1). Higher scores indicated poor performance. In order to prevent a switch in age norms from one test session to the next for any given individual, the age at the first administration was used for scoring also at the second and third administration. The two cardinal measures were found to be highly intercorrelated ($r^2 = 0.56$) and their mean score was, therefore, used as the overall measure of neuropsychological performance.

A 21-item ADHD questionnaire was developed for this study. Most of the items were selected in accordance with DSM-IV diagnostic criteria for ADHD and oppositional defiant disorder (ODD) with eight items reflecting inattention, six items reflecting hyperactive-impulsive behaviour, and four items reflecting oppositional defiant behavior. Sluggish cognitive tempo (SCT) is found to be highly correlated with ADHD inattention symptoms (Skirbekk et al. 2011), and three SCT items selected for the ADHD questionnaire correspond to items included in the Achenbach System of Empirically Based Assessment. Each of the 21 items were rated on a four point Likert scale (0 = not at all true, 1 = just a little true, 2 = pretty much true, 3 = very much true). The questionnaire was completed daily from Monday to Friday every week by parents and teachers, so that treatment effects could be measured in both school and home settings. Each item rating was based on the informants' overall impression from the total time spent in the child's presence. For each child, a total score that represented the level of ADHD symptoms in each of the 6 weeks was calculated the following way: First, a mean weekly score for each of the four symptom areas was calculated based on ratings from every weekday rated. Internal consistency based on the mean weekly scores for the four symptom areas rated by parents and teachers in the placebo condition was satisfactory (Cronbach's $\alpha = 0.74$). Next, the mean weekly scores for the four symptom areas were summarized into a mean weekly full scale score. Finally, the mean weekly full scale scores from parent and teacher were averaged to create the total score.

Statistical analysis

Data were analyzed with SPSS PASW Statistics 18. Paired sample *t* tests were used to analyze differences between parents' and teachers' pretreatment assessment of sample characteristics. A mixed between-within subject analysis of variance (ANOVA) was conducted to assess the overall treatment effect at high and low dosage conditions. The cb-CPT-MTS and the ADHD questionnaire were available as outcome measures at high dosage conditions, and the ADHD questionnaire was available as an outcome measure at low dosage conditions. A treatment with three levels (placebo, methylphenidate, dextroamphetamine) was chosen as the within-subject factor, and drug order (six counterbalanced drug orders) as the between-subject factor. In each case, three post-hoc pairwise comparisons were performed to compare the effects of placebo, methylphenidate, and dextroamphetamine. A Bonferonni adjustment for multiple comparisons was used to protect against type I errors by selecting $p < 0.01$ as the significance level. Effect size (partial eta square = η_p^2) was calculated in the multivariate test, and are categorized as follows: 0.01 = small, 0.06 = moderate, 0.14 = large effect size (Cohen 1988). Paired-sample *t* tests were run to detect possible differences between high dosage and low dosage conditions for each of the two stimulants.

Single-subject analyses were used to qualify and quantify individual responses to stimulants. The ADHD questionnaire, which was available at both high and low dosages, served as the outcome measure in these analyses. To measure a drug response, a standard effect size value (ES) was calculated for parent and teacher separately by subtracting the mean weekly full scale score in the treatment condition from the mean weekly full scale score in the placebo condition and dividing the result by the SD of the placebo (Evans et al. 2001). An ES of at least 0.5 was defined as a clinically valid change. A positive value reflected a favorable response. ES was categorized as deterioration ($ES \leq -0.5$), no change ($-0.5 < ES < 0.5$), moderate improvement ($0.5 \leq ES < 1.5$), and

large improvement (ES ≥ 1.5) and graded as follows: Large improvement = 2, moderate improvement = 1, and no improvement = 0. The graded scores from parent and teacher ratings were then summarized in an overall response strength score and categorized as follows:

Strong favorable response: Overall response strength score = 3–4
Mild favorable response: Overall response strength score = 1–2
No response: Overall response strength score = 0
Mixed response was defined as a combination of a favorable response and deterioration.
Adverse response was defined as deterioration as the only reported change.

Results

Sample

A total of 36 children – 29 boys and 7 girls – completed the study. Mean age was 11.4 years (SD = 1.4) and mean IQ was 90.9 (SD = 17.2).

Table 2 shows the sample to be characterized by high levels of ADHD symptoms and executive disabilities. Moderate to high levels of internalized and externalized psychiatric symptoms were also reported. No significant differences between parent and teacher ratings appeared, except that teachers reported significantly higher scores on the Behavioral Rating Inventory of Executive Function (BRIEF) Metacognition Index. ADHD subtypes and comorbidity were as follows: ADHD combined subtype ($n = 25$, 69%), ADHD inattentive subtype ($n = 10$, 28%), ADHD hyperactive-impulsive subtype ($n = 1$, 3%), anxiety/ depressive disorder ($n = 9$, 25%), ODD ($n = 20$, 55%), learning disability ($n = 22$, 61%), and Asperger syndrome ($n = 1$, 3%).

Group analyses of treatment effects

A mixed between-within subject ANOVA was conducted to determine the overall treatment effect for each outcome measure separately.

Table 3 shows a significant overall effect of stimulants associated with a large effect size on the cb-CPT-MTS and the ADHD questionnaire at high dosage conditions and on the ADHD questionnaire at low dosage conditions. The post-hoc comparisons in all three cases found significant treatment effects for both dextroamphetamine and methylphenidate compared with placebo. No significant superiority for one or the other stimulant was detected. A significant drug order*treatment interaction was detected for the cb-CPT-MTS, but not for the ADHD questionnaire. A post-hoc analysis of the cb-CPT-MTS first period data, using independent samples t test, demonstrated a result similar to the crossover analysis, in that dextroamphetamine ($p = 0.016$, $\eta^2 = 0.23$) and methylphenidate ($p = 0.046$, $\eta^2 = 0.18$) were associated with significant treatment effects and large effect sizes, and that no significant difference between the two stimulants was found.

Paired sample t tests, based on the ADHD questionnaire data, showed high dosage dextroamphetamine to be significantly more efficient than low dosage dextroamphetamine ($p = 0.02$). No significant difference between dosages was found for methylphenidate.

Single-subject analyses of treatment effects

Single-subject analyses aimed at qualifying and quantifying how individual children responded to dextroamphetamine and methylphenidate. A standard effect size value for each response was first computed for parent and teacher ratings separately, and graded according to a set of criteria. The graded scores from the two informants were then summarized in an overall response strength score that was used to determine the quality (favorable response, no response, deterioration) and quantity (response strength) associated with an individual child's response to each stimulant.

The overall distribution of drug responses listed in Table 4 is virtually identical for the two stimulants; for an individual child, however, the responses to the stimulants frequently differed qualitatively or quantitatively. Dextroamphetamine and methylphenidate each produced a favorable response in 26 children (72%), but not always in the same child. To elaborate, 19 children (53%) responded favorably to both stimulants, and 14 children (39%) responded favorably to only one type of stimulant, with cases equally distributed between dextroamphetamine and methylphenidate. The number of favorable responders increased to 33 (92%) after both stimulants had been tried. No favorable response to either stimulant was found in three children (8%).

Methylphenidate turned out to be the better drug in 13 cases, and dextroamphetamine turned out to be the better drug in another 13; they were equally favorable in 7 cases. For six children for whom methylphenidate was the better drug, dextroamphetamine produced a favorable response of lesser strength. Likewise, methylphenidate was associated with a favorable response of lesser strength in six children for whom dextroamphetamine was

Table 2. Sample Characteristics: ADHD Symptoms of Inattention and Hyperactivity-Impulsivity, Internalized and Externalized Psychiatric Symptoms, and Executive Functioning in Daily Life – All Rated by Parents and Teachers Prior to Enrolment in the Stimulant Trial and Expressed as T Scores

	n		*Parent*		*Teacher*		
Instrument and subscale	*Parent*	*Teacher*	*Mean*	*SD*	*Mean*	*SD*	*Parent vs. teacher Paired* t *test*
CRS DSM-IV Inattention	34	34	74.4	10.0	72.7	9.2	ns.
CRS DSM-IV Hyperactive-Impulsive	34	34	74.7	15.0	69.1	13.7	ns.
CBCL/TRF Internalizing	32	32	59.8	9.0	57.8	8.7	ns.
CBCL/TRF Externalizing	32	32	62.2	11.6	63.1	10.0	ns.
BRIEF Behavior Regulation Index	36	34	68.0	13.9	72.5	16.1	ns.
BRIEF Metacognition Index	36	34	69.5	7.7	74.2	11.1	$p = 0.014$

ADHD, attention-deficit/hyperactivity disorder; CRS, Conner's Rating Scale; DSM-IV, American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; CBCL, Child Behaviour Checklist; TRF, Teacher Report Form; BRIEF, Behaviour Rating Inventory of Executive Functions.

Table 3. Group-Level Analyses of the Effects of Dextroamphetamine (DEX), Methylphenidate (MPH), and Placebo (PLA) at High and Low Dosages

		PLA		DEX		MPH		Overall effect			
Outcome variables	n	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	F	p	η_p^2	*Contrasts*
Cb-CPT-MTS - high-dosages	32	1.5	1.4	0.6	1.2	0.8	1.5	$20.3_{(2, 25)}$	< 0.001	.62	DEX, MPH < PLA
ADHD questionnaire - high-dosages	32	22.2	10.4	15.6	9.1	17.3	10.7	$9.6_{(2, 25)}$	0.001	.43	DEX, MPH < PLA
ADHD questionnaire - low-dosages	33	22.5	10.4	18.2	8.4	19.1	9.5	$9.1_{(2, 26)}$	0.001	.41	DEX, MPH < PLA

η_p^2 = effect size in the form of partial eta squared.

$p < 0.01$ was selected as significance level based on a Bonferonni adjustment for multiple comparisons. See text for a more detailed description of outcome measures.

ADHD, attention-deficit/hyperactivity disorder; Cb-CPT-MTS, computer-based continuous performance test combined with a motion tracking system.

rated as better. The mean increase in the overall response strength score from the drug with a favorable response of lesser strength to the better drug was 64% (mean increase from 1.8 to 3.0) for cases with either dextroamphetamine or methylphenidate rated as the better drug.

High dosage was rated as the best dosage twice as often as was low dosage. For a smaller subset of the sample, there was no difference as a function of dosage. Each of the two stimulants was associated with a mixed response in five children. An adverse response to dextroamphetamine was found in three children and an adverse response to methylphenidate was found in four children.

Decreased appetite and delayed sleep onset were frequently reported in both stimulant conditions compared with the placebo condition; however, side effects negated the better drug in one case only; this child switched from methylphenidate to dextroamphetamine.

Discussion

This study examined short-term clinical gains from including both dextroamphetamine and methylphenidate in a stimulant trial in children diagnosed with ADHD, by comparing treatment effects associated with the two stimulants both at the group- and single-subject levels.

Table 4. Distribution of Individual Responses to Dextroamphetamine (DEX) and Methylphenidate (MPH) Based on an Overall Response Strength Score Calculated from the ADHD Questionnaire Rated by Parents and Teachers ($N = 36$)

	DEX	*MPH*	*DEX = MPH*
Favorable drug response			
Better drug	13	13	7
Favorable but not better	6	6	
Better dosage for better drug			
High	6	7	4
Low	2	3	3
High and low are equal	5	3	0
Distribution of all responses for total sample			
Strong response	14	13	
Mild response	12	13	
No response	2	1	
Mixed response	5	5	
Adverse response	3	4	

A standard effect size value of at least 0.5 in either direction was needed to qualify as a drug response. See statistics for a detailed description of how standard effect size values and overall response strength scores were calculated.

ADHD, attention-deficit/hyperactivity disorder.

Group-level analyses revealed a significant overall treatment effect and a large effect size for stimulants on the cb-CPT-MTS, which reflects improvement in test performance associated with the regulation of attention and motor activity. A similar treatment effect was associated with the ADHD questionnaire, reflecting a reduction in ADHD symptoms rated in natural settings. Pairwise comparisons revealed a significant treatment effect both for methylphenidate and dextroamphetamine at both high and low dosage conditions, compared with the placebo. These findings are in line with a number of studies reporting that stimulants have improved performance on cb-CPT-MTS measures (Tabori-Kraft et al. 2007; Teicher et al. 2008; Lis et al. 2010; Vogt and Willimas 2011) and that they have reduced parent- and teacher-rated ADHD symptoms (Pelham et al. 1990; Elia et al. 1991; Greenhill et al. 2001; Faraone et al. 2005). The treatment effect in the dextroamphetamine high dosage condition was significantly stronger than in the low dosage condition. No such difference was found for methylphenidate, a result that possibly may be explained on the basis of the drug protocol applied in our study. Total daily dosage of dextroamphetamine increased by 100% from the low dosage condition (10 mg) to the high dosage condition (20 mg), whereas total daily dosage for methylphenidate increased by 33% from the low dosage (30 mg) to the high dosage (40 mg) condition. An increase in total daily dosage of >33% may be needed to produce a significant difference between methylphenidate dosages.

No significant superiority of any one stimulant was detected on either outcome measure at the group level. Several other studies comparing methylphenidate and dextroamphetamine directly report a similar finding (Arnold et al. 1978; Pelham et al. 1990; Elia et al. 1991). However, the superiority of methylphenidate in reducing teacher-rated ADHD symptoms (Efron et al. 1997) and motor activity recorded by a portable activity device (Borcherding et al. 1989) and the superiority of dextroamphetamine on complex mathematical tasks (Elia et al. 1993) have been reported. How dextroamphetamine and methylphenidate differ from each other on specific outcome measures remains to be determined, but differences among drug protocols (dose levels, number of daily administrations, total daily dosage proportions) should also be considered as an explanation for these inconsistencies. A lack of direct comparative studies complicates a final conclusion on this issue.

Although the single-subject analyses showed a virtually identical overall distribution of responses associated with the two stimulants (Table 4), for an individual child, methylphenidate and dextroamphetamine frequently produced responses unequal in

quality or quantity. These findings underline the crucial place of single-subject analyses in comparative studies. Each stimulant produced a favorable response in 72% of the sample, and the number of favorable responders increased to 92% when both stimulants had been tried. These results are in the same range as those reported in several other studies (Arnold et al. 1978; Elia et al. 1991; Arnold 2000). The increase in the number of favorable responders has often been emphasized in comparative trials. Less attention has been given to the increased possibility for optimal response strength for individuals with favorable responses of unequal strength to the two stimulants. The present study found a 64% mean increase in an overall response strength score from the drug associated with a favorable response of lesser strength to the better drug.

A recent report shows that the prevalence of methylphenidate use in school-aged children diagnosed with ADHD exceeds that of dextroamphetamine use by >65:1 in Norway and by >100:1 across the Nordic countries (Zoega et al. 2011), and clearly indicates methylphenidate to be the only stimulant tested in a large number of trials. Such a bias is likely to influence the outcome by reducing the number of favorable responders and increasing the risk that a potentially suboptimal favorable response to methylphenidate will be considered acceptable in a subset of children. A comparative study that enrolled children in treatment with methylphenidate supports this claim, in that 50% of the children were found to respond more strongly to dextroamphetamine, and were discharged on that stimulant (Elia et al. 1991).

Including both teachers and parents as informants increases the likelihood of mixed responses, and the two stimulants were each associated with mixed responses in five children. In line with an analysis of results from two other stimulant trials (Faraone et al. 2005), our study found low agreement between parent and teacher reports of deterioration or lack of improvement. It has been suggested that the effects of stimulants may be selective and dependent upon the demands of the environment (Porrino et al. 1983; Swanson et al. 2002) and that ratings are shown to be influenced by characteristics of the informant (Gomez et al. 2003). To include only parent or teacher ratings removes the possibility of detecting cases with opposite responses at home and in school. Furthermore, agreement between informants for any given individual enhances the validation of responses in stimulant trials.

Limitations

The drugs were not camouflaged in identical capsules, increasing the risk for identification of drug order. This issue was addressed in the evaluation meeting with parents and teachers by the end of the trial period for each participant. In only one case had a parent with certainty identified the drug order. That particular child was removed from the study.

The ADHD questionnaire, used to rate ADHD symptoms during the stimulant trial, was developed for this study and cannot be considered equivalent to well-established ADHD rating scales even though the selection of items mostly correspond to DSM-IV criteria of inattention, hyperactivity-impulsivity, and ODD, and a four point Likert scale was used for rating of each item. Most ADHD rating scales include all 18 inclusion criteria and are not primarily developed for use in clinical trials. Rating of items is usually based on averaged impressions over time spans up to six months, and psychometrics build mostly on such data and not on data from short-term stimulant trials. As daily ratings were preferred in this study to capture day-to-day variations in behavior during each week, the number of items was limited to 21 (ADHD, 14 items; ODD, 4 items; SCT, 3 items) to make it feasible to score the questionnaire each day.

No differences between the stimulants were detected at group level on any outcome measure in this study. Extrapolating these results beyond the drug protocol and the outcome measures used in the present study must be done with caution. Also, the sample size might not have been sufficient to detect subtle differences between stimulants at the group level.

The multivariate test revealed a significant drug order*treatment interaction associated with the cb-CPT-MTS, a finding that threatened the validity of the cb-CPT-MTS crossover data. Results for the cb-CPT-MTS were instead based on analyses of the first period data. The first period data showed similar results to the crossover data, however, in that both stimulants were associated with a significant treatment effect and large effect size, and no significant difference between the two stimulants was detected.

The results reported are short-term clinical gains from including both dextroamphetamine and methylphenidate in the stimulant trial. Long-term outcome of the outlined clinical practice was not addressed in this study, however, and awaits future research.

Conclusions

Methylphenidate and dextroamphetamine were significantly effective in reducing rated ADHD symptoms in natural settings and in improving performance on a neuropsychological test of attention and activity. No significant superiority for one stimulant over the other was detected at the group level. Dextroamphetamine and methylphenidate also produced a favorable response in an equal number of children; however, for an individual child, the two stimulants frequently produced qualitatively or quantitatively different responses.

Clinical implications

The present guidelines suggest that methylphenidate is the first-line medication in Nordic countries, and prevalence rates of ADHD drugs in these countries show a strong preference for methylphenidate over dextroamphetamine. Such a bias is likely to reduce the potential benefits of stimulants for children with ADHD. By routinely including both methylphenidate and dextroamphetamine in stimulant trials, the possibility of a favorable response and optimal response strength will increase for an individual child, and the overall benefits of stimulant treatment for children with ADHD are likely to improve, at least in the short term.

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