Minimizing Adverse Events While Maintaining Clinical Improvement in a Pediatric Attention-Deficit/Hyperactivity Disorder Crossover Trial with Dextroamphetamine and Methylphenidate

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Abstract

Objective: The purpose of this study was to investigate whether the availability of both dextroamphetamine and methylphenidate provides an opportunity to minimize adverse events in a pediatric attention-deficit/hyperactivity disorder (ADHD) stimulant trial.

Methods: Thirty-six medication-naïve children 9–14 years of age, diagnosed with ADHD, were enrolled for 6 weeks in a crossover trial, with 2 weeks of methylphenidate, dextroamphetamine, and a placebo in a randomly assigned, counter-balanced sequence. Barkley's Side-Effect Rating Scale (SERS), rated by parents, was used to assess adverse events. SERS were available for 34 children, and data were analyzed both at the group and the single-subject level.

Results: The side-effect profiles of dextroamphetamine and methylphenidate appeared similar at the group level. Overall, insomnia and decreased appetite were the only adverse events associated with the stimulants as compared with placebo. No significant increase from placebo to stimulant conditions was detected on SERS items reflecting emotional symptoms. Furthermore, dextroamphetamine and methylphenidate did not differ from each other on any SERS item, except that dextroamphetamine was associated with higher severity of "insomnia" and a higher prevalence of "unusually happy." Single-subject analyses showed that one or more adverse events were reported in 14 children (41%), and were evenly distributed between those with dextroamphetamine as the drug that showed the greatest reduction in their ADHD symptoms ("best drug") and those with methylphenidate as their best drug. Among children in whom both stimulants were associated with a decrease in ADHD symptoms, a clinically valid difference between the two stimulants in total adverse events score was found in 7 (39%) of the 18 cases. In these children, the availability of both stimulants provided an opportunity to minimize adverse events, while maintaining a reduction in ADHD symptoms.

Conclusions: The availability of both dextroamphetamine and methylphenidate may contribute to minimize adverse events in a subsample of children in pediatric ADHD stimulant trials.

Clinical Trials Registry: The study was first registered in clinical trials September 28, 2010. Clinical Trials.gov Identifier: NCT01220440.

Introduction

STIMULANTS ARE WIDELY PRESCRIBED AS A TREATMENT FOR pediatric attention-deficit/hyperactivity disorder (ADHD) in European countries and North America (Graham et al. 2011; Greenhill et al. 2002) and are usually recommended as part of multimodal treatment strategies (Greenhill et al. 2002; Hodgkins et al. 2012). Methylphenidate and dextroamphetamine are both highly effective in reducing ADHD symptoms (Arnold 2000; Faraone 2009; Faraone and Buitelaar 2010). In addition, these medications are found to improve social behavior (Pelham et al.

1990), neuropsychological functioning (Pietrzak et al. 2006), and academic performance (Powers et al. 2008). Long-term benefits in mental health (Biederman et al. 2009) and vocational outcome (Halmoy et al. 2009) have also been reported.

Stimulant treatment, however, is significantly associated with adverse events (Graham and Coghill 2008; Graham et al. 2011). Although mild adverse events are common, with insomnia and reduced appetite being the most pronounced (Barkley et al. 1990; Hodgkins et al. 2012), serious adverse events are rare (Greenhill et al. 2002; Graham and Coghill 2008), and patients may in most cases continue to benefit from the effectiveness of stimulant

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treatment (Cortese et al. 2013). A significant dose-response effect has been consistently reported in relation to decreased appetite, whereas dose-response effects related to other symptoms have been found either to be absent or to vary among studies (Barkley et al. 1990; Ahmann et al. 1993; Greenhill et al. 2001). Several reviews have concluded that the side-effect profiles of methylphenidate and amphetamine-products appear similar at the group level (Arnold 2000; Brown et al. 2005; Hodgkins et al. 2012). In their comparison of methylphenidate and amphetamine products in a meta-analysis, Faraone and Buitelaar (2010) warn, however, that comparisons are hindered by an absence of direct comparative trials.

Karabekiroglu et al. (2008) reported that the severity of emotional symptoms (irritability, tendency to cry, anxiety, euphoria), as assessed by Barkley's Side-Effect Rating Scale (SERS), were rated significantly lower in the methylphenidate condition than at baseline. Ahmann et al. (1993) found, however, that several items referring to emotional symptoms and physical complaints were rated substantially higher at baseline than during the placebo period, and argued that the use of baseline data in the evaluation of side effects may overestimate the improvements and underestimate the adverse effects of medication. This argument gains further support from a review on placebo effects associated with stimulant treatment in pediatric ADHD (Waschbusch et al. 2009), in that subjective measures are shown to be highly vulnerable to placebo effects. Waschbusch et al. have, therefore, emphasized the importance of including a placebo control when subjective measures, such as rating scales, are used as outcome measures.

Studies comparing methylphenidate to a placebo, however, have also reported significant overall improvements in side-effect rating scale items that refer to emotional symptoms, a decrease in anxiety being the most consistently reported improvement (Barkley et al. 1990; Ahmann et al. 1993; Sonuga-Barke et al. 2009). In a study addressing the causes of improvements associated with methylphenidate on rating scale items purported to elicit mention of potential adverse events, the results suggested that these unexpected findings may be the result of the inclusion of items that reflect core/secondary features of ADHD or normally occurring behavioral/physical complaints in children (Rapport et al. 2008).

According to the evidence outlined here, adverse events assessed with common side-effect rating scales may be analyzed most precisely for each item separately, and assessed as a change from placebo to stimulant, to provide better control for both placebo effects and symptoms normally occurring independent of treatment. Furthermore, to analyze differences between two stimulants without reference to a placebo control potentially obscures the direction of change. This issue becomes evident in a comparative study (Efron et al. 1997b), in which the severity of side effects was reported to be significantly higher on dextroamphetamine than on methylphenidate on the six rating scale items: "Insomnia," "prone to crying," "sadness," "nightmares," "irritability," and "anxiety." In fact, the severity scores were lower in both stimulant conditions than at baseline on the last four of these items, and both dextroamphetamine and methylphenidate were associated with a significant reduction in severity scores on the "irritability" and "anxiety" items, compared with baseline. This means that both stimulants probably produced improvements rather than adverse events on the "irritability" and "anxiety" items, and that methylphenidate was associated with significantly greater improvement than dextroamphetamine was. In Hodgkins et al.'s review (2012) comparing methylphenidate and amphetamine products, the Efron et al. results were referred to exclusively in the context of adverse events, with no mention of the results reflecting improvement differences in

irritability and anxiety. The direction of change is critical: Adverse events usually indicate that the specific stimulant or the applied dosage is not well tolerated, whereas an improvement indicates a beneficial effect of the treatment.

The few crossover studies comparing methylphenidate and dextroamphetamine have primarily presented group-level analyses of adverse events (Arnold et al. 1978; Pelham et al. 1990; Elia et al. 1991, 1993; Efron et al. 1997b), but reports have also shown that adverse events associated with the two stimulants may differ for an individual child (Elia et al. 1991, 1993; Efron et al. 1997b). This finding suggests that in the subsample of children for whom dextroamphetamine and methylphenidate are both associated with a reduction in ADHD symptoms, the availability of both stimulants may provide an option for reducing adverse events. To our knowledge, this issue has never been systematically addressed in crossover studies comparing these stimulants.

Objective of the Study

The objective of this study was to investigate whether the availability of both dextroamphetamine and methylphenidate in a pediatric ADHD stimulant trial would contribute to minimize adverse events. It was hypothesized that adverse events associated with the two stimulants appear similar at the group level, but may differ substantially in individual children. The availability of both stimulants was expected to provide an opportunity to minimize adverse events in a subsample of children in whom both stimulants were associated with a reduction in ADHD symptoms.

Methods

Participants

Participants were children referred to the Neuropsychiatric Unit, Østfold Hospital from four outpatient child and adolescent psychiatric clinics, all under the umbrella of Østfold Hospital Trust. Before they could be enrolled, the children underwent a comprehensive psychiatric assessment that according to formalized guidelines (www.adhd-behandlingslinje.no) included a medical examination, a review of major developmental domains, a diagnostic interview, behavioral ratings, and testing. Parents, teachers and children themselves served as informants. The diagnosis was made by a psychologist, psychiatrist, or pediatrician and confirmed by a specialist in neuropsychology before the children were included in the study. All children met diagnostic criteria of ADHD according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV TR) (American Psychiatric Association 2000) and were rated ≥ 2 SD above the mean on Conners' Rating Scale DSM-IV Inattention subscale and/or DSM-IV Hyperactivity-Impulsivity subscale. Additional criteria for enrolment in the trial were: 1) Being between 9.0 and 14.0 years of age at enrolment, 2) having had no prior treatment with stimulants, and c) stimulant treatment approved by a pediatrician or psychiatrist. The exclusion criteria were any one or more of the following: 1) Moderate or severe intellectual disability, 2) psychosis, 3) brain injury, 4) epilepsy, 5) sensory deficits and/or motor impairment that could influence test performance, and 6) inability of parents or guardians to provide reliable observations because of their severe problems or stress, or because they spent insufficient time with the child on a daily basis.

Thirty-six children completed the study. SERS data were missing for two children (ID: 5 and 9), reducing the sample available for the analyses of adverse events to 34 participants.

Study design

In a six-week crossover trial, each child received 2 weeks of methylphenidate, dextroamphetamine, and placebo, respectively, in order to allow a head-to-head comparison of the two stimulants. 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). Children were randomly and evenly assigned to one of six counterbalanced drug orders by drawing lots.

Immediate-release 10 mg methylphenidate tablets (Novartis), immediate-release 5 mg dextroamphetamine tablets (UCB Pharma Ltd.) and placebo tablets (Krageroe Pharmacy) were administered. 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 has a longer serum half-life and duration of action than methylphenidate (Greenhill et al. 2002). In line with the National Institute for Health and Care Excellence (NICE) guideline, dextroamphetamine was administered only twice daily (<http://guidance.nice.org.uk/CG72/Guidance/pdf/English>), morning and afternoon respectively. To ensure an equal number of daily administrations in each drug condition, placebo tablets were administered at lunch during the dextroamphetamine condition. Delivery patterns (morning + lunch + afternoon) were: Methylphenidate low dosage (10 mg + 10 mg + 10 mg) and high dosage (15 mg + 15 mg + 10 mg), dextroamphetamine low dosage (5 mg + 1 placebo tablet + 5 mg) and high dosage (10 mg + 2 placebo tablets + 10 mg), and placebo low dosage (1 tablet + 1 tablet + 1 tablet) and high dosage (2 tablets + 2 tablets + 2 tablets).

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 the children, parents, or teachers. Tablets with similar colors, shapes, and textures were administered, but the drugs were not camouflaged in identical capsules. Parents who administered the medication at home were required to confirm prior to the trial that they were unfamiliar with stimulants. The psychologist who met parents, teachers and children was blind to drug orders.

Ethics

The regional committee of medical research ethics approved the study protocol and informed consent form prior to the study. Parents or guardians provided written informed consent before the children were enrolled.

Pretreatment assessment

Before enrollment in the study, each child underwent an extensive psychiatric assessment. As part of the pretreatment assessment, intelligence was assessed with the official Norwegian version of the Wechsler Intelligence Scale for Children – Third Edition (Wechsler 2003) or the Wechsler Abbreviated Scale of Intelligence (Wechsler 2007), depending upon the clinic where the testing was done. The DSM-IV Inattention Subscale and the DSM-IV Hyperactivity-Impulsivity Subscales from the Conners' Rating Scale (CRS) – Revised, Long Form, Parent and Teacher Edition (Conners 1997; Conners et al. 1998) were used to quantify ADHD symptoms. The Internalizing and Externalizing groupings from the Child Behavior Checklist (CBCL) and Teacher Rating Form (TRF), Achenbach System of Empirically Based Assessment

(ASEBA) (Achenbach and Rescorla 2001) were used to assess internalized psychiatric symptoms (symptoms of anxiety and depression) and externalized psychiatric symptoms (symptoms of opposition, defiance, and rule-breaking behavior).

Assessment of adverse events

Barkley's Side-Effect Rating Scale (SERS) was used in our study to assess adverse events associated with stimulants. SERS is a rating scale addressing sleep, appetite, emotional symptoms, energy level, physical complaints, and social engagement. The version utilized in our study deviates slightly from the Norwegian translation of SERS (http://helseforde.no/fagfolk/samhandling/praksiskonsulentordninga_pko/Documents/PKO-prosjekt/Bivirkningsskjema.doc). Although the Norwegian translation contains 2 items in addition to the 17 original SERS items, these 2 items were removed for the purposes of this study, leaving the original 17. In addition, the "nail biting" item was replaced with "nausea" before the start of the study, as nail biting has been found either to be unaffected by (Barkley et al. 1990) or to decrease with stimulants (Ahmann et al. 1993), and nausea has been shown to be an adverse event associated with stimulant treatment (Cascade et al. 2010). Each item was rated on a scale of 0 to 9 (0 = not present; 9 = severe problem). Parents were instructed to rate SERS in cooperation with their child at the end of each week during the trial.

Statistical analysis

Data were analyzed with SPSS PASW Statistics 18. The assumption of normality was violated on the SERS variables, as scores were skewed towards zero. Therefore, Friedman tests were selected to analyze the main effect on each of the 17 SERS items across the placebo, and dextroamphetamine and methylphenidate high-dosage conditions. To compare the effects of the drugs, three post-hoc pairwise comparisons were performed for each item associated with an overall treatment effect using Wilcoxon signed rank test with an adjustment for multiple comparisons (three comparisons, $p < 0.016$). Differences between high and low dosages were analyzed in the same way for these items.

The adverse events associated with medication can also be calculated as the percentage of subjects displaying a given symptom in each treatment condition. The term "symptom" is preferred over the term "side effect," as this method does not control for symptoms that occur naturally, independent of drug treatment. In this context, a symptom is traditionally defined with an item score of ≥ 1 and a severe symptom is defined with an item score of ≥ 7 (Barkley et al. 1990). McMemar's test was used to analyze the differences among placebo, dextroamphetamine, and methylphenidate in proportion of symptoms (score ≥ 1) on each SERS item separately with an adjustment for multiple comparisons (three comparisons, $p < 0.016$).

For an individual child, adverse events associated with each SERS item were assessed as a change from placebo to either stimulant. Unfortunately, there is no validated definition of what constitutes a valid change on a SERS item that can be applied to categorize an adverse event for an individual child. A change in rating scale scores of $>20\%$ (Elia et al. 1991), $>25\%$ (Sumner et al. 2010), and $>40\%$ (Schachar et al. 2008) have all been applied. In our study, most scores on the SERS variables were in the lower end of a range from 0 to 9, which means that an item score change of 1 in these cases would be equivalent to an item score change of at least $>25\%$. There is a high risk of false positives associated with accepting an item score change of 1 as valid, however. To reduce this risk and still maintain a high degree of

TABLE 1. SAMPLE CHARACTERISTICS

Instrument and subscale	n	Parent		Teacher		Parent vs. teacher
		Mean	SD	Mean	SD	Paired t test
CRS DSM-IV Inattention Subscale	32	74.0	10.3	72.4	9.3	n.s.
CRS DSM-IV Hyperactive-Impulsive Subscale	32	74.7	14.8	68.3	13.6	n.s.
CBCL/TRF Internalizing grouping	31	59.4	8.9	57.9	8.9	n.s.
CBCL/TRF Externalizing grouping	31	61.7	11.3	62.5	10.6	n.s.

CRS, Conner's Rating Scale; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; CBCL, Child Behavior Checklist; TRF, Teacher Report Form.

sensitivity to change, an increase of ≥ 2 in an item score from placebo to either stimulant condition was interpreted as an adverse event. An item score change from placebo to stimulant of < 2 was interpreted as no adverse event. Accordingly, an adverse event refers to a score change of $> 20\%$ of the item's scale range (20% of item's scale range of 0–9 = 1.8). Based on these criteria, the number of adverse events and their mean severity were calculated for each child in the stimulant condition who showed the greatest reduction in his or her ADHD symptoms (best drug). Adverse events in relation to the best drug are a primary concern, because this is the stimulant condition most likely to be selected for long-term treatment. The assessment of best drug for individual children was based on an ADHD questionnaire rated by parents and teachers, and a change from placebo to each of four stimulant conditions were calculated, using standard effect size values, and categorized either as “no favorable response” (no change, deterioration), “mild favorable response,” or “strong favorable response” accordingly (Ramtvedt et al. 2013).

Finally, differences between the two stimulants in terms of the load of adverse events they produced in individual children were analyzed. This difference has clinical relevance only in children in whom both stimulants were found to reduce their ADHD symptoms, because a switch from one stimulant to the other is an option

for these children. To assess differences in the total load of adverse events, a total-adverse-events score associated with dextroamphetamine and methylphenidate was calculated for each child, defined as the number of SERS items associated with adverse events, multiplied by their mean severity. A clinically valid difference in total adverse events scores refers to a balance between sensitivity and specificity, which can be regarded as useful in clinical practice. A difference in total adverse events score of ≥ 6 between dextroamphetamine and methylphenidate in either direction was defined as a clinically valid difference, based on the following calculation: A range score difference of 20% in the number of adverse events (range of 0–17; 20% difference = 3.4) multiplied by a range score difference of 20% in mean severity (range of 0–9; 20% difference = 1.8), which was rounded to 6.

Results

Sample

Thirty-four children – 27 boys and 7 girls – were included in the analyses of side effects. Mean age was 11.3 years (SD = 1.5) and mean intelligence quotient (IQ) was 90.8 (SD = 17.7).

Sample characteristics were assessed as part of the pretreatment assessment (see Methods section) and are listed in Table 1. Parent

TABLE 2. GROUP-LEVEL ANALYSES OF SEVERITY ASSOCIATED WITH EACH OF 17 SERS ITEMS IN THE PLACEBO CONDITION (PLA), AND DEXTROAMPHETAMINE (DEX-H) AND METHYLPHENIDATE (MPH-H) HIGH-DOSAGE CONDITIONS

SERS items	PLA Mean (SD)	DEX-H Mean (SD)	MPH-H Mean (SD)	Friedman test		Wilcoxon signed rank test Pairwise comparison*
				$\chi^2(2, n = 34)$	p	
Insomnia	1.3 (2.1)	3.2 (3.3)	2.0 (2.8)	13.67	<0.01	DEX > PLA; MPH > PLA; DEX > MPH
Decreased appetite	1.4 (1.6)	2.4 (2.5)	2.7 (2.9)	7.54	0.02	MPH > PLA
Stomachache	0.4 (0.7)	0.4 (1.0)	0.8 (1.7)	1.75	0.42	—
Headache	0.7 (1.2)	0.5 (1.2)	0.9 (2.1)	1.87	0.39	—
Dizziness	0.4 (1.0)	0.4 (0.8)	0.4 (1.3)	0.31	0.86	—
Nausea	0.4 (0.8)	0.7 (1.4)	1.0 (2.0)	0.22	0.90	—
Irritability	2.8 (2.3)	1.9 (2.2)	2.2 (2.6)	3.05	0.22	—
Sadness	1.3 (1.7)	1.0 (1.8)	1.4 (2.3)	2.28	0.32	—
Tendency to cry	1.4 (2.0)	1.2 (2.1)	2.3 (3.0)	4.65	0.10	—
Anxiety	0.6 (1.1)	0.5 (1.3)	1.0 (2.4)	1.92	0.38	—
Nightmares	0.3 (0.7)	0.2 (0.5)	0.2 (0.8)	4.39	0.11	—
Staring/daydreaming	0.9 (1.3)	0.8 (1.5)	0.3 (0.7)	10.46	<0.01	MPH < PLA
Talks little to others	0.5 (1.0)	0.4 (0.7)	0.9 (1.7)	3.64	0.16	—
Uninterested in others	0.5 (1.0)	0.5 (1.2)	0.7 (1.6)	0.91	0.64	—
Tics	0.4 (1.0)	0.3 (1.1)	0.4 (1.3)	3.50	0.17	—
Drowsiness	1.4 (1.5)	1.2 (2.0)	1.0 (2.0)	3.00	0.22	—
Unusually happy	0.6 (0.9)	1.2 (2.1)	0.5 (1.4)	8.40	0.02	—

SERS, Barkley's Side-Effect Rating Scale rated by parents.

*Pairwise comparisons that remained significant after adjustment for multiple comparisons are listed.

and teacher ratings showed high levels of ADHD symptoms in the sample, combined with moderately elevated levels of internalized and externalized psychiatric symptoms. Each set of symptoms were reported to be equally present in the home and at school, as shown by no significant differences between parent and teacher ratings, analyzed by a paired-sample *t* test. ADHD subtypes were distributed as follows: ADHD combined subtype ($n=23$, 68%), ADHD inattentive subtype ($n=10$, 29%), and ADHD Hyperactive-Impulsive Subtype ($n=1$, 3%). The sample was also characterized by a high level of comorbidity: Anxiety/depressive disorder ($n=8$, 24%), oppositional defiant disorder (ODD) ($n=19$, 56%), learning disorders ($n=21$, 62%), and Asperger syndrome ($n=1$, 3%). None of the children met the criteria for intellectual disability.

Group-level analyses of severity and prevalence

Results from the Friedman test conducted for each of the 17 SERS items are listed in Table 2. Group mean values for each item in the placebo and either stimulant high-dosage condition are shown, together with χ^2 values and *p* values. For items associated with a significant main effect, pairwise comparisons that remained significant after an adjustment for multiple comparisons, as analyzed by Wilcoxon signed rank test, are also presented.

A main effect was detected on the items "insomnia," "decreased appetite," "staring/daydreaming," and "unusually happy." Both stimulants were associated with a significant increase in the severity of insomnia, but the effect was significantly stronger for dextroamphetamine than for methylphenidate. Further, pairwise comparisons indicated that only methylphenidate was associated with a significant decrease in appetite and in staring/daydreaming, compared with the placebo, whereas no differences between the stimulants were detected on these two items. Even though "unusually happy" was associated with an overall treatment effect, pairwise comparisons revealed no significant differences among the three treatment conditions in severity on this item. The severity of adverse events associated with stimulant high dosages did not differ significantly from the severity of adverse events associated with stimulant low dosages on any of the four items associated with a significant main effect.

Table 3 presents the percentage of children displaying a given symptom, as assessed by SERS, in the placebo condition, and in the dextroamphetamine and methylphenidate high-dosage conditions. For each item, the percentage of children experiencing a symptom (symptom ≥ 1 ; severe symptom ≥ 7) is listed. Also shown are differences among the three treatment conditions in the prevalence of a given symptom that remained significant after an adjustment for multiple comparisons, as analyzed by McNemar's test.

"Insomnia" was associated with a higher prevalence in the dextroamphetamine condition than in the placebo condition ($p=0.008$), and "unusually happy" was significantly more prevalent in the dextroamphetamine condition than in the methylphenidate condition ($p=0.006$). No other significant differences in the prevalence of symptoms in the three drug conditions were detected.

Single-subject analyses of adverse events

The number of adverse events and their mean severity, as assessed by SERS, were summarized for each child in the stimulant condition associated with the greatest reduction in ADHD symptoms (best drug). Results are shown in Table 4.

Overall, 20 children (59%) experienced no adverse events and 14 children (41%) experienced adverse events; 8 children experienced only one adverse event and 6 children experienced two or more. One child (ID: 8) who experienced one adverse event was a

TABLE 3. PREVALENCE OF SYMPTOMS IN THE PLACEBO (PLA), AND DEXTROAMPHETAMINE (DEX-H) AND METHYLPHENIDATE (MPH-H) HIGH-DOSAGE CONDITIONS, EXPRESSED AS PERCENTAGE OF 34 CHILDREN DISPLAYING A SYMPTOM (SCORE ≥ 1) AND A SEVERE SYMPTOM (SCORE ≥ 7) ON EACH OF 17 SERS ITEMS

Items	PLA	DEX-H	MPH-H
Insomnia			
% ≥ 1	38 (13)	65 (22)*	44 (15)
% ≥ 7	3 (1)	24 (8)	9 (3)
Decreased appetite			
% ≥ 1	50 (17)	62 (21)	62 (21)
% ≥ 7	0 (0)	9 (3)	12 (4)
Stomachaches			
% ≥ 1	26 (9)	18 (6)	24 (8)
% ≥ 7	0 (0)	0 (0)	3 (1)
Headaches			
% ≥ 1	24 (8)	24 (8)	24 (8)
% ≥ 7	0 (0)	0 (0)	3 (1)
Dizziness			
% ≥ 1	15 (5)	26 (9)	15 (5)
% ≥ 7	0 (0)	0 (0)	3 (1)
Nausea			
% ≥ 1	18 (6)	29 (10)	26 (9)
% ≥ 7	0 (0)	0 (0)	3 (1)
Irritability			
% ≥ 1	74 (25)	62 (21)	56 (19)
% ≥ 7	6 (2)	6 (2)	9 (3)
Sadness			
% ≥ 1	50 (17)	35 (12)	35 (12)
% ≥ 7	0 (0)	3 (1)	6 (2)
Tendency to cry			
% ≥ 1	41 (14)	38 (13)	50 (17)
% ≥ 7	3 (1)	6 (2)	15 (5)
Anxiety			
% ≥ 1	21 (7)	24 (8)	24 (8)
% ≥ 7	0 (0)	0 (0)	6 (2)
Nightmares			
% ≥ 1	12 (4)	9 (3)	9 (3)
% ≥ 7	0 (0)	0 (0)	0 (0)
Staring/daydreaming			
% ≥ 1	35 (12)	35 (12)	21 (7)
% ≥ 7	0 (0)	0 (0)	0 (0)
Talking little to others			
% ≥ 1	24 (8)	29 (10)	29 (10)
% ≥ 7	0 (0)	0 (0)	0 (0)
Uninterested in others			
% ≥ 1	24 (8)	26 (9)	21 (7)
% ≥ 7	0 (0)	0 (0)	0 (0)
Tics			
% ≥ 1	18 (6)	12 (4)	12 (4)
% ≥ 7	0 (0)	0 (0)	3 (1)
Drowsiness			
% ≥ 1	53 (18)	35 (12)	29 (10)
% ≥ 7	0 (0)	3 (1)	3 (1)
Unusually happy			
% ≥ 1	29 (10)	44 (15)**	15 (5)
% ≥ 7	0 (0)	6 (2)	3 (1)

SERS, Barkley's Side-Effect Rating Scale rated by parents.

*McNemar's test, DEX > PLA, $p=0.008$; **McNemar's test, DEX > MPH, $p=0.006$.

TABLE 4. SINGLE-SUBJECT ANALYSES OF ADVERSE EVENTS IN THE STIMULANT CONDITION ASSOCIATED WITH THE GREATEST REDUCTION IN ADHD SYMPTOMS (BEST DRUG)

ID	Stimulant associated with the greatest reduction in ADHD symptoms	Adverse events		
		Number	Mean severity	Listing of all adverse event scores
1	MPH	3	3.3	3.0, 5.0, 2.0
3	MPH	0	0.0	
7	MPH	0	0.0	
10	DEX = MPH ^a	0	0.0	3.0, 3.0, 4.0, 2.0
16	MPH	4	3.0	
18	MPH	1	4.0	
20	MPH	0	0.0	4.0
21	DEX = MPH ^a	0	0.0	
22	MPH	0	0.0	
25	DEX = MPH ^a	0	0.0	3.0
26	MPH	1	3.0	
28	MPH	1	3.0	
29	MPH	9	4.8	3.0, 6.5, 5.0, 5.5, 5.5, 5.5, 3.0, 4.0, 5.0
31	MPH	0	0.0	
34	MPH	1	4.0	
2	DEX	0	0.0	2.5
4	DEX	0	0.0	
6	DEX	1	2.5	
11	DEX	0	0.0	4.0
12	DEX	1	4.0	
14	DEX	7	2.5	
15	DEX	0	0.0	4.5, 2.0, 2.0, 3.0, 2.0, 2.0, 2.0
17	DEX	0	0.0	
23	DEX	5	3.9	
27	DEX = MPH ^a	1	2.0	4.0, 4.0, 3.0, 3.5, 5.0
30	DEX	0	0.0	
32	DEX	2	5.5	
33	DEX	0	0.0	7.0, 4.0
35	DEX	0	0.0	
13	DEX = MPH	0	0.0	
19	DEX = MPH	0	0.0	4.5
8	Nonresponder ^b	1	4.5	
24	Nonresponder ^b	0	0.0	
36	Nonresponder ^b	0	0.0	

An increase in item score ≥ 2 from placebo to either stimulant on any of the 17 SERS items (Barkley's Side-Effect Rating Scale rated by parents) was interpreted as an adverse event.

^aAmong children in whom the two stimulants had equally strong impact on attention-deficit/hyperactivity disorder (ADHD) symptoms, the stimulant producing the fewest adverse events was selected. That stimulant is boldface.

^bIn nonresponders, the stimulant condition that is associated with the best outcome on SERS is presented.

DEX, dextroamphetamine; MPH, methylphenidate.

nonresponder, in whom further stimulant treatment was not considered an option. Among the 31 children responding to one or both stimulants with a reduction in ADHD symptoms, adverse events were present in 13 cases (42%). Children with dextroamphetamine as their best drug, displayed an average of 1.2 adverse events, and those with methylphenidate as their best drug displayed, on average, 1.3 adverse events.

Table 5 presents the total adverse events scores associated with dextroamphetamine and methylphenidate for the 18 children in whom both stimulants were associated with a reduction in ADHD symptoms. Clinically valid differences in total adverse event scores between dextroamphetamine and methylphenidate are also listed.

A clinically valid difference in total adverse event score between the two stimulants was identified in 7 (39%) out of 18 children. In the subsample in whom methylphenidate produced the greatest reduction in ADHD symptoms, a clinically valid difference in total adverse

events score between the two stimulants appeared in four children (ID: 3, 22, 28, and 29). Methylphenidate was associated with a lower adverse events score in three of these children, but in the fourth case (ID: 29), methylphenidate was associated with a highly elevated adverse events score. Intolerable adverse events made it necessary to switch that child from methylphenidate to dextroamphetamine after the end of the initial trial, and by doing so we maintained a favorable reduction in ADHD symptoms for the child, combined with a substantial decrease in adverse events. For children in whom dextroamphetamine showed the greatest reduction in ADHD symptoms, that stimulant was also associated with a clinically valid lower total adverse events score compared with methylphenidate in one case (ID: 33). In children in whom the two stimulants were equally effective in reducing ADHD symptoms, methylphenidate was found in two cases to be associated with clinically valid, lower total adverse events scores than dextroamphetamine (ID: 10, 21).

TABLE 5. COMPARISONS OF TOTAL ADVERSE EVENTS SCORES ASSOCIATED WITH DEXTROAMPHETAMINE (DEX) AND METHYLPHENIDATE (MPH) IN CHILDREN IN WHOM BOTH STIMULANTS WERE ASSOCIATED WITH A REDUCTION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) SYMPTOMS

ID	<i>Total adverse events score^a</i>		<i>Clinically valid difference between stimulants (≥ 6)</i>	<i>Stimulant associated with the greatest reduction in ADHD symptoms</i>
	DEX	MPH		
3	9.0	0.0	MPH < DEX: 9.0	MPH
18	6.0	4.0	No	MPH
22	19.0	0.0	MPH < DEX: 19.0	MPH
28	9.0	3.0	MPH < DEX: 6.0	MPH
29 ^b	4.5	43.0	DEX < MPH: 38.5	MPH
34	0.0	4.0	No	MPH
11	0.0	0.0	No	DEX
12	4.0	2.0	No	DEX
14	17.5	16.5	No	DEX
23	19.5	16.5	No	DEX
33	0.0	30.5	DEX < MPH: 30.5	DEX
35	0.0	2.5	No	DEX
10	10.0	0.0	MPH < DEX: 10.0	DEX = MPH
13	0.0	0.0	No	DEX = MPH
19	0.0	0.0	No	DEX = MPH
21	7.5	0.0	MPH < DEX: 7.5	DEX = MPH
25	2.5	0.0	No	DEX = MPH
27	2.0	4.0	No	DEX = MPH

^aTotal adverse events score = number of adverse events multiplied by mean severity in a given stimulant condition, as assessed by Barkley's Side-Effect Rating Scale (SERS) rated by parents.

^bThis child was switched from MPH to DEX after the end of the initial trial because of intolerable adverse events.

Discussion

The main objective of the study was to investigate whether the availability of both dextroamphetamine and methylphenidate provided an opportunity to minimize adverse events in a pediatric ADHD stimulant trial. The main finding is that adverse events associated with dextroamphetamine and methylphenidate appear similar at the group level, but may differ in individual children. This difference provides the opportunity to minimize adverse events in the subsample of children in whom both stimulants were associated with a reduction in ADHD symptoms.

Insomnia and decreased appetite were significantly associated with stimulants at the group level, a finding consistently reported in the literature (Greenhill et al. 2001; Cascade et al. 2010; Hodgkins et al. 2012). Contrary to expectations, stimulants (as compared with the placebo) were not found to have a significant overall effect on emotional symptoms (irritability, sadness, anxiety, tendency to cry). Comparisons of severity and prevalence across 17 SERS items revealed only two significant differences between the two stimulants: Dextroamphetamine was associated with higher severity of "insomnia" and a higher prevalence of "unusually happy" than was methylphenidate. It should be mentioned that dextroamphetamine did not differ significantly from placebo in the prevalence of "unusually happy." Efron et al. (1997b) also found that dextroamphetamine was associated with a significantly higher severity of "insomnia", but the same held true in that study for emotional symptoms (irritability, anxiety, sadness, tendency to cry). Several other studies, however, detected no stimulant difference in emotional symptoms (Pelham et al. 1990; Elia et al. 1991; Pelham et al. 1999; Pliszka et al. 2000). Overall, results suggest that the side-effect profiles associated with dextroamphetamine and methylphenidate appear similar but not identical at the group level, a conclusion in line with several reviews comparing methylphenidate

and amphetamine products (Arnold 2000; Brown et al. 2005; Hodgkins et al. 2012).

Thirteen children (42%) of the 31 who responded favorably to one or both stimulants experienced one or more adverse events in association with their best drug. Those with methylphenidate as their best drug experienced an average of 1.3 adverse events, and those with dextroamphetamine as their best drug experienced an average of 1.2 adverse events; a result close to that reported in another placebo-controlled pediatric ADHD stimulant trial comparing adverse events associated with methylphenidate and mixed amphetamine salts, using a side-effect rating scale similar to SERS (Manos et al. 1999). Another important finding in our study was that only 1 child needed to be switched from one stimulant to the other because of intolerable adverse events after the end of the initial trial, and all of the 31 children who responded favorably to one or both stimulants were able to continue stimulant treatment. Efron et al. (1997b) have reported similar results from their crossover study. Prevalence of adverse events vary largely among studies; however, the percentage of children experiencing one or more adverse events have been reported to be 22% in one study (Barbarelli et al. 2006) and 55% in another (Thorell and Dahlstrom 2009). Comparisons are complicated for several reasons. The assessment method may influence the reports of prevalence of adverse events (Lee et al. 2013). Study design (open trial and/or baseline versus placebo-controlled) may also affect the reported prevalence of adverse events (Ahmann et al. 1993; Rapport et al. 2008). Moreover, studies vary in their operationalization of adverse events, in their selection of rating scale items, and in the duration of the trial.

The load of adverse events associated with dextroamphetamine compared with methylphenidate was found to differ substantially in 7 out of the 18 children who responded to both stimulants with a decrease in ADHD symptoms. The clinical importance of this

finding is that the availability of both stimulants resulted in an opportunity to reduce adverse events in these 7 children. In fact, by trying only one stimulant, either methylphenidate or dextroamphetamine, some of these children could have experienced unnecessary adverse events. In clinical practice, one stimulant is usually tried first, and if no favorable effects on ADHD symptoms are found, or severe adverse events occur, the recommendation is to test another stimulant (Greenhill et al. 2002). The prevalence of methylphenidate use in school-aged children, however, outnumbers prescriptions of amphetamine products by >100:1 across the Nordic countries (Zoega et al. 2011), and a marked imbalance in prescribing patterns for the two classes of stimulants for the treatment of ADHD is also the case in the United Kingdom (Hodgkins et al. 2012). Such a bias indicates that amphetamine products seldom are tried despite the fact that studies employing single-subject analyses to compare methylphenidate and dextroamphetamine consistently show that the inclusion of both stimulants optimizes the reduction of ADHD symptoms and may contribute to a reduction in adverse events (Arnold et al. 1978; Pelham et al. 1990; Elia et al. 1991; Green 1996; Efron et al. 1997a,b; O'Malley et al. 2000; Ramtvedt et al. 2013). Utilizing the availability of both stimulants fully may potentially enhance treatment continuation that is found to be affected by both the beneficial outcome and the load of adverse events associated with the treatment (Toomey et al. 2012). The biased preference for methylphenidate reflects a clinical practice in which the potential for optimizing the treatment outcome is not fully utilized. Clinical guidelines may need to emphasize more strongly the benefits associated with the availability of both stimulants.

Our result showing no effect of stimulants on emotional symptoms differs from the results of the Ahmann et al. (1993) and Sonuga-Barke et al. (2009) studies, in which stimulants were associated with a reduction in prevalence and severity of emotional symptoms. The sample size in our study may have been insufficient to detect such an impact, however. In fact, two other studies reporting no impact of stimulants on emotional symptoms based on parent ratings of SERS (Barkley et al. 1990; Lee et al. 2011) also had smaller sample sizes than the studies reporting such an impact. The issue is further complicated by the fact that studies reporting a favorable effect of stimulants on emotional symptoms differ somewhat in the emotional symptoms they report as being affected. Moreover, adverse effects on emotional symptoms have been reported in some studies; in a comparative study lasting for 11 weeks, both dextroamphetamine and methylphenidate, compared with a placebo, were associated with a significant increase in "not happy" (Elia et al. 1991), and an increase in tearfulness was found to be associated with stimulants in the Multimodal Treatment of ADHD (MTA) study (Greenhill et al. 2001). Parent ratings, but not SERS scores, were used in the assessment of adverse events in these two studies. Differences between studies in terms of sample size, duration of trial, design, and methodology may have contributed to these inconsistencies. From a clinical point of view, the key fact emanating from the majority of these studies is that stimulants either demonstrated no overall effect on emotional functioning or reduced the severity/prevalence of emotional symptoms, but some conflicting results emphasize the point that emotional symptoms should be monitored during stimulant treatment.

Limitations

In this study, we analyzed adverse events of stimulants in a short-term trial, using parents (in cooperation with their children)

as the informants. Teacher ratings may provide additional information about adverse events. Furthermore, regular medical examinations are needed in order to monitor the potential appearance of adverse events related to cardiac functions, blood pressure, weight, and growth. Some adverse events – suicide-related events and psychotic symptoms, for example – are extremely rare, and unlikely to occur in small samples and in short-term trials.

The sample size in this study was small, and may have been insufficient to detect less pronounced differences in adverse events between drug conditions at the group level. Each drug condition lasted for only 1 week, and a longer time span may be necessary for the observer to register subtle adverse events that could otherwise go unnoticed. In addition, adverse events may manifest themselves or disappear over time, and short-term assessments are not well suited to capture these fluctuations. Fixed doses were administered in our study. There was variability in mg/kg among the children, a factor that may have been clinically significant.

Because the drugs in this study were not camouflaged in identical capsules (although tablets with similar form, color and texture were distributed in pill dispensers), there was a risk that the drug order could be identified. This issue was addressed in the evaluation meeting with parents and at the end of the trial period for each participant. In only one case did the parent of a child in this study identify the drug order, and that child was removed from the study.

Conclusions

Adverse events associated with dextroamphetamine versus methylphenidate appear similar at the group level, but may differ substantially in individual children. Overall, insomnia and decreased appetite were significantly associated with stimulants. No treatment effect on emotional symptoms was detected. Most of the children experienced no or modest adverse events.

Clinical Significance

The availability of both dextroamphetamine and methylphenidate in stimulant trials provided an opportunity to minimize adverse events in children in whom both stimulants were associated with a reduction in ADHD symptoms; however, this option is not fully utilized in clinical practice because of a biased preference for methylphenidate. Guidelines may need to emphasize more strongly that the availability of both stimulants provides an opportunity to optimize the outcome in stimulant trials.

Future research on adverse events associated with stimulants would benefit from larger sample sizes and long-term observations and registrations with the use of multiple assessment methods and multiple informants.

Disclosures

Henning Aabech is a member of the Strattera Advisory Board, Eli Lilly Norway AS, and a participant in an ADHD Expert Group Meeting held by Shire Nordic Regional Office, Sweden AB, Oslo May 30, 2013. Bjørn Erik Ramtvedt and Kjetil Sundet have no financial relationships with any pharmaceutical company or any other conflict of interests.

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