

Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial

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ABSTRACT

Background. Data on the efficacy and safety of methylphenidate in adults with attention deficit/hyperactivity disorder (ADHD) are lacking in Europe. This study was undertaken to report on the efficacy and safety of methylphenidate in an adult out-patient population with ADHD, and to compare results with US data.

Method. A double-blind randomized cross-over trial comparing methylphenidate and placebo in 45 adults with ADHD with childhood onset was performed in a dose-titration design. Methylphenidate was titrated from 0.5 mg/kg per day in week 1 up to 1.0 mg/kg per day in week 3.

Results. Response rates using methylphenidate varied between 38 and 51%, and using placebo between 7 and 18% ($p < 0.05$), depending on outcome measure used. Although the overall percentage of subjects having any side effect on both methylphenidate and placebo was rather high, side effects on methylphenidate over and above those on placebo were few and mild.

Conclusions. Methylphenidate proves to be an effective and well tolerated treatment for symptoms of ADHD in adults in the short term. Future research should study the long-term response and clarify the impact of gender, co-morbidity, socio-economic status and IQ on response rates in adults with ADHD.

INTRODUCTION

The recognition of attention-deficit/hyperactivity disorder (ADHD) in adults is rapidly growing in Europe. Many professionals have noticed the results of follow-up studies in children with ADHD, showing considerable persistence of the disorder into adulthood (Biederman *et al.* 2000; Barkley *et al.* 2002). The

prevalence of ADHD in adults based on epidemiological research has been estimated at 4.7% (Murphy & Barkley, 1996*a*). ADHD in children as well as adults, is highly co-morbid (Biederman *et al.* 1993; Kooij *et al.* 2001). Recent research has shown that adult ADHD is over-represented in populations with substance use disorders, depression and anxiety disorders (Alpert *et al.* 1996; Milberger *et al.* 1997; Fones *et al.* 2000). This co-morbidity complicates diagnosis and treatment of ADHD in adults.

In the US, many articles and handbooks about diagnosis and treatment of adult ADHD

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have been published. At the same time in Europe, the diagnosis of ADHD in adults leads to many diagnostic and treatment dilemmas to solve. Although US data underscore the descriptive, face, predictive and concurrent validity of ADHD in adults (Spencer *et al.* 1998), scepticism currently leads to under-diagnosis and under-treatment of the adult form of this disabling disorder in Europe. The diagnosis of ADHD in adults as well as the treatment with psychostimulants, have not yet reached the same level of acceptance as in the USA.

Psychostimulants remain a viable first-choice strategy for the pharmacotherapeutic treatment of ADHD. Numerous controlled studies and more than 40 years of clinical experience in children have demonstrated the efficacy and safety of psychostimulants for ADHD (Findling *et al.* 1998). An overview of clinical research in adults with ADHD between 1976 and 2001, shows 5 open and 11 double-blind controlled studies using stimulant medications, mostly methylphenidate (Kooij *et al.* 2001; Prince *et al.* 2002). Except for one open study from our group, controlled studies from Europe are lacking. Response rates in controlled studies range from 25% to 78%. Differences in response rates appear to depend on variability in diagnostic criteria, dose of stimulant prescribed, rates of co-morbidity and response definitions. Higher dosing of stimulants results in more robust responses (Spencer *et al.* 2001). The frequent co-morbidity accompanying ADHD leads to diagnostic difficulties and treatment dilemmas like the order of treatment of the different disorders and the impact of co-morbidity on treatment outcome.

The few controlled studies using stimulants in adult ADHD are all of US origin. There is clearly a need for replication of these data in Europe, to investigate similarities and differences in population and treatment outcome, in order to further validate the diagnosis of ADHD in adults. To our knowledge, this is the first European study comparing methylphenidate and placebo in a large sample of adults diagnosed with ADHD. Mostly, clinical trials fail to answer certain questions of clinical practice due to inherent design features. One of those questions is whether past or current co-morbidity influences response rates of methylphenidate compared to placebo. In this

cross-over trial we included those subjects resembling patients in daily clinical practice.

METHOD

Subjects

Subjects were 45 out-patient adults with ADHD. They were self-referred or referred by other clinicians for assessment of ADHD to the out-patient clinic of GGZ Delfland in Delft, The Netherlands. The DSM-IV diagnosis of childhood-onset and current ADHD was determined by a psychiatrist's clinical evaluation supplemented by the Dutch version of the DSM-IV ADHD rating scale for current symptoms (DuPaul *et al.* 1998). All ADHD types were eligible. Subjects with co-morbid psychiatric disorders were included, unless these disorders required to be treated first or when treatment with methylphenidate was contra-indicated. We prospectively excluded subjects with clinically significant medical conditions, abnormal baseline laboratory values, a history of tic disorders, mental retardation (IQ < 75), organic brain disorders, clinically unstable psychiatric conditions (i.e. suicidal behaviours, psychosis, mania, physical aggression, currently ongoing substance abuse), current use of psychotropics, prior use of methylphenidate or amphetamines, as well as pregnant or nursing women. This study was approved by the local Medical Ethical Committee of the Reinier de Graaf Hospital in Delft. All subjects completed a written informed consent form before inclusion in the study.

Assessments

Prior to inclusion, patients underwent a standard clinical assessment consisting of a psychiatric evaluation by one of two experienced psychiatrists (S.K. or L.K.) using a semi-structured diagnostic interview for ADHD and co-morbid disorders, the Dutch version of structured diagnostic interviews for retrospective diagnosis of ADHD and other disruptive disorders of childhood, i.e. oppositional defiant disorder (ODD) and conduct disorder (CD) as well as antisocial personality disorder (ASP) in adults (DIS-L, N, O, P; Robins *et al.* 1995), a structured diagnostic interview for psychiatric disorders, the Composite International Diagnostic Interview (CIDI, version 2.1, lifetime; Robins *et al.* 1988), a semi-structured diagnostic

interview for borderline and antisocial personality disorders based on DSM-IV criteria, the International Personality Disorder Examination (IPDE; Loranger *et al.* 1994; Duijsens *et al.* 1999). Further assessments comprised a medical history, a physical examination including blood pressure, heart rate and weight measurement as well as laboratory assessments (complete blood cell count, liver, kidney, thyroid, glucose function tests and electrocardiogram). Using the CIDI we assessed anxiety disorders, mood disorders, substance and alcohol use disorders, and eating disorders. The CIDI generates diagnostic information about both past and current disturbances.

For current ADHD-symptoms during the last 6 months, we used a Dutch version of the DSM-IV ADHD rating scale, based on the 18 DSM-IV items for ADHD (DuPaul *et al.* 1998). To facilitate reliability, five complex items (item IA-a, IA-d, H-a, H-c, H-d) were reformulated into two single statements. Thus, the questionnaire consisted of 23 items in total. The wording of the items was slightly adjusted to adults. Each item was to be rated by the physician on a scale from 0–3 (0=rarely or never; 1=sometimes; 2=often; 3=very often). In rendering each item on the scale, the word 'often' was eliminated from the wording in the original DSM-IV list, so that the frequency could be chosen as an answer. Inattention and hyperactive/impulsive items alternated in their sequence listed on the scale. A symptom was considered present if the answer given to the item was 'often' or 'very often' (score 2 or 3). This threshold reflects the wording in all of the DSM-IV items as the frequency of occurrence to be clinically relevant.

To be given a full diagnosis of adult ADHD, subjects must have (1) met 6 of 9 DSM-IV criteria of inattention and/or hyperactivity/impulsivity for a diagnosis of ADHD in childhood and at least 5 of 9 criteria in adulthood, (2) described a chronic persisting course of ADHD symptoms from childhood to adulthood, and (3) endorsed a moderate to severe level of impairment attributed to the ADHD symptoms. A cut-off point of 5 of 9 criteria was set for adult diagnosis of ADHD based on literature and epidemiological data using the same DSM-IV ADHD Rating Scale (Murphy & Barkley, 1996a; Biederman *et al.* 2000).

In order to obtain information about lifetime ADHD symptoms and impairment, the patient, the partner and if available the parents were interviewed. Information on school reports was examined in order to build the diagnosis in childhood.

To assess intellectual functioning, we administered a short form (Block Design, Picture Arrangement, Vocabulary and Arithmetic) of the Dutch WAIS-III. The reliability of this short form has not been established for the WAIS-III, but for the WAIS-R the correlation with full administration is 0.93 (McNemar, 1974).

Outcome measures

The outcomes of this study comprise three main domains of symptoms: ADHD, depression and anxiety. In addition we assessed impairment and adverse events. To assess symptoms of ADHD, we used the Dutch self-report-version of the DSM-IV ADHD rating scale (DuPaul *et al.* 1998) which has been shown to be sensitive to drug effects in paediatric (Barkley, 1990) and adult (Spencer *et al.* 1995) samples. For the analyses the scores were first averaged over days of the week and subsequently over all 23 items.

Severity of ADHD was assessed with the Clinical Global Impression Scale for ADHD (CGI-ADHD). The CGI has often been used in psychopharmacology research and has been shown to be drug sensitive (NIMH, 1985). We used the global severity subscale of the CGI (1 indicates not ill; 7, extremely ill) in our analyses.

For the assessment of depressive symptoms we used the physician based 17-item Hamilton Depression Scale (HAM-D) (cut-off clinical depression >16). For anxiety we used the 14-item physician based Hamilton Anxiety Scale (HAM-A) (cut-off clinical anxiety >21). These are widely used scales with established psychometric properties (Hamilton, 1959, 1960).

We assessed functional impairment using the Dutch version of the Sheehan Disability Scale (SDS) ranging from 0 to 10 in 3 domains (functioning in work, social contacts/leisure time and family) (Sheehan *et al.* 1996). Functioning was further assessed using the Global Assessment of Functioning scale (GAF). The GAF scale ranges from 10 to 100 (APA, 1994).

In addition the subjects recorded adverse events. We slightly modified the Side Effects

Rating Scale from Barkley (Barkley & Murphy, 1998). The 14 items were rated from 0 to 3 (0 indicating 'never'; 3 indicating 'very often'). All assessments were made at baseline and at the end of the first and second treatment period, except for the DSM-IV ADHD rating scale, the CGI-ADHD and adverse events list, which were administered weekly.

Outcome definitions

The primary outcome in this study was clinical response defined as a decrease of at least 2 points on the investigator based CGI-ADHD severity scale over the total treatment period (3 weeks), as well as a 30% symptom reduction or more as measured by the self-reported DSM-IV ADHD rating scale. Secondary outcomes were the level of DSM-IV symptoms of ADHD, as well as symptom levels of depression and anxiety, global functioning (GAF), and impairment (SDS). Safety measures were the occurrence of adverse events (dichotomous), blood pressure, weight, heart rate and number of adverse events (all continuous).

Intervention

A randomized, placebo-controlled, double-blind cross-over trial comparing methylphenidate with placebo was performed. There were two 3-week treatment periods with 1 week of washout in between. The order of treatment (methylphenidate–placebo or placebo–methylphenidate) was randomized by the pharmacist using a computer generated list. Weekly supplies of methylphenidate or placebo were dispensed by the pharmacy in identically appearing tablets of 10 mg. Medication was prescribed under double-blind conditions in four or five times a day dosing. Subjects used a device (Memos) containing compartments for the tablets and a timer in order to dose four or five times a day on time. Dosing was adjusted to five times a day when rebound occurred. Compliance was monitored by electronic registration of the opening of the device, at each visit to the pharmacy. Compliance was defined as >80% of time opening the device within 15 min after the timer's signal. Study medication was titrated up from low to high doses to avoid exposure to high initial doses of active medication and to minimize side effects. Study treatment started with 0.5 mg/kg per day by week 1, followed by

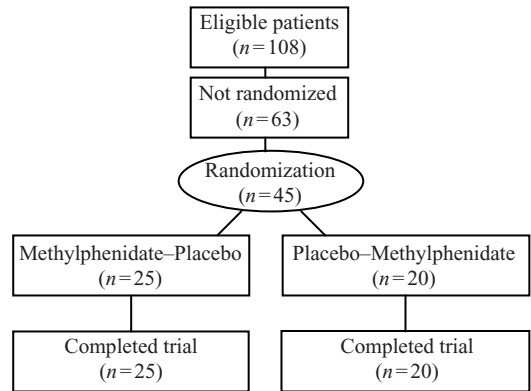


FIG. 1. CONSORT diagram (see text).

0.75 mg/kg per day by week 2, and up to 1.0 mg/kg per day by week 3, unless adverse effects emerged. This titration approach was chosen in accordance with clinical practice and the trial of Spencer *et al.* (1995). To control for possible substance use, patients were asked two times during the study to provide a urine sample.

Statistical analysis

The two randomized groups were first compared with respect to baseline variables. Dichotomous outcomes were compared and tested for statistical significance of treatment effects using the McNemar test for paired proportions. All continuous outcomes were statistically tested for treatment effects using the paired *t* test. Since dose titration took place over the full 3-week treatment period, and to allow a fully developed effect of methylphenidate to be estimated, the results for weeks 3 (last week of first period) and 7 (last week of second period) were used for subsequent statistical analyses. The level of significance (alpha) was 0.05 (two-sided). We additionally explored the association between response to methylphenidate (relative to placebo) and age, gender and co-morbidity at baseline in subgroup analyses. These associations were statistically tested using the χ^2 test, or in case the expected number in a cell was lower than five, Fisher's exact test.

RESULTS

Study sample

After screening 108 subjects, 63 were not eligible (Fig. 1): 15 withdrew consent to the trial and

Table 1. Demographic and clinical characteristics

Characteristic	Value
Number of subjects	45
Male, <i>n</i> (%)	24 (53.3)
Mean age (range)	39.1 (20–56)
Marital status	
Married/relationship, <i>n</i> (%)	28 (62.2)
Single/divorced/living with parents, <i>n</i> (%)	17 (37.8)
School failure, <i>n</i> (%)	34 (76)
Repeated grade, <i>n</i> (%)	14 (31)
Special class, <i>n</i> (%)	8 (18)
Tutoring, <i>n</i> (%)	12 (27)
Educational level	
Lower educational level, <i>n</i> (%)	26 (58)
High school, <i>n</i> (%)	14 (31)
University, <i>n</i> (%)	5 (11)
Cognitive testing	
Full scale IQ, mean (s.d.; range)	101 (18; 76–142)
Working, <i>n</i> (%)	31 (69)
Social security/sickness benefit, <i>n</i> (%)	13 (29)
Impairment	
SDS, mean (s.d.)	7.6 (1.1)
Current GAF, mean (s.d.)	57 (6.1)
Any co-morbid axis I disorder, <i>n</i> (%)	35 (78)
Multiple (≥ 2) disorders, <i>n</i> (%)	23 (66)
Total number of axis I disorders (mean)	104 (3.0)
Past, <i>n</i>	81
Current (≤ 6 months), <i>n</i>	23
Any mood disorder, <i>n</i> (%)	23 (66)
Past, <i>n</i> (%)	17 (49)
Current (≤ 6 months), <i>n</i> (%)	6 (17)
Multiple mood disorders (≥ 2), <i>n</i> (%)	6 (17)
Mood disorders, <i>n</i>	28
Major depression, <i>n</i>	15
Dysthymia, <i>n</i>	7
Bipolar I disorder, <i>n</i>	6
HAM-D baseline, mean (s.d.)	8.0 (5.8)
HAM-D baseline ≥ 6 , <i>n</i> (%)	4 (9)
Any anxiety disorder, <i>n</i> (%)	22 (63)
Past, <i>n</i> (%)	10 (29)
Current (≤ 6 months), <i>n</i> (%)	12 (34)
Multiple (≥ 2) anxiety disorders, <i>n</i> (%)	8 (23)
Anxiety disorders, <i>n</i>	34
Obsessive-compulsive disorder, <i>n</i>	3
Specific phobia, <i>n</i>	12
Social phobia, <i>n</i>	9
Panic disorder, <i>n</i>	3
Agoraphobia, <i>n</i>	3
Generalized anxiety disorder, <i>n</i>	2
Post-traumatic stress disorder, <i>n</i>	2
HAM-A baseline, mean (s.d.)	7.8 (6.0)
HAM-A ≥ 21 , <i>n</i> (%)	2 (4)
Any substance use disorder (SUD), <i>n</i> (%)	18 (51)
Past, <i>n</i> (%)	15 (43)
Current (≤ 6 months), <i>n</i> (%)	3 (9)
Multiple (≥ 2) SUDs, <i>n</i> (%)	9 (26)
SUDs, <i>n</i>	37
Alcohol abuse, <i>n</i>	11
Alcohol dependence, <i>n</i>	3
Cannabis abuse, <i>n</i>	2
Cannabis dependence, <i>n</i>	2
Nicotine dependence, <i>n</i>	11
Nicotine withdrawal, <i>n</i>	6
Other SUD, <i>n</i>	1
Bulimia nervosa, <i>n</i> (%)	3 (9)
Past, <i>n</i> (%)	1 (3)
Current (≤ 6 months), <i>n</i> (%)	2 (6)

Table 1 (cont.)

Characteristic	Value
Co-morbid antisocial/borderline personality disorder, <i>n</i> (%)	15 (33)
Prior treatment, <i>n</i> (%)	39 (87)
Age first treatment (<i>n</i> = 41), mean (range)	18.3 (2–43)
2–20 years, <i>n</i> (%)	25 (61)
> 21 years, <i>n</i> (%)	16 (39)

we excluded 41 subjects due to clinically significant medical conditions (4), abnormal baseline laboratory values (1), clinically unstable psychiatric conditions (7), current use of psychotropics (11) and prior use of methylphenidate or amphetamines (18). After diagnostic assessment, 7 patients were ineligible due to currently ongoing substance abuse (5), hypertension (1) and severe depression that urgently required treatment (1). Eligible and ineligible subjects did not differ significantly in age or gender. Forty-five subjects (41%) were randomized. 25 were treated with methylphenidate followed by placebo, and 20 with placebo followed by methylphenidate. Table 1 shows the demographic and psychiatric characteristics of these subjects. The subjects were out-patient adults, of whom equal numbers of each gender were included (24 men and 21 women) between 20 and 56 years of age (mean 39 years). All subjects satisfied diagnostic criteria for current ADHD with at least 5 of 9 symptoms of inattention and/or hyperactivity/impulsivity, and a childhood onset with at least 6 of 9 symptoms in one or both symptom domains. Collateral information was available of 41 family members (34 parents and 7 siblings) and 28 partners. All family members and partners confirmed the diagnosis to a certain extent. The extent varied between 'very likely' (25 partners and 26 family members), 'likely' (3 partners and 7 family members) and 'possible' (8 family members).

According to the DSM-IV ADHD rating scale for current symptoms, 43 patients met criteria for ADHD, combined type and 2 for ADHD, hyperactive/impulsive type. All subjects completed the trial. One subject completed the last week of the study 1 week later for logistic reasons. One subject used morphine in the fifth week, as measured with urine control and confirmed by urinary analysis. Data of both

Table 2. Raw scores of primary outcome measures (mean, s.d.), by treatment-order group (Mph–Plac/Plac–Mph) and week of treatment

Outcome measure	Wk 1	Wk 2	Wk 3	Wk 5	Wk 6	Wk 7
DSM-IV ADHD Rating Scale*						
Mph–Plac	1.57 (0.55)	1.44 (0.66)	1.37 (0.65)	1.47 (0.55)	1.48 (0.59)	1.45 (0.59)
Plac–Mph	1.62 (0.56)	1.54 (0.62)	1.55 (0.56)	1.42 (0.56)	1.42 (0.59)	1.24 (0.74)
CGI-Severity ADHD†						
Mph–Plac	4.96 (1.46)	4.40 (1.35)	4.36 (1.47)	5.48 (0.96)	5.32 (1.18)	5.40 (1.50)
Plac–Mph	5.05 (0.76)	4.95 (1.19)	4.80 (1.47)	4.95 (1.47)	4.80 (1.70)	4.40 (1.70)

* $p=0.064$ and † $p=0.026$, Mph compared to placebo, in cross-over analysis at endpoint (see text).

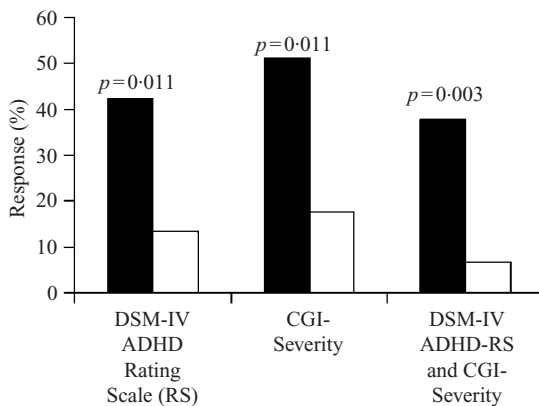


Fig. 2. Summary of response (%) to methylphenidate (■) and placebo (□) in the cross-over analysis at the end of the treatment period, according to three different definitions of response (see text); p values from McNemar test.

subjects have been included in the analyses according to the intention to treat principle.

After randomization, the two treatment order groups (methylphenidate–placebo, and placebo–methylphenidate) did not differ on any of the demographic and clinical characteristics as described in Table 1.

Average daily doses of methylphenidate and placebo by the end of week 1 were 0.5 mg/kg (0.31–0.55 mg/kg) and 0.5 mg/kg (0.45–0.55 mg/kg) respectively; by week 2: 0.75 mg/kg (0.31–0.82 mg/kg) and 0.76 mg/kg (0.69–0.82 mg/kg); by week 3: 0.91 mg/kg (0.54–1.04 mg/kg) and 0.98 mg/kg (0.71–1.04). 16/45 subjects using methylphenidate preferred the five instead of four times a day dosing in the third week v. 6/45 subjects using placebo.

According to the combined DSM-IV ADHD rating scale and CGI-severity outcome measure,

7% responded to placebo v. 38% to methylphenidate (Fig. 2). This difference being the primary measure of efficacy was statistically significant ($p=0.003$). These figures were 0 and 16 in week 1, and 7 and 29 in week 2, respectively.

If response was based solely on the DSM-IV ADHD rating scale, i.e. based on the subject's rating only, these percentages at endpoint were somewhat higher: 13% and 42% respectively ($p=0.011$). In the first week they were 4% and 20%, in the second week 11% and 31% respectively. In terms of CGI-severity, i.e. based on investigator's assessment, 18% responded to placebo at endpoint, and 51% to methylphenidate ($p=0.011$). In the first week these percentages were 4% and 24%, in the second week 16% and 44% respectively.

In Table 2 mean symptom levels per week for both groups separately are shown according to outcome measure. After 3 weeks of methylphenidate a substantially lower symptom level as measured by both the DSM-IV ADHD rating scale as well as the CGI-severity was observed than during placebo treatment. On average, methylphenidate use was associated with a 0.19 lower DSM-IV ADHD rating scale score ($p=0.064$) and a 0.72 lower score on the CGI-severity score ($p=0.026$) compared to placebo.

Compliance data were available for 41 subjects: 13 were non-compliant v. 28 compliant (compliance = taking medication > 80% of time within 15 min after the timer's signal). Response rates differed between compliant and non-compliant subjects: 43% responded in the compliant (12/28) v. 23% (3/13) in the non-compliant group (Fisher's exact test, $p=0.31$). This trend reached no significance due to small sample sizes.

Compared to placebo, 0.93 lower score on the SDS was observed after methylphenidate treatment ($p=0.029$). Better functioning on methylphenidate was also apparent from a 2.5 higher GAF score, but this was not statistically significant ($p=0.104$). Methylphenidate was associated with higher symptom levels of depression and anxiety than placebo, as was apparent from higher HAM-D and HAM-A scores: 2.4 ($p=0.002$) and 2.9 ($p=0.002$) points, respectively. When defined as a HAM-D >16, 11% ($n=5$) had depression after methylphenidate compared to 9% ($n=4$) after placebo. When defined as a HAM-A >21, 7% ($n=3$) had anxiety after methylphenidate compared to 4% ($n=2$) after placebo.

Exploratory analyses revealed that the clinical response to methylphenidate was not clearly affected by gender, age, lifetime or current (within the last 6 months) co-morbidity, severity of anxiety and depression or intelligence (details can be obtained from the first author on request).

Adverse effects

While treated with methylphenidate 82% of the subjects reported any adverse effect on the Side Effects Rating Scale, v. 69% during treatment with placebo ($p=0.11$). The mean number of adverse effects was 0.9 higher during methylphenidate than during placebo ($p=0.004$). The only adverse effect that occurred significantly more often using methylphenidate than using placebo, was loss of appetite (22% v. 4%; $p=0.039$). Sleeping problems (33% v. 22%; $p=0.27$), headache (16% v. 4%; $p=0.18$), tachycardia (9% v. 2%; $p=0.25$), dizziness (16% v. 7%; $p=0.34$), abdominal complaints (13% v. 4%; $p=0.22$), dry mouth (24% v. 7%; $p=0.06$) and tics (7% v. 2%; $p=0.5$) were somewhat more prevalent during methylphenidate than during placebo treatment, but these differences were not statistically significant. The rate of other adverse effects was similar for methylphenidate and placebo. Adverse effects were no reason for drop-out. However, 8 patients (18%) lowered their dose due to adverse effects using methylphenidate, compared to none using placebo. One patient lowered the dose due to headache after the first week, and 7 due to nervousness/irritability before starting the highest dose in the third week.

Further, compared to placebo, the systolic blood pressure was 0.13 mmHg higher after methylphenidate but this was not statistically significant ($p=0.954$). The diastolic blood pressure remained virtually unchanged. Mean heart rate was 4.8 beats/min higher ($p=0.002$) and mean body weight was 1.7 kg lower ($p<0.001$) after methylphenidate treatment compared to placebo.

DISCUSSION

Efficacy and safety

This is the first European randomized double-blind study comparing methylphenidate to placebo in a large sample of adults with ADHD. Indeed, ADHD in adults can be identified and reliably diagnosed using the same diagnostic procedures as in the USA, using collateral information about childhood onset of symptoms and current functioning.

We demonstrated that short-acting methylphenidate with an average daily dose of 0.9 mg/kg per day, is an effective and well tolerated treatment in the short term. Response started at the lowest dose in the first week and proved more robust using higher doses. This is in accordance to other paediatric and adult studies using a stepwise increase in dose (Rapport *et al.* 1987; Spencer *et al.* 1995). In addition, short-term use of methylphenidate was associated with improved functioning in daily work, social activities and family life. Placebo response was low. This is also in accordance with other studies using methylphenidate in children and adults with ADHD (Spencer *et al.* 1996).

No marked effect of gender, age, lifetime or current (within the last 6 months) co-morbidity, intelligence or severity of anxiety and depression on the effectiveness of methylphenidate could be found. However, definite conclusions cannot be drawn as to the influence of these factors due to small sample sizes, and therefore limited statistical power.

Although methylphenidate as compared to placebo slightly and significantly increased the level of depressive and anxiety symptoms, the clinical significance of these findings was unclear. Above, no serious symptoms of anxiety or depression emerged in the short-term that led to adjust clinical management of any of the subjects. Future research should clarify the

course of depressive and anxiety symptoms during treatment with methylphenidate in the long-term.

The mean higher heart rate and mean lower body weight during methylphenidate treatment were not clinically significant and no subject required alteration of the dose as a consequence. These changes are in accordance with the literature (Spencer *et al.* 1995). Although the overall percentage of subjects having any side effect on both methylphenidate and placebo was rather high, side effects on methylphenidate over and above those on placebo were few and mild. Only loss of appetite happened statistically significantly more frequently when comparing methylphenidate with placebo. Adverse effects were no reason for dropout. Most patients were able to tolerate the highest average daily dose of 0.9 mg/kg per day. The frequency of dose reduction and the frequency and the kind of adverse effects are in accordance with the literature in controlled studies in children and adults using methylphenidate (Barkley *et al.* 1990; Spencer *et al.* 1995).

Comparison with US studies

In the eight controlled trials in adults with ADHD using methylphenidate response rates between 25% and 78% have been reported. Discrepancies in response rates have been attributed to differences in ascertainment, sample characteristics with varying levels of comorbidity, diagnostic methods and daily doses. Of all studies performed, we used the largest sample ($n=45$ v. $n=8-37$, mean 25). Our response rates, varying between 38% and 51% depending on outcome measure used, are in accordance to other studies. Results of these studies, however, are difficult to compare, as no information about ascertainment and comorbidity was provided, diagnostic criteria and outcome measures were not well defined and lower doses of methylphenidate were used (0.4–0.7 mg/kg per day) (Prince & Wilens, 2002). The most similar US study from Spencer *et al.* (1995), used the same double-blind crossover design, outcome measures and outcome definitions, and the same dose titration to 0.9 mg/kg per day. The reported response rate was 78%. A difference between the two studies is the use of only investigator-based outcome measures (Spencer), whereas we used both

investigator-based and subject-based ratings (CGI-Severity respectively DSM-IV ADHD rating scale). The investigator-based response rate was slightly higher than that based on the subjects' ratings only; the combined outcome measure showing the lowest response rate. This use of combined investigator and subject ratings might be partly responsible for the differences in outcome.

In addition, possible explanations for our lower response rate are the following differences: a different ascertainment and referral pattern (psychiatric outpatients v. high intellectual and socio-economical functioning academic underachievers), we excluded less subjects (enrolment 41% v. 29%), and included more lifetime co-morbid disorders (mean 3.0 v. 2.6), and more cluster B personality disorders (33% v. 13% its predecessor, conduct disorder). Almost every subject had a history of prior psychiatric or psychological treatment (87%) compared to none in the Spencer study, and 61% of those subjects started treatment before the age of 20 years. In addition, our population had a higher history of school failure (76% v. 43%) and lower mean IQ (101 v. 114) leading conceivably to a lower educational (this study 58%) and socio-economical level (Spencer's study: 74% highest socio-economic strata).

The conclusion could be that our more psychiatrically disturbed outpatient population, being more impaired on various measures, shows lower response rates than a more intellectual population being referred for underachievement. The population we included in this trial seems more representative of the patients seen in daily clinical practice, where many children and adults with ADHD suffer from two or more co-morbid disorders (Biederman *et al.* 1993; Murphy & Barkley, 1996*b*; Kooij *et al.* 2001), and adults with ADHD often have co-morbid personality disorders (Mannuzza *et al.* 1993). In addition, adults with ADHD have a mean duration of 12.5 years previous psychological or psychiatric treatment (Kooij *et al.* 2001) and lower educational levels and socio-economic status (SES) due to underachievement (Seidman *et al.* 1998). Possibly, the use of subject-based ratings leads to lower response rates than the use of investigator's ratings. This could be attributable to the

subjects' difficulties in reflecting on their own behaviour, leading to under-reporting.

The high percentage of lifetime co-morbid substance use disorders (51%) is characteristic for the adult population. An important research question is whether ongoing treatment with methylphenidate can reduce substance abuse in this population. In children with ADHD, treatment with methylphenidate proved to reduce the risk of substance abuse to a normal level; a recent review in adults with ADHD and substance abuse indicated the same conclusion (Wilens *et al.* 2003).

Recently, new stimulant preparations for ADHD have or will soon come to the market in the USA, all using long-acting delivery systems. These long-acting, once daily psychostimulant medications are likely to improve the adherence to prescribed regimens and the level of care for adults with ADHD. In future research using larger samples and a long-term design, the impact of gender, IQ, history of prior treatment, and co-morbidity on response rates using (long-acting) methylphenidate and other medications should be further clarified.

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