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ORIGINAL PAPER

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A randomised, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/hyperactivity disorder

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Abstract *Introduction* Attention-deficit/hyperactivity disorder (ADHD) affects many adults who had ADHD in childhood. Although stimulants and methylphenidate in particular are a common off-label treatment for adult patients with ADHD in European countries, little is known about their long-term efficacy and safety. *Methods* A randomized, 24-week double-blind, placebo-controlled, parallel-design study of extended-release methylphenidate (MPH ER) in 359 adult individuals with ADHD according to DSM-IV. Standardized instruments were used for diagnosis. Treatment was started with MPH ER doses of 10 mg/day and titrated up to 60 mg/day, depending on individual efficacy and tolerability. Mean daily MPH SR dose was 0.55 mg/kg. *Results* Treatment with MPH ER resulted in clinical and statistically significant reductions of ADHD symptoms rated with the Wender-Reimherr adult attention deficit disorder scale (WRAADDS) and symptoms of inattention and hyperactivity/impulsivity according to DSM-IV, respectively. Improvements were maintained significant versus placebo up to week 24 of treatment. At endpoint, 61% of the subjects receiving MPH ER were rated as responders according to the a priori definition of response of more than 30% reduction of the WRAADDS score, compared to 42% in the placebo group. The second defined response criterion of much or very much improved on the clinical global impression scale (CGI) was fulfilled by 55% of subjects receiving MPH ER and 37% of subjects receiving placebo. MPH ER treatment was associated with a statistically significant increase of pulse at week 4 (72 bpm at baseline, 77 bpm at week 4). There were no significant differences of heart rate or blood pressure between treatment and placebo groups at any time point. *Discussion* MPH ER treatment in low to moderate doses was effective and safe in the treatment of ADHD in adults. Efficacy measures were clinical and statistically significant and robustly sustained during the 24-week observation period. In this study, no clinical significant effects on blood pressure but a transient increase of the heart rate were found. The interpretation of the results is limited by the low dose-range used in this study, the high drop-out rate and placebo-response which might have affected the therapeutic effect size.

Key words ADHD · adults · methylphenidate · randomized trial · placebo · efficacy · long-term

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Introduction

Adult attention-deficit hyperactivity disorder (ADHD) is a chronic disorder with a cross-national prevalence of 3.4% [10]. In child- and adolescent psychiatry, stimulants and the noradrenergic agent atomoxetine are licensed worldwide for the treatment of ADHD. In many non-European countries they are also licensed for the treatment of adults with ADHD. Unfortunately there is no approved treatment for adults suffering from ADHD among the countries of the European Union (EU). However, methylphenidate (MPH) has been declared uniformly by different European guideline groups as the first choice therapy in adult ADHD [8, 21]. Just recently this point of view has been underlined by the NICE Guideline Development Group [19].

There is little doubt that stimulants and MPH in particular, are effective in the treatment of ADHD even in adults. Beginning with the study by Wood et al. [37] numerous randomized, double-blind, placebo-controlled investigations have explored the effects of MPH in adult ADHD [4, 5, 14, 31, 32, 35]. With the exception of Mattes et al. [16] and Kuperman et al. [15] all studies came to the conclusion that MPH is an effective treatment not only in child or adolescent ADHD but also in the treatment of adults with ADHD. Adverse events reported in the above mentioned studies were comparable.

It is important to note that the above mentioned studies were exclusively short term investigations lasting 6–8 weeks and provide limited information regarding safety and efficacy of MPH in medium or long term administration. Thus we performed a 24-week study with extended-release methylphenidate (MPH ER) in order to evaluate the robustness of the treatment effects and prevalence of adverse events under chronic administration of MPH ER. Although treatment with low MPH doses have been shown to be effective in treatment of adult ADHD [11, 23], there is no doubt that maximum reduction of ADHD psychopathology might be achieved with high doses of 1.0 mg/kg and more [9]. However, if MPH ER has to be administered chronically over periods of months or years, it seems not only important to produce a maximum symptom reduction with just tolerable high MPH doses, but to dispose of a treatment regime that also warrants high compliance and does not interfere with the patients' requirements of daily living. Here we were interested to explore whether low doses of MPH ER in medium term prescription may result in a clinically meaningful reduction of ADHD symptoms accompanied with convincing results regarding tolerability and compliance.

Methods and materials

Subjects

Subjects were outpatients with ADHD aged >18 years. For study inclusion the subject had to fulfil the DSM-IV criteria for ADHD. The diagnosis was established by psychiatric expert assessment including a German version of the ADHD Rating Scale-IV (ADHD RS-IV [7], ADHD-DC [29]). This instrument is based on the 18 psychopathological DSM-IV criteria for ADHD and the additional DSM-IV criteria referring to the age of onset, pervasiveness, functional disabilities and burden.

The German version of the structured clinical interviews for DSM disorders (SKID-I and -II) [36] was used to assess axis I and II comorbid psychiatric diagnoses. Individuals with low intelligence (IQ < 85), schizophrenia, bipolar disorder, acute depressive episode, acute anxiety disorders and other unstable psychiatric conditions were excluded, as were subjects with any serious medical illness. Also subjects with evidence of drug or alcohol dependence during the preceding 6 months, pregnant or nursing women, persons who had participated in a previous drug trial in the last 30 days and individuals treated with any psychopharmacological drug in addition to study medication were not included. A washout period of at least 2 weeks was necessary for any psychopharmacological drug before study inclusion. Urine screening for drugs of abuse was performed at the screening visit, at weeks 8 and 24, and could be repeated at any time of the study at the investigator's discretion.

The study was approved by the ethical committee of the State of the Saarland. All patients provided written informed consent. Furthermore the study was registered with the Federal Opium Agency at the Federal Institute for Drugs and Medical Devices. Moreover the trial was registered at ClinicalTrials.gov (NCT00619840).

Procedure

A multi-center, double-blind, randomized, placebo-controlled, 24-week study with parallel-group design was conducted. Clinicians and research staff from 28 study centres across Germany were well experienced in diagnosing and treating adult ADHD patients and were trained to the instruments used in the trial. The participants (mean number 13 participants/study centre) were randomized to MPH ER or placebo at a ratio of 2:1. MPH ER is a MPH preparation manufactured by Medice Company (Germany) with a proportion of 50% immediate release MPH and 50% of extended release MPH. The effective time of action is at least 7 h. The drug was described and compared with other long acting MPH medications by the European guideline group [3].

Medication was titrated b.i.d. after breakfast and lunch during the first 5 weeks to a maximum dose of 60 mg/day, starting with 10 mg/day. Lower daily doses were administered in the case of intolerable adverse events and if higher daily doses did not lead to increased improvement. The interval between the two doses should be 6–8 h. The minimum maintenance dose after week 5 was 20 mg/day. A standardised disease management programme consisting of 7 sessions was administered to all participants of the study. The programme was designed especially for the study to avoid ethical objections to keeping subjects on placebo therapy for at least 24 weeks. Disease management sessions were performed at baseline, weeks 1, 3, 5, 8, 12 and 18. During these sessions patients received information about ADHD aetiology and symptoms, support in perception of symptoms and specific problems, help with the management of self-regulation and emotional problems, time management and performing daily routines.

Assessments

For the assessment of the inclusion and exclusion criteria each subject underwent a comprehensive clinical assessment by a certified psychiatrist using standardized rating scales and interviews. The examination included medical history, physical examination, vital parameters, body weight, liver function tests, complete blood count EEG and ECG in the case of a history of cardiac problems.

As mentioned above, ADHD was diagnosed according to DSM-IV criteria. Whenever possible, a retrospective assessment of childhood ADHD symptoms was made by report of informants. In

addition, the German short version of the Wender Utah rating scale (WURS) [34] was administered to all subjects in order to make sure that childhood ADHD symptoms were present by a retrospective self report of the patient [24, 25].

The primary outcome measure was the total score of the German version of the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) [26, 28, 34]. When the study design was constructed the WRAADDS was the only internationally accepted ADHD interview with an authorized German translation and validation on a German population [26, 27]. Other instruments which were used frequently in treatment studies of adult ADHD like the Conners Adult ADHD rating scale observer version (CAARS) [6] or the ADHD rating scale-IV [7] were neither translated in German nor validated. The WRAADDS consists of 28 items, which are collected during an interview by a clinical expert. The items belong to 7 psychopathological domains. Beside the 3 DSM-IV domains inattention, impulsivity and hyperactivity the WRAADDS has 4 additional domains: hot temper, affective lability, emotional overreactivity and disorganization. The additional 4 syndromes are thought to be typical for the psychopathology in adult ADHD. Each item can be rated on a 0–2 Lickert scale. WRAADDS assessments were performed at screening, baseline and at weeks 1, 2, 3, 4, 5, 6, 8, 12, 18 and 24. Subjects were required to have a WRAADDS total score of at least 28 points at baseline to be included into the study.

A second outcome instrument was the Conners adult adhd rating scale self report long form (CAARS-S:L) [6]. We used the DSM-IV ADHD symptoms total subscale (DATS) as secondary efficacy parameter. This score refers exclusively to the 18 items of the DSM-IV, which constitute the diagnosis of ADHD. The CAARS-S:L was administered at screening, baseline and at each visit.

Overall severity, improvement, overall therapeutic effects and tolerability were assessed with the clinical global impression scale (CGI) [20]. CGI ratings were performed at baseline and at weeks 8 and 24.

Adverse events were studied by free registration of complaints of the patients and by use of the 40 somatic item sheet of the AMDP-system [2, 12].

Statistical analysis

The total score of the WRAADDS is the sum of all items (in case of missing items the sum was divided by the number of items answered and multiplied by 28). Only the final value after 24 weeks was included in the test statistics. Missing data were imputed using the LOCF procedure. The confirmatory analysis was performed on the intent-to-treat (itt) population. Best- and worst-case analyses were performed to confirm the robustness of the trial conclusions. If patients discontinued the study prematurely, the missing WRAADDS score was substituted by 56 (worst case) or 0 (best case).

To compensate for the potential danger of the variance's being dependent on the mean all values were transformed to their ranks for analysis of the primary criterion, used to form a ranked list and mean ranks were calculated in case of ties. The factors and/or covariates "study group", "study site" (as random factor) and "WRAADDS baseline value" were included in a hierarchical mixed linear model. For the purposes of this analysis, type 1 error was set at 0.01. For all other secondary and explorative analyses, type 1 error was 0.05.

The secondary parameters were analysed as appropriate to their scaling.

Results

A sample of 363 patients was randomized. Four patients were excluded because of major protocol violations. A total of 241 patients were randomized to MPH ER and 118 individuals to placebo (Fig. 1). The distribution of genders was approximately equal (Table 1) in both treatment groups. There were no statistically significant differences in terms of subjects' mean age between the MPH ER and the placebo population. No differences in age of ADHD onset, body weight, IQ, ADHD severity, ADHD symptom score by ADHD-DC, WURS-k scores or CGI severity ratings could be found at the beginning of the treatment phase (Table 1). The incidence of comorbid conditions according to SKID-I interviews is shown in Table 2. The proportion of individuals who had received earlier stimulant treatment was equal (38.2 vs. 38.3%) in both groups.

A total of 110 subjects discontinued the study prematurely. The drop-out rate was lower in the MPH ER group compared to the placebo group (24 vs. 43%; Fisher's Exact Test, $P < 0.001$). As shown in Fig. 1, most subjects receiving placebo (25%) dropped out

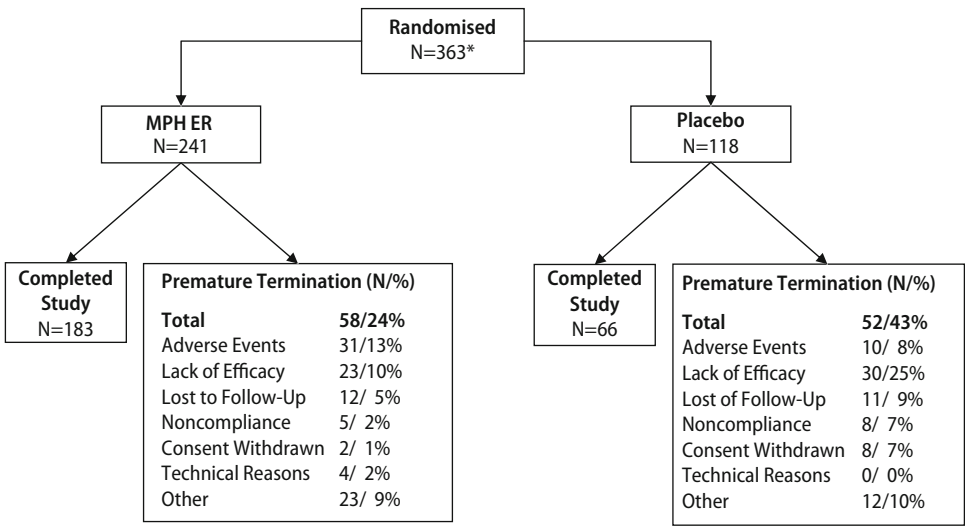

Fig. 1 Flow diagram of subject progress

* 4 subjects were excluded from the ITT population due to major protocol violations

Table 1 Demographic and clinical characteristics of sample (ITT)

	MPH ER (ITT) $N = 241$	Placebo (ITT) $N = 118$	P values
Age (years)	35.2 ± 10.1	33.8 ± 10.6	Wilcoxon U test, p = 0.24
Sex*			Fisher's Exact Test, $P = 0.9$
Male	120 (50%)	58 (50%)	
Female	119 (49%)	60 (51%)	
Body weight (kg)	78.0 ± 17.2	77.3 ± 16.7	Wilcoxon U test, $P = 0.76$
IQ	110.4 ± 14.4	109.7 ± 14.4	Wilcoxon U test, $P = 0.72$
Age at ADHD onset (years)	5.8 ± 2.0	5.7 ± 2.2	Wilcoxon U test, $P = 0.53$
WURS-k (screening)	44.2 ± 11.9	43.1 ± 10.8	Wilcoxon U test, $P = 0.42$
ADHD-DC score** (screening)			Wilcoxon U test,
Inattention	7.6 ± 1.0	7.8 ± 1.1	$P = 0.16$,
Hyperactivity/impulsivity	7.1 ± 1.1	7.1 ± 1.1	$P = 0.31$
WRAADDS score (baseline)	44.8 ± 7.2	45.5 ± 6.8	Wilcoxon U test, p = 0.45
CAARS-S:L DSM-IV ADHD total (baseline)	119.2 ± 29.6	117.9 ± 26.2	Wilcoxon U test, $P = 0.70$
CGI severity of illness (baseline)	5.0 ± 0.80	5.1 ± 0.70	Wilcoxon U test, $P = 0.60$

Data are presented as N (%) or mean ± SD
*2 missings
**The ADHD-DC is designed as a quantitative measure of ADHD symptoms according to DSM-IV items on a 0–2 scale. The maximum sum scores for inattention and hyperactivity/impulsivity, respectively, is 18 points

due to lack of efficacy, whereas adverse events (13%) were the most common reason for drop-outs in the MPH ER group.

Efficacy

The mean daily doses at week 24 were 41.2 ± 18.2 mg in the MPH ER group and 40.8 ± 19.6 mg in the placebo group (Wilcoxon U test, $P = 0.94$). These are equivalent to 0.55 ± 0.27 mg/kg body weight MPH ER and 0.55 ± 0.29 mg/kg body weight placebo, respectively (Wilcoxon U test, $P = 0.99$).

The confirmatory analysis of covariance showed a decrease of the ADHD psychopathology as measured by the WRAADDS in both groups at the end of week 24. The difference between MPH ER and placebo regarding WRAADDS total scores was statistically significant (Wilcoxon U test) at all assessments after the end of the titration phase (Fig. 2). Until week 24 there was a slight increase in ADHD symptoms of the placebo group whereas the scores decreased still further in the MPH group. Stability of therapeutic effects during the maintenance phase was evaluated by comparing WRAADDS total scores at week 24 with week 8. No weakening for the MPH ER efficacy could be shown, rather, there was a further decrease over time in the group receiving MPH ER (paired Wilcoxon-Test, $P = 0.04$). The total effect size (ES) on the primary outcome measure was 0.39.

A total of 30% of the patients terminated the study prematurely. Thus no observable primary outcome measure was available. In the best- and worst-case analyses the results were comparable to the ITT-LOCF population. The difference between MPH ER and placebo patients at week 24 remained significant in favour of MPH ER.

Regarding the psychopathological domains of the WRAADDS we found significant treatment effects favouring MPH ER in all of the 7 syndromes: inattention (ES 0.41), hyperactivity (ES 0.30), hot temper (ES 0.33), affective lability (ES 0.19), emotional overreactivity (ES 0.45), disorganization: (ES 0.31), impulsivity: (ES 0.27).

The CAARS-DATS score declined in both groups during the first 8 weeks with a more marked reduction in the MPH ER group (Fig. 3). After week 8 treatment effects were statistically superior in the MPH ER group as compared to subjects treated with placebo. At week 24, the difference between the MPH ER and the placebo group was statistically significant (Wilcoxon U test, $P = 0.016$). Subjects receiving MPH ER showed additional decline of CAARS-DATS score

Table 2 Probable and confirmed DSM-IV diagnoses according to SCID-I(N)

	MPH ER (ITT) lifetime/current	Placebo (ITT) lifetime/current
Bipolar disorders	4/0	3/0
Major depression	29/0	15/0
Depression NOS	20/12	11/11
Dysthymia	0/11	0/6
Affective disorder caused by specific factor	4/0	3/0
Substance-induced depressive disorder	4/0	2/0
Psychotic disorders	0/0	0/0
Alcohol abuse/dependence	5/0	7/0
Drug abuse/dependence	11/1*	10/0
Panic disorder	5/0	2/0
Phobic disorders	32/17	18/9
Generalized anxiety disorder	3/0	1/0
Anxiety disorder caused by specific factor	1/0	0/0
Substance-induced anxiety disorder	1/0	0/0
Anxiety disorder NOS	9/6	5/3
Obsessive-compulsive disorder	10/8	4/0
PTSD	3/1	2/0
Somatization disorder/Hypochondriasis	ND/19	ND/7
Body dysmorphic disorder	ND/1	ND/1
Adjustment disorders	4/12	0/3
Others	0/1	0/1

*Patient had to be excluded during the study; *ND* not done

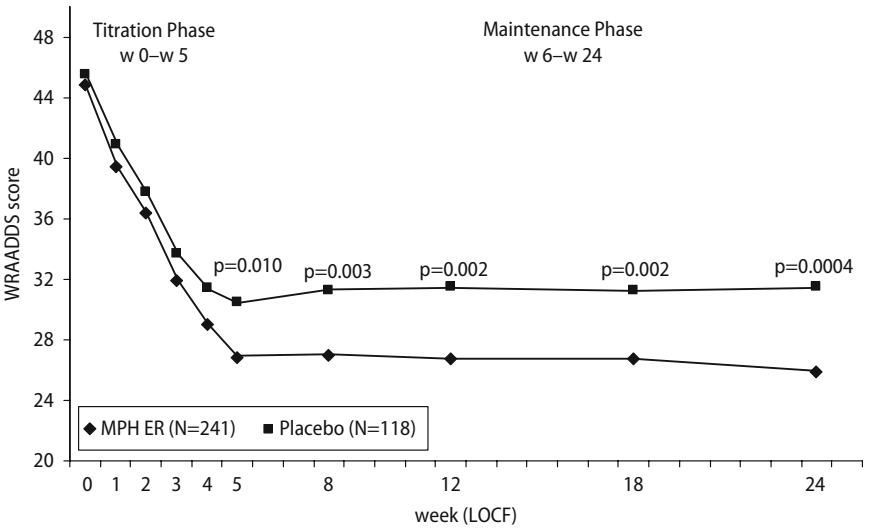

Fig. 2 Chance of WRAADDS scores in the MPH ER and the placebo group by time. LOCF analysis

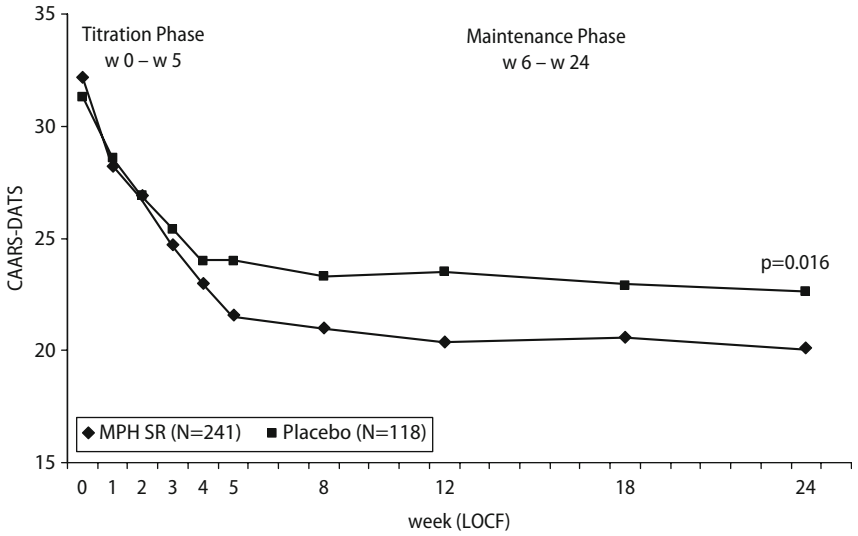

Fig. 3 Chance of CAARS-S:L DSM-IV ADHD Total item scores (CAARS-DATS) in the MPH ER and the placebo group by time. LOCF analysis

between week 8 and week 24 when analysed for changes (paired Wilcoxon test, $P = 0.0008$). The ES on the CAARS-DATS score was 0.28.

With the use of a categorical a priori definition of treatment response (30% reduction of psychopathology by the WRAADDS at week 24) 61% of the MPH ER individuals were rated as responders compared to 42% of the placebo patients (Fig. 4). The difference in responders was statistically significant (Fisher's exact test, $P = 0.001$).

The prevalence of individuals rated as having global improved "much" or "very much" in the CGI was significantly higher in the MPH ER group (54.6%) as compared with the placebo group (36.6%) (Fig. 5 a). The expert CGI ratings of "vast" and "decided" improvement regarding the therapeutic effect were 60.1 and 38.2%, respectively (Fig. 5b). The therapeutic effect of MPH ER assessed by CGI was significantly superior compared to placebo (Wilcoxon U test, $P = 0.0003$).

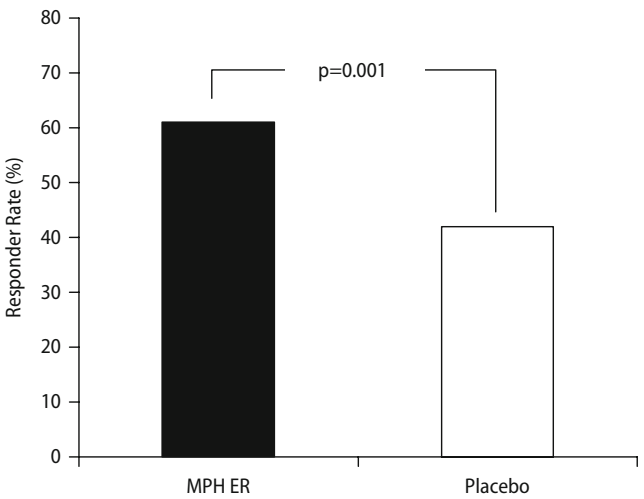

Fig. 4 Responder rate of the MPH ER and the placebo group (compared with Wilcoxon U test). Response was defined as minimum 30% decline of the WRAADDS $P = 0.001$ score from baseline to week 24

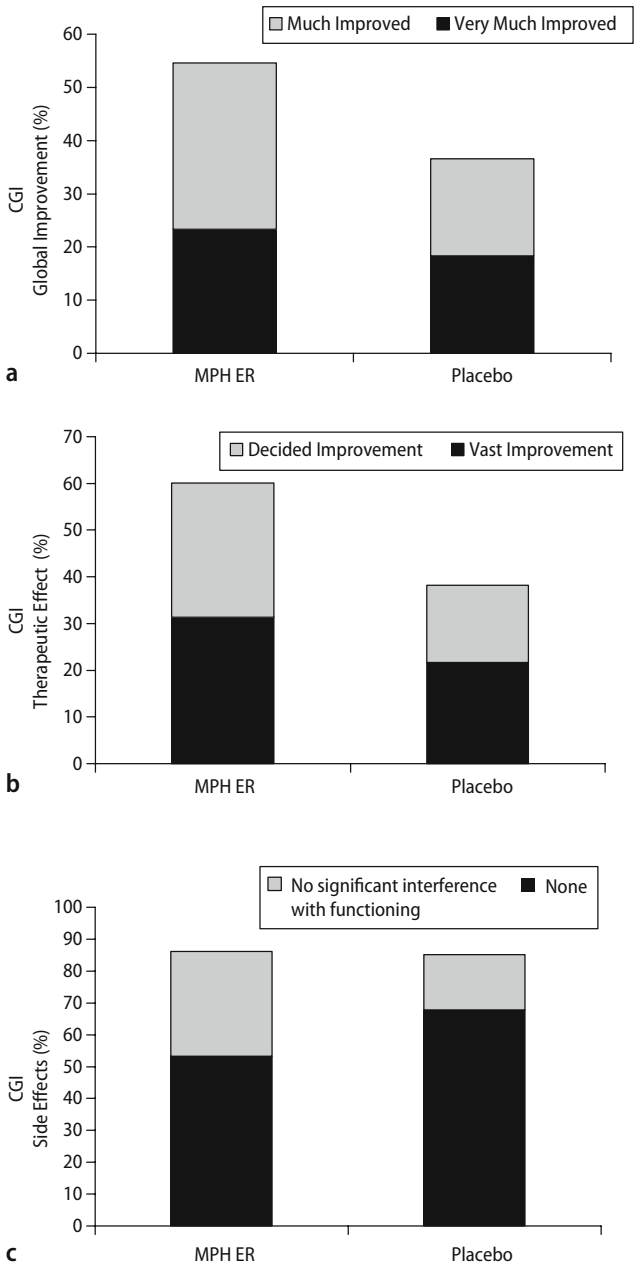

Fig. 5 CGI expert ratings of global improvement (**a**), therapeutic effect (**b**) and side effects (**c**) at week 24 compared to baseline. All of the three differences were statistically significant (Wilcoxon *U* test)

Adverse events

Reduced appetite, dry mouth, sleep disturbances, palpitations, increased thirst, disturbances of menstruation, libido decline and other symptoms were more frequent in the MPH ER group (Table 3). Somnolence, reduced duration of sleep and gastric discomfort were more frequent in the placebo group. There were no differences in neurological abnormalities between subjects receiving MPH ER or placebo, in terms of rigor, decreased muscle tone, dyskinesia, hypokinesia, akathisia, ataxia and nystagmus. In the MPH ER group tremor was detected more often than in the placebo group at week 4 (7 vs. 0%, $P = 0.0095$). Most adverse events were recorded during the titration phase at week 4.

A global assessment of tolerability at study completion showed "good" and "very good" tolerability in 79.3% of the MPH ER group and 89.7% of the placebo group. Regarding CGI ratings of side effects, no side effects or side effects with no functional significance were observed in 86.2% of the subjects treated with MPH ER and 85.2% treated with placebo (Fig. 5c). The proportion of subjects with no adverse events was higher in the placebo group (43%) than in the MPH ER group (26%). At week 24 CGI ratings of side effects were more favourable for the placebo group than for the MPH ER group (Wilcoxon *U* test, $P = 0.0023$).

Table 3 Adverse events measured by somatic symptom scale of AMDP

MPH ER > Placebo	Max. difference at week	MPH ER (%)	Placebo (%)
Decreased appetite	W4	38	13
Dry mouth	W4	30	16
Difficulties falling asleep	W4	25	18
Palpitations	W4	23	9
Excessive thirst	W4	24	12
Menstrual difficulties	W18	11	0
Reduced libido	W24	11	3
Hyperhidrosis	W24	12	1
Hot flashes	W1	10	5
Diarrhea	W8	9	4
Seborrhea	W24	8	2
Breathing difficulties	W4	8	1
Tremor	W4	7	0
Cardiac pain	W4	7	1
Blurred vision	W8	5	1
Paresthesia	W1	4	0
Nausea	W4	9	3
Placebo > MPH ER		**Placebo (%)**	**MPH ER (%)**
Drowsiness	W5	47	30
Shortened sleep	W12	26	15
Gastric discomfort	W2	16	10
Excessive apetite	W5	16	6
Chills	W2	14	9
Heaviness in legs	W12	13	5
Micturition difficulties	W4	5	1
Vomiting	W2	2.6	0.4

Vital signs and other effects

There was a small and statistically non-significant increase of systolic blood pressure in the MPH ER treatment group at week 24 as compared with baseline (Table 5). The mean heart rate in the MPH ER group showed an increase, which was statistically significant compared to placebo at weeks 4, 5, 8 and 18. The maximum difference compared to placebo was 5 bpm at weeks 4 and 5. At week 24 there was still a difference between the MPH ER and the placebo group

Table 4 Week by week pulse values (bpm)

	MPH ER	Placebo	*P* values
Baseline	72 ± 10	73 ± 12	0.2660
Week 4	77 ± 11	72 ± 9	<0.0001
Week 8	77 ± 11	72 ± 10	0.0016
Week 12	77 ± 11	74 ± 9	0.0659
Week 18	77 ± 11	74 ± 9	0.0286
Week 24	76 ± 11	74 ± 11	0.1169

P values are given for treatment group differences

Table 5 Systolic and diastolic blood pressure by study group at baseline and week 24

	MPH ER	Placebo	*P* values
Baseline			
Systolic	121 ± 12	121 ± 16	0.4177
Diastolic	78 ± 8	78 ± 10	0.3990
Week 24			
Systolic	124 ± 13	123 ± 15	0.1243
Diastolic	78 ± 9	78 ± 10	0.2688

P values are given for treatment group differences

(pulse rate 76 vs. 74), but this finding failed to reach statistical significance (Table 4).

No relevant differences were found between the study groups concerning body weight. In both groups the mean body weight at baseline was 78 kg in the MPH ER group and 77.3 kg in the placebo group. At week 24 both groups displayed a mean body weight of 77 kg (Wilcoxon *U* test, week 24, $P = 0.86$).

Regarding laboratory findings—blood count, coagulation tests, serum chemistry and thyroid parameters—no clinical significant effects were detected. At week 24 mean concentrations of uric acid and triglycerides were statistically significant higher in the placebo group compared to subjects treated with MPH ER (Wilcoxon *U* test, $P = 0.0261$ and 0.0035, respectively) and the mean total thyroid hormone (tT4) concentration was slightly elevated in the MPH ER group (Wilcoxon *U* test, $P = 0.0462$).

Discussion

Numerous controlled studies and a meta-analysis by Faraone et al. [9] have demonstrated that short-term administration of MPH can reduce inattention, hyperactivity and impulsivity in adults suffering from ADHD [13, 23]. As far as we know from literature this study is the first randomized, placebo-controlled investigation of MPH ER in the treatment of adult ADHD with an observation period of 24 weeks. The number of 363 adults with ADHD randomised in this study is large in comparison with earlier investigations. B.i.d. treatment with MPH ER in low doses improved significantly ADHD psychopathology as compared with placebo. This finding was detected with different techniques of data collection: expert rating (WRAADDS), self rating (CAARS-SL) and global expert assessment (CGI). Most importantly, this study demonstrated that efficacy of MPH ER was maintained from the end of the titration phase until study completion, whilst placebo effects slightly diminished. This indicated robust efficacy of MPH ER in the treatment of adult ADHD.

However the ES of 0.39 on the ADHD symptoms assessed with the WRAADDS and 0.28 with the CAARS was only small to medium. Investigations with higher MPH doses of 1.0 mg/kg and more achieved much better ES. In accordance with Faraone's meta-analysis [9] the mean ES of high dose studies was 1.3. In this study the average daily dose was only 0.55 mg/kg, which is slightly above the minimum level of MPH recommended for treatment in children, adolescents and adults according to the European treatment guidelines [3, 33] and far from the recommended maximum dose of 100 mg/day [19]. Earlier studies with low dose administration of MPH demonstrated ES at a level comparable with our findings. For example, Gualtieri et al. [11] reported an ES of 0.3, using dosages of 0.6 mg/kg MPH. Referring to the meta-analysis of Faraone et al. [9] the mean ES of low dose (mean 0.63 mg/kg) MPH studies was 0.7. Thus it is clear that the design of our study may have resulted in underdosing of some patients, leaving room for optimizing treatment response. This view is corroborated by the results of a D-MPH study with 4 treatment arms reported just recently [30]. The ES for the reduction of the ADHD psychopathology was 0.83 in the 40 mg/day group compared with 0.53 in the 20 mg/day group. However, relatively low ES were found in non–MPH treatment studies of adult ADHD. ES of 0.35–0.40 were reported on short term atomoxetine administration [18].

Moreover, it has to be considered that the low ES in our study also results from a marked placebo response, which has substantial influence on the evaluation of this parameter. The problem of placebo response will be discussed later.

As we had planned to investigate medium to long term effects of chronic MPH ER administration, it was not our intention to perform a short-time, high dose MPH study to demonstrate optimum treatment effects. In clinical practice some patients respond to very low MPH doses. Reimherr et al. [23] reported response to mean daily MPH doses of 0.2–1.3 mg/kg, indicating significant treatment effects even at very low dose levels with excellent tolerability. Similar findings were described by Medori et al. [17]. The responder rates defined as 30% symptom decline on an ADHD rating scale of two treatment groups receiving 18 and 36 mg/day OROS-MPH were 50.5 and 48.5% respectively as compared with 27.4% in placebo patients. The results of our study show that a majority of patients may benefit from medium term low dose administration of MPH ER, but there still remains a meaningful number of patients needing

higher doses of MPH ER for a sufficient decline of ADHD psychopathology.

Referring to the recent MPH treatment studies performed by Kooij et al. [14], Spencer et al. [31], Biederman et al. [4] and Reimherr et al. [23], we observed a very similar profile of adverse events in our study. Decreased appetite, sleep problems and dry mouth were frequent and typical for the MPH ER group. In contrast to previous studies we also observed an association of menstrual problems and decreased libido with MPH ER treatment. For obvious reasons it is clear that such side effects do not appear in studies with ADHD children and adolescents and would unlikely be detected in short-term studies with adult ADHD patients. Since this observation is a new finding, more research is needed to evaluate possible implications of long-term MPH treatment on sexual dysfunctions.

Treatment with MPH ER was well tolerated, although adverse events were the main reason for premature discontinuations in the MPH ER group. However, most side effects were observed during the titration phase and were moderate and short-lasting. Slow titration and low to moderate daily doses during the maintenance phase might account for the good tolerability of the study drug beyond the titration phase. We found a slight but not significant decrease of the body weight in both populations. A decrease of body weight has been described in previous MPH trials [14]. Thus it is of interest to see that chronic administration of low-dose MPH ER has only limited effects on body weight and is not critical in terms of clinical relevance.

An increase of systolic blood pressure has been found in previous short-term investigations [4, 31]. In this study no significant effects on blood pressure were observed. However, a statistical significant elevation in heart rate was observed during titration in the MPH ER treatment group. Therefore, controls of vital signs should be recommended when adults are treated with low dose MPH ER.

The study has certain limitations that should be addressed. Despite profound differences in the study design the proportion of 61% MPH ER responders according to WRAADDS total scores was in line with earlier studies using extended release formulations of MPH. Biederman et al. [4] reported 66% responders, Reimherr et al. [23] a responder rate of 42% and Jain et al. [13] detected in 66% a normalization of ADHD psychopathology. Spencer et al. [30] reported responder rates between 53.7 and 61.1% for doses of 20 to 40 mg/day D-MPH.

By contrast the rate of 42% placebo responders in our study was surprisingly high even in comparison with studies detecting 4–13% placebo responders [14, 23, 32, 35]. However, there are studies with relatively high placebo response rates. Kuperman et al. [15] found 27%, Biederman et al. [4] revealed 39% placebo responders. Spencer et al. [30] detected 34% placebo responders and Jain et al. [13] reported a normalization rate with the CAARS ADHD Index of 46% in placebo patients. An OROS-MPH study by Medori et al. [17] published just recently found 27% placebo responders. Interestingly, in a 24-week study with atomoxetine in adults with ADHD, which was comparable regarding the design of our study, a high placebo response was detected, too [1]. Thus it seems clear that the placebo response in our study has been relatively high. But it cannot be stated, that this is a problem exclusively observed in our investigation.

Several factors should be discussed regarding the high response to placebo in this study. First, the decline of ADHD symptoms in the placebo group might be at least partially due to effects of the disease management programme that was offered to all of the patients for ethical reasons. Furthermore, it should be considered that the placebo response might have been influenced by our prolonged and flexible titration schedule over 5 weeks. Due to their short term design earlier studies used forced titration schedules. Thus it is interesting to note that the study by Biederman et al. [4] which had demonstrated a placebo response rate like ours used a flexible dose regimen, too. According to Biederman et al. [4] it should be also mentioned that a cohort effect might be responsible for the high placebo response in recent studies, since ADHD has been increasingly recognized and treated during the last decade.

One might further speculate that the high placebo response rate may be related to the use of the WRAADDS as the primary outcome measure in this study. In this respect it has to be mentioned that the use of the WRAADDS in our study was not the first or an isolated application. The WRAADDS has been used successfully as secondary efficacy parameter among the atomoxetine trials [18, 22] and as primary efficacy parameter in an MPH study by Reimherr et al. [23]. The WRAADDS comprises not only the classical DSM-IV syndromes of inattention, hyperactivity and impulsivity. The WRAADDS goes beyond DSM-IV and includes aspects of affective lability and emotional overreactivity, stress intolerance and disorganization, which were found to be part of the adult ADHD psychopathology [26, 34]. Thus, in comparison to DSM-IV the WRAADDS gathers a broader spectrum of psychopathology. However, the DSM-IV items were primarily designed for the use in childhood ADHD and no study has been published so far regarding the developmental suitability in adult ADHD. Thus in treatment studies concerning adult ADHD it is justified from our point of view not only to investigate the DSM–IV psychopathology but also symptom domains occurring in 90–95% of adults with ADHD [26, 34]. The response or non-response to MPH of this type of psychopathology may provide material to find an answer to the question which is part of the psychopathology of ADHD in adults or

which sort of psychopathology should be excluded from the ADHD concept.

However, our data do not corroborate the suggestion that the WRAADDS may be inappropriate for trials like this. The differences of the treatment effects between placebo and MPH ER patients were more accentuated and the ES higher when ADHD symptoms were assessed with the WRAADDS in comparison with the CAARS or the CGI. Moreover, regarding the 7 subscales of the WRAADDS significant treatment effects favoring MPH were detected among all subscales: inattention, hyperactivity, hot temper, emotional overreactivity, affective lability, disorganization and impulsivity. The ES were between 0.19 (affective lability) and 0.45 (emotional overreactivity), suggesting no profound differences regarding the therapeutic response of the DSM-IV psychopathology in comparison with additional WRAADDS domains.

Another field of limitations is the large drop-out rate in combination with the use of LOCF as imputation method. A total of 30% of the randomized patients did not complete the full follow-up. In the above mentioned 24-week atomoxetine study [1] the overall drop-out rate was even higher (58%) indicating that the premature terminations might be a general problem related to the long placebo-controlled observation period, which was three to four times longer than in earlier investigations. As a consequence we had a sizable amount of imputed data. This may lead to concerns regarding the robustness of the conclusions drawn from the data. Thus we conducted best-case and worst-case analyses of covariance. They revealed similar results as the ITT-LOCF investigation. The difference between verum and placebo remained significant in both alternatives indicating MPH ER as the better treatment to reduce ADHD symptoms. Nevertheless, we cannot definitely rule out that the high drop-out rate of our study may have influenced the results of our study.

In conclusion our low-dose MPH ER study showed a small to medium improvement of ADHD symptoms in a majority of subjects. The ES of our study were smaller than in earlier investigations with higher dosages. The described effects remained robust over a 24-week observation period. Tachyphylaxis was not observed. A certain group of patients did not improve from the low dose treatment. Apparently they were seeking for higher MPH doses. The tolerability of the treatment was good. Significant drug effects on the heart rate during the titration phase lead to the recommendation of constant controls of vital signs during the treatment of adults with MPH.

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