

Long-term efficacy and safety outcomes with OROS-MPH in adults with ADHD

THEMATIC SECTION
Attention-Deficit Hyperactivity
Disorder (ADHD)



Jan K. Buitelaar¹, Götz-Erik Trott², Maria Hofecker³, Sandra Waechter⁴, Joris Berwaerts⁵,
Joachim Dejonckheere⁶ and Barbara Schäuble⁷

¹ Department of Cognitive Neuroscience, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

² Child and Adolescent Psychiatry, Aschaffenburg, Germany

³ Private Practice, Spalenring, Basel, Switzerland

⁴ Janssen-Cilag Europe, Switzerland

⁵ Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ, USA

⁶ SGS Life Science Services, Mechelen, Belgium

⁷ Janssen Cilag Medical Affairs Europe, Middle East & Africa, Neuss, Germany

Abstract

Methylphenidate (MPH) is widely prescribed for adults with attention deficit hyperactivity disorder (ADHD), but data on long-term treatment and maintenance of effect are lacking. Osmotic release oral system-methylphenidate (OROS-MPH) was evaluated in a 52-wk open-label study in subjects who had previously completed a short-term placebo-controlled trial and short-term open-label extension. Efficacy was assessed using the investigator- and subject-rated Conners' Adult ADHD Rating Scales (CAARS:O-SV and CAARS:S-S), and the Clinical Global Impression – Severity (CGI-S), Sheehan Disability Scale (SDS) and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Subjects completing ≥ 52 wk of treatment were eligible for a 4-wk randomized, placebo-controlled withdrawal phase in which loss of treatment effect was assessed using CAARS:O-SV and CGI-S. In the open-label phase ($n=156$), mean CAARS:O-SV score decreased from baseline by 1.9 ± 7.8 ($p < 0.01$), and small, statistically significant improvements from baseline were observed for CAARS:S-S, CGI-S and SDS. In the double-blind phase (OROS-MPH, $n=23$; placebo, $n=22$), CAARS:O-SV increased from double-blind baseline in the OROS-MPH and placebo arms (4.0 ± 7.6 vs. 6.5 ± 7.8 , not statistically significant). Long-term OROS-MPH treatment was well tolerated, and there was no evidence of withdrawal or rebound after discontinuation. In conclusion, the short-term benefits of OROS-MPH continue during long-term open-label treatment. Maintenance of efficacy in a placebo-controlled withdrawal design remains to be confirmed in larger patient populations.

Received 18 January 2011; Reviewed 5 May 2011; Revised 12 May 2011; Accepted 21 June 2011;
First published online 29 July 2011

Key words: Adults, attention deficit hyperactivity disorder, long-term treatment, OROS-MPH.

Introduction

Attention deficit hyperactivity disorder (ADHD) persists into adulthood as a chronic neurobehavioural disorder in a substantial number of persons diagnosed in childhood (Faraone *et al.* 2006). Based on national and international guidelines as well as consensus statements, the treatment of choice for adults with ADHD is methylphenidate (MPH) (Kooij *et al.* 2010; National Collaborating Centre for Mental Health,

2009; Social and Health Directory, 2010). The efficacy and safety of both short- and long-acting MPH have been demonstrated in numerous clinical trials in adults with ADHD in the USA (Adler *et al.* 2009; Biederman *et al.* 2010; Spencer *et al.* 2005) and in Europe (Bouffard *et al.* 2003; Kooij *et al.* 2004; Medori *et al.* 2008). In a previous study with osmotic release oral system-methylphenidate (OROS-MPH) (the LAMDA trial), treatment was associated with significant improvement in core symptoms of ADHD [Conners' Adult ADHD Rating Scale (CAARS)] relative to placebo, as well as improvements in daily functioning and global condition (Medori *et al.* 2008). These benefits were maintained or further improved in a 7-wk open-label extension (Buitelaar *et al.* 2009).

Address for correspondence: Professor J. K. Buitelaar, Department of Cognitive Neuroscience (204), PO Box 9101, 6500 HB Nijmegen, The Netherlands.

Tel.: +3124 3610750 Fax: +31 24 3610989

Email: j.buitelaar@psy.umcn.nl

Data on outcomes of MPH treatment beyond 6 months in adults with ADHD are, however, limited (Bejerot *et al.* 2010; Wender *et al.* 2011).

Data in the literature are also limited regarding the maintenance of effect of long-term medication, particularly in adults. A randomized, placebo-controlled withdrawal study of atomoxetine that included two discontinuations of medication has been conducted in children and adolescents (Buitelaar *et al.* 2007; Michelson *et al.* 2004). After 12 wk of stabilization treatment, relapse – defined as a return to 90% of baseline severity – occurred in 22% and 38% of atomoxetine- and placebo-treated subjects, respectively, during 9 months of continuation or withdrawal (Michelson *et al.* 2004). In the second randomized discontinuation phase, relapse rates after 12 months of stabilization were 3% *vs.* 12% for atomoxetine- and placebo-treated subjects, respectively, during 6 months of continuation or withdrawal (Buitelaar *et al.* 2007). Maintenance of efficacy of OROS-MPH was evaluated in a small double-blind, placebo-controlled, 4-wk withdrawal period in subjects who responded in a preceding active medication period (Biederman *et al.* 2010). Of 23 subjects who had previously responded to OROS-MPH in a 6-wk acute efficacy trial followed by 24 wk of maintenance treatment, two subjects (18%) experienced relapse after switching to placebo compared to no patient who continued OROS-MPH, although the difference was not statistically significant.

To provide long-term safety, efficacy, functioning and quality-of-life data in adults receiving OROS-MPH, subjects who completed the LAMDA trial were enrolled in an open-label study of ≥ 52 -wk duration. Maintenance of effect was evaluated in a 4-wk randomized, double-blind, placebo-controlled withdrawal phase in subjects who completed the present open-label study.

Methods

Subjects

Subjects were adult men or women aged 18–65 yr with a diagnosis of ADHD according to DSM-IV criteria. Diagnosis was based on the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID; Conners *et al.* 1999), which confirms the chronic course of ADHD symptomatology from childhood to adulthood, with some symptoms present before age 7 yr. In addition, a CAARS total score (sum of Inattention and Hyperactivity/Impulsivity scores) of ≥ 24 at screening for the initial LAMDA study was required. The Structured Clinical Interview for DSM-IV (SCID-I/P)

was used to evaluate the presence of other comorbidities and exclusionary symptoms (see below). ADHD was not diagnosed if symptoms were better accounted for by another psychiatric disorder (e.g. mood, anxiety, psychotic, personality disorder). Key exclusion criteria were a history of poor response or intolerance to MPH; presence of any current clinically unstable psychiatric condition (e.g. acute mood disorder, bipolar disorder, acute obsessive-compulsive disorder); diagnosis of substance use disorder (abuse/dependence) according to DSM-IV criteria within the last 6 months. Other exclusion criteria included family history of schizophrenia or affective psychosis; serious illnesses (e.g. hepatic or renal insufficiency or significant cardiac, gastrointestinal, psychiatric, or metabolic disturbances); hyperthyroidism, myocardial infarction, or stroke within 6 months of screening; and history of seizures, glaucoma, or uncontrolled hypertension. In addition, subjects with a treatment gap of > 30 d after the end of the 7-wk open-label extension of the LAMDA study were not eligible for the present study.

Study design

The present study was completed in July 2008 and was conducted in 23 of the 51 sites (7/13 European countries) that participated in the LAMDA study.

Subjects who initially entered the 5-wk, double-blind, randomized, placebo-controlled, parallel-group, fixed-dose LAMDA study (Medori *et al.* 2008) were eligible for a 7-wk open-label, flexible-dose extension if they completed the 5-wk double-blind phase or discontinued study medication due to poor tolerability (after a minimum of 7 d of treatment in the double-blind phase) (Buitelaar *et al.* 2009). Completers of the 7-wk open-label phase (including those who had received placebo in the initial 5-wk trial) were eligible for the present open-label study. Subjects who had at least 52 wk of treatment with OROS-MPH were eligible for a 4-wk, randomized, double-blind, placebo-controlled withdrawal phase if they had received a stable OROS-MPH dose for 4 wk at the end of the open-label study. Subjects in the withdrawal phase were randomly assigned in a 1:1 ratio to one of two groups receiving either continued treatment with the same dose of OROS-MPH or placebo.

Written informed consent was obtained from all patients before entering the open-label study, with separate consent required to enter the double-blind withdrawal phase. As a result, the timing of the open-label phase discontinuation was known to the subjects and investigators.

Subjects who entered the present open-label study immediately after LAMDA continued their previous OROS-MPH dose. Subjects who experienced an interruption of study drug between the open-label phase of LAMDA and the current study were titrated from 18 mg/d to a clinically optimal dose. Subjects were maintained on a flexible dose of OROS-MPH (18, 36, 54, 72 or 90 mg/d) throughout the open-label study. The dosage could be increased or decreased by 18-mg increments as needed to a maximum of 90 mg/d; dose alterations were based on clinical observations of response and tolerability and were made entirely at the discretion of the investigator.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. The study protocol was approved by independent ethics committees at each participating site.

Assessments

ADHD symptoms were evaluated using CAARS. The primary assessment in each study phase was the CAARS Observer-rated – Short Version (CAARS:O-SV), which comprises 18 investigator-rated items corresponding to the 18 DSM-IV-defined ADHD symptoms and provides a total score referred to as the CAARS:O-SV total ADHD symptom score and two subscale scores (Inattention and Hyperactivity/Impulsivity) (Conners *et al.* 1999). The CAARS Self-rated Short Version (CAARS:S-S) is a 26-item, self-report, 4-point rating scale that measures symptoms based on DSM-IV criteria for ADHD (Conners *et al.* 1999). Investigators who performed CAARS assessments successfully completed a formal training and qualification programme organized by the study sponsor. Other outcome measures included the 7-point Clinical Global Impression – Severity (CGI-S) and Change (CGI-C) scales, the former rating the degree of illness from 1 (not ill) to 7 (extremely severe), and the latter rating the level of improvement relative to baseline from 1 (very much improved) to 7 (very much worse) (NIMH, 1985). Functional impairment was assessed using the Sheehan Disability Scale (SDS), designed to measure impairment in three domains (work, social and home life or family responsibilities) with a self-administered 10-point visual analogue scale (Sheehan *et al.* 1996). Quality of life was measured using the 14-item Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q), which evaluates the level of enjoyment and satisfaction relating to physical health, feelings, work,

household duties, work and leisure-time activities, and social relations. Each domain is assessed on a 5-point scale from very poor to very good, and the domains are aggregated to produce an overall score (Endicott *et al.* 1993). The instrument is not disease-specific and has been used in a number of clinical trials, including clinical trials in adults with ADHD, and sensitivity to treatment effects with MPH has been demonstrated (Mick *et al.* 2008). Safety evaluations included monitoring of adverse events, clinical laboratory tests, vital signs, and physical examination. Electrocardiogram (ECG) recordings were made in a subset of subjects.

During the present open-label study, clinic visits were carried out every 12 wk, with safety parameters and adverse events assessed at each visit. Efficacy assessments were carried out at baseline and endpoint, except in Germany, where CAARS:O-SV, CAARS:S-SV and CGI-S scores were also evaluated every 12 wk. In the double-blind withdrawal phase, safety and efficacy assessments were carried out at baseline and endpoint (4 wk), with an additional assessment of safety and CAARS:O-SV score at week 2. ‘Baseline’ was defined as the first visit of the present study; for patients who continued into the open-label study immediately after completing LAMDA, the end-of-study visit in LAMDA could serve as the baseline visit for the present study.

Statistical analysis

Safety and efficacy were evaluated in the intent-to-treat (ITT) population, defined for the open-label and double-blind phases as all subjects who received at least one dose of study medication in the respective phase.

In the open-label phase, adverse events were summarized, including data on severity and outcome of treatment-emergent adverse events of special interest (protocol-specified cardiovascular and psychiatric adverse events), and summary statistics were generated for cardiovascular parameters and efficacy data.

Sample size for the double-blind phase was based on a conservatively expected change in CAARS:O-SV total score from double-blind baseline of +3 for continued MPH and +10 for placebo over a 4-wk period, based on clinical assessment. With a two-sided type-I error of 5% and a power of 90%, 37 eligible subjects per treatment group were required. It was therefore planned to enrol a total of 80 subjects into the double-blind withdrawal phase. During the double-blind phase, the primary and, where appropriate, secondary efficacy variables were analysed at each time-point

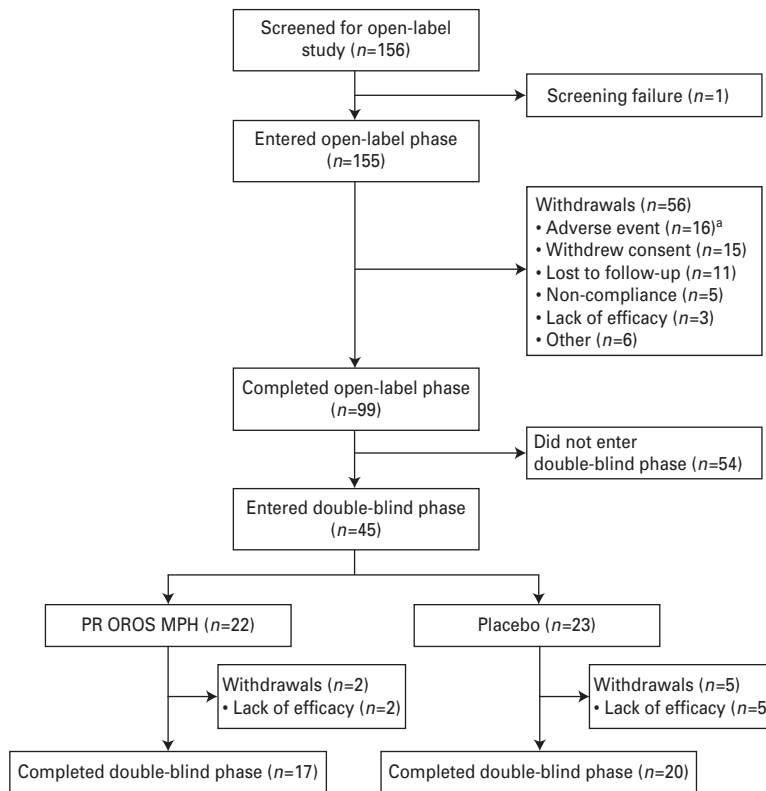


Fig. 1. Patient disposition in the open-label and double-blind phases of the study. ^a Includes one patient who discontinued because of an adverse event that began before entry into the present study. PR, Prolonged release.

(2 and 4 wk) and at endpoint by analysis of covariance (ANCOVA), including treatment, country, age and sex as factors, and baseline score as a covariate. Treatment effects were estimated based on least-squares means of the difference between the continued treatment group and placebo.

Additional pre-specified analyses to evaluate loss of therapeutic effect in the double-blind phase included the percentage of subjects with a ≥ 1 -point increase in CGI-S score from double-blind baseline and the percentage of subjects with a ≥ 2 -point increase in CGI-S score from double-blind baseline or discontinuation because of lack of efficacy during the double-blind period.

Post-hoc analyses performed to evaluate possible rebound effects during the placebo-controlled withdrawal period were based on mean change from open-label baseline in CAARS:O-SV total score and percentage of subjects with a ≥ 1 -point increase in CGI-S score from open-label baseline at double-blind endpoint.

Adverse events in the open-label phase were summarized and summary statistics were generated for cardiovascular parameters and efficacy data. For

the evaluation of possible withdrawal symptoms, adverse events were assessed from the beginning of the double-blind withdrawal phase to the last post-baseline visit in the double-blind period.

Results

Open-label phase

Of 337 subjects who completed the LAMDA trial, 156 were screened for the present open-label study; the most common reason for not entering screening was that the subject's country or individual study site did not participate ($n=121$). One patient did not meet the inclusion criteria, and thus 155 subjects entered the open-label study (Fig. 1). Baseline demographics and disease characteristics are shown in Table 1. Median age at baseline was 36 yr and 54% of patients were male. Median age at diagnosis of ADHD was 33 yr and most patients had combined-type ADHD (68%). A family history of ADHD was present in 74% of patients, and 36% had a family history of other psychiatric disorders. As per the inclusion and exclusion criteria, few patients had active, stable

Table 1. Demographic and disease characteristics at the start of the open-label and double-blind phases

	Open-label OROS-MPH (<i>n</i> = 155)	Double-blind	
		Placebo (<i>n</i> = 22)	OROS-MPH (<i>n</i> = 23)
Age, yr			
Mean \pm s.d.	35.0 \pm 10.6	35.1 \pm 9.8	37.5 \pm 12.0
Range	18–60	20–52	21–62
Sex, <i>n</i> (%)			
Male	84 (54.2)	7 (31.8)	11 (47.8)
Female	71 (45.8)	15 (68.2)	12 (52.2)
Age at ADHD diagnosis			
Mean \pm s.d.	30.1 \pm 14.4	26.4 \pm 15.3	28.1 \pm 17.4
Range	3–60	4–49	4–60
ADHD subtype (childhood, based on CAADID), <i>n</i> (%)			
Combined	114 (73.5)	13 (59.1)	16 (69.6)
Predominantly inattentive	35 (22.6)	8 (36.4)	5 (21.7)
Predominantly hyperactive-impulsive	5 (3.2)	1 (4.5)	2 (8.7)
Not specified	1 (0.6)	0	0
ADHD subtype (adulthood), <i>n</i> (%)			
Combined	106 (68.4)	12 (54.5)	12 (52.2)
Predominantly inattentive	43 (27.7)	10 (45.5)	8 (34.8)
Predominantly hyperactive-impulsive	5 (3.2)	0	3 (13.0)
Not specified	1 (0.6)	0	0

CAADID, Conners' Adult ADHD Diagnostic Interview for DSM-IV.

psychiatric comorbidities at baseline [alcohol/substance abuse: *n* = 1 (1%); mood and anxiety disorders: *n* = 16 (10%); personality disorders: *n* = 1 (1%)].

In total, 125 subjects (80.6%) were receiving at least one concomitant medication at baseline. The most frequently used medication classes were analgesics (*n* = 58, 37.4%), anti-inflammatory and anti-rheumatic products (*n* = 48, 31.0%) and systemic antibiotics (*n* = 32, 20.6%). Drugs classified as psychoanaesthetics (e.g. antidepressants) or psycholeptics (e.g. benzodiazepines and non-benzodiazepine hypnotics) were each used by 20 subjects (12.9%).

Overall, 99 subjects (63.9%) completed the open-label phase. The main reasons for trial discontinuation during the open-label phase were the occurrence of an adverse event (*n* = 16, 10.3%), withdrawal of consent (*n* = 15, 9.7%) and loss to follow-up (*n* = 11, 7.1%). Mean (\pm s.d.) treatment duration in the open-label phase (safety population) was 437.1 \pm 206.8 d (median 503.0 d, range 15–747 d). The mean daily dose of OROS-MPH was 52.8 \pm 21.0 mg (median 53.9 mg, range 18–90 mg). The most frequent modal daily doses were 36 mg (33.3%) and 54 mg (24.2%), with 7.2, 18.2 and 16.3% of patients receiving a modal dose of 18, 72 or 90 mg, respectively.

Safety

In total, 126 subjects (81.3%) experienced at least one treatment-emergent adverse event during the open-label study (Table 2). The most common treatment-related adverse events were restlessness, headache and drug effect decreased, each in nine subjects (5.6%). Seventeen serious adverse events were reported in 12 (7.7%) subjects, comprising one case each of hip arthroplasty, hip surgery, lipoma excision, mastectomy, tonsillectomy, recurrent breast cancer, uterine leiomyoma, menorrhagia, uterine haemorrhage, deafness, haemorrhoids, allergy to arthropod sting, concussion, whiplash injury, investigation (reported term: 'diagnostic curettage'), intervertebral disc protrusion, and thrombosis. None was considered by the investigator to be related to treatment. No deaths were reported during the study. Fifteen (9.7%) subjects withdrew from the study because of an adverse event, with one additional patient withdrawing because of an adverse event that had begun before entering the open-label study. Adverse events leading to withdrawal in more than one patient were insomnia, depressed mood, and hypertension (all *n* = 2, 1.3%). Treatment-emergent adverse events of special interest reported by more than one patient were

Table 2. Summary of adverse events occurring during the open-label phase

Adverse event, <i>n</i> (%)	OROS-MPH (<i>n</i> = 155)
Any adverse event	126 (81.3)
Discontinued because of adverse event	15 (9.7) ^a
Serious adverse event	12 (7.7)
Treatment-related adverse event ^b	62 (40.0)
Most common adverse events (≥5% of subjects)	
Headache	33 (21.3)
Nasopharyngitis	31 (20.0)
Influenza	10 (6.5)
Restlessness	12 (7.7)
Back pain	11 (7.1)
Insomnia	11 (7.1)
Drug effect decreased	9 (5.8)
Hypertension	9 (5.8)
Depressed mood	8 (5.2)

^a One additional patient discontinued because of an adverse event that began before entry into the present study.

^b Adverse event considered by the investigator to be possibly, probably or very likely to be related to study medication.

hypertension (*n* = 9, 5.8%), palpitations (*n* = 6, 3.9%) and anxiety (*n* = 4, 2.6%). Except for one patient with palpitations categorized as severe and one patient with anxiety categorized as severe, adverse events of interest were mild to moderate in severity, and none was classified as serious.

Mean changes from baseline in blood pressure and pulse rate during the open-label study were small (Table 3). Abnormally high systolic (>140 mmHg) and diastolic (>90 mmHg) blood pressure values at any post-baseline visit during the open-label phase were reported in 21.7% and 17.1% of subjects, respectively, with 9.2% of subjects recording a pulse rate >100 bpm (Table 3). Body weight and body mass index (BMI) remained stable throughout the study, with mean (\pm S.D.) changes of 0.7 ± 4.8 and 0.23 ± 1.61 kg, respectively.

Efficacy

CAARS:O-SV total score slightly improved (decreased) throughout the open-label phase, and was significantly lower at endpoint *vs.* baseline [last observation carried forward (LOCF) analysis; Fig. 2; Table 4]. Significant improvements from baseline were also seen in the CAARS:O-SV Hyperactivity/Impulsivity and Inattention subscale scores, CAARS:S-S score, CGI-S, and SDS scores. No significant change in Q-LES-Q was reported (LOCF analysis) (Table 4). The percentage of subjects categorized as 'not ill', 'borderline ill', or 'mildly ill' on the CGI-S

Table 3. Cardiovascular parameters during the open-label phase

Parameter (mean \pm S.D.)	OROS-MPH (<i>n</i> = 155)
Systolic blood pressure (mmHg)	
Baseline	123.0 \pm 13.2
Endpoint	123.5 \pm 12.6
Change	0.3 \pm 14.0
Diastolic blood pressure (mmHg)	
Baseline	75.7 \pm 8.4
Endpoint	77.1 \pm 10.2
Change	1.4 \pm 9.7
Pulse rate (bpm)	
Baseline	76.9 \pm 13.3
Endpoint	77.8 \pm 11.7
Change	0.9 \pm 14.4
Subjects meeting clinically relevant criteria at any visit, <i>n</i> (%)	
Systolic blood pressure >140 mmHg	33 (21.7)
Diastolic blood pressure >90 mmHg	26 (17.1)
Pulse rate >100 bpm	14 (9.2)

increased from 69.0% at baseline to 75.5% at endpoint (Fig. 3).

Double-blind phase

Of 99 subjects who completed the open-label study, 45 (45%) consented to enter the double-blind phase, of

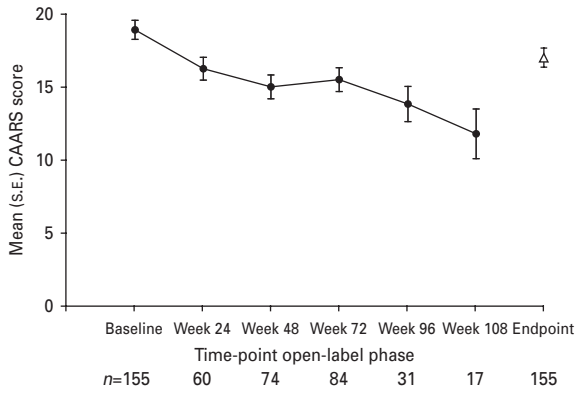


Fig. 2. Conners’ Adult ADHD Rating Scale Observer-rated – Short Version (CAARS:O-SV) total score during the open-label phase.

whom two (4%) randomized to OROS-MPH and five (11%) randomized to placebo withdrew because of lack of efficacy (Fig. 1). Demographic and disease characteristics at double-blind baseline were generally similar in the placebo and OROS-MPH arms, and were also similar to those at open-label baseline (Table 1). There was, however, an apparent imbalance in CAARS:O-SV score between the placebo (12.1 ± 5.3) and OROS-MPH (16.5 ± 7.5) arms.

Mean doses of OROS-MPH or placebo equivalent during the double-blind phase were 43.0 ± 16.9 mg [median (range), 36 (18–72) mg] and 54.8 ± 23.9 mg [54 (18–90) mg], respectively.

Efficacy

Mean CAARS:O-SV total score increased from double-blind baseline in both treatment arms, with no significant difference for change from baseline between placebo and OROS-MPH (Fig. 4; Table 5). Six (26.1%) subjects in the OROS-MPH arm and eight (36.4%) in the placebo arm experienced an increase (worsening) of >50% from baseline in CAARS:O-SV total score, while 13 subjects (56.5%) and 10 subjects (45.5%), respectively, experienced an increase of <30% in CAARS total score.

CGI-C scores indicated statistically significantly less worsening of symptoms at double-blind endpoint compared to double-blind baseline in the OROS-MPH arm [median (range) 4.0 (1–6)] than in the placebo arm [5.0 (2–7)]. At endpoint, the percentages of subjects who were considered minimally to very much worse relative to baseline were 30.4 and 59.1% in the OROS-MPH and placebo arms, respectively ($p=0.0422$) (Fig. 5). No patient in the OROS-MPH arm was considered to be ‘very much worse’. At double-blind endpoint, the percentage of subjects

Table 4. Efficacy parameters during the open-label phase (LOCF analysis)

Parameter ^a (mean ± s.d.)	OROS-MPH (n = 155)
CAARS:O-SV total score	
Baseline	18.9 ± 8.3
Endpoint	17.0 ± 8.3
Change	-1.9 ± 7.8**
CAARS:O-SV hyperactivity/impulsivity subscale	
Baseline	8.8 ± 4.4
Endpoint	7.9 ± 4.6
Change	-0.9 ± 4.4**
CAARS:O-SV inattention subscale	
Baseline	10.1 ± 5.1
Endpoint	9.1 ± 5.0
Change	-1.0 ± 4.6**
CAARS-S:SV	
Baseline	29.6 ± 13.1
Endpoint	26.5 ± 13.5
Change	-3.1 ± 9.6***
Clinical Global Impression – Severity	
Baseline	3.1 ± 1.0
Endpoint	2.8 ± 1.1
Change	-0.3 ± 1.1**
Q-LES-Q	
Baseline	60.0 ± 15.1
Endpoint	61.9 ± 16.6
Change	1.4 ± 15.2
Sheehan Disability Scale	
Baseline	12.8 ± 6.6
Endpoint	11.1 ± 6.3
Change	-1.7 ± 6.2***

CAARS, Conners’ Adult ADHD Rating Scale; CAARS:O-SV, CAARS Observer-rated – Short Version; CAARS:S-SV, CAARS Self-rated Short Version; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.

^a A reduction in score represents an improvement for all scales except Q-LES-Q.

** $p \leq 0.01$, *** $p < 0.001$ vs. baseline (two-sided paired *t* test).

rated as moderately, markedly, or severely ill on the CGI-S was 59.1% in the placebo group and 30.4% in the OROS-MPH group (compared to 13.6% and 0%, respectively, at double-blind baseline). No significant differences in secondary efficacy parameters other than CGI-C were observed between the treatment arms, although there was a consistent trend to numerically better outcomes with OROS-MPH (Table 5).

Loss of treatment effect and rebound

Loss of treatment effect during double-blind treatment, in terms of increases from double-blind baseline

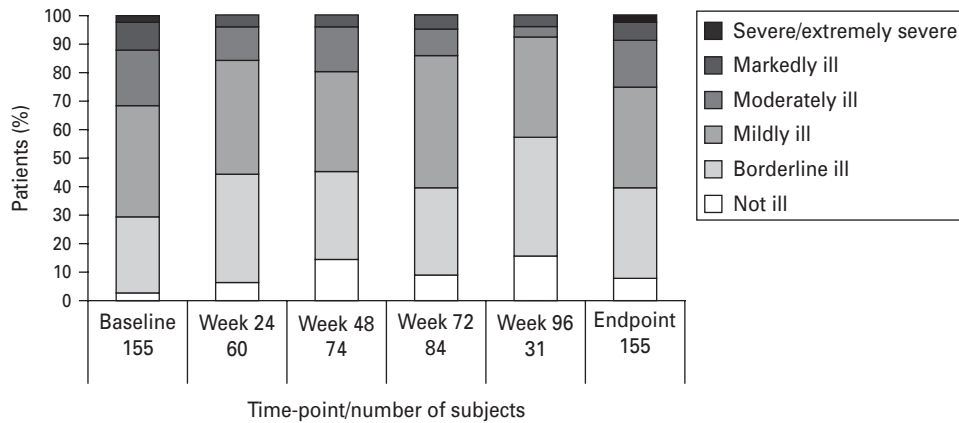


Fig. 3. Categorization of Clinical Global Impression – Severity scores over time during the open-label phase.

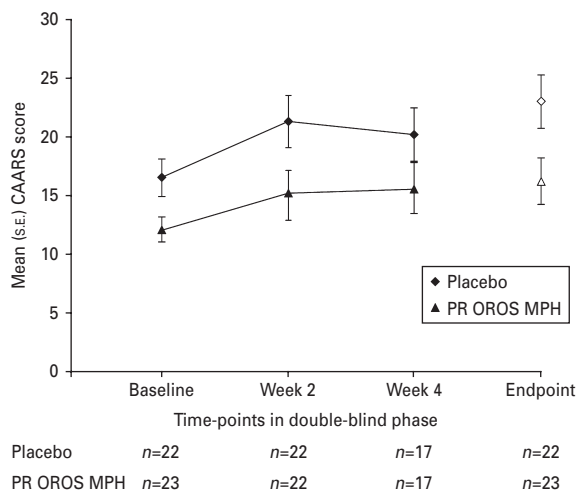


Fig. 4. Conners' Adult ADHD Rating Scale Observer-rated – Short Version (CAARS:O-SV) total score during the double-blind phase. PR, Prolonged release.

in CGI-S score at double-blind endpoint, was observed in more subjects in the placebo arm than in the OROS-MPH arm, although the differences were not statistically significant (Fig. 6).

Based on mean changes in CAARS:O-SV total score from open-label baseline, subjects who received placebo were more likely to experience worsening of ADHD symptoms at double-blind endpoint, while those who continued OROS-MPH did not show a change in ADHD symptoms in general (mean change in CAARS:O-SV total score, 4.5 vs. -0.3 , respectively). A greater percentage of subjects randomized to placebo (55%) experienced an increase in CGI-S score of ≥ 1 point from open-label baseline to double-blind endpoint compared to those who continued treatment with OROS-MPH (30%).

Safety

During double-blind treatment, 30.4% and 36.4% of subjects in the OROS-MPH and placebo arms, respectively, experienced at least one adverse event (Table 6). No individual adverse event was reported in more than two subjects per treatment group. The only serious adverse event was a patient receiving placebo diagnosed with recurrent breast cancer who underwent mastectomy and reconstructive surgery; this was not considered by the investigator to be related to treatment. Adverse events considered by the investigator to be at least possibly related to treatment were reported in three subjects (13.0%) in the OROS-MPH arm and five subjects (22.7%) in the placebo arm. The only cardiovascular adverse events of special interest were two cases of reported hypertension in subjects receiving OROS-MPH, and no psychiatric adverse events of special interest occurred during the double-blind phase. There were no adverse events suggestive of a withdrawal reaction in subjects assigned to placebo during the double-blind phase.

Mean blood pressure and pulse rate decreased in subjects switched to placebo, with minimal changes in subjects who continued OROS-MPH (Table 7). Abnormally high diastolic blood pressure (> 90 mmHg) and pulse rate (> 100 bpm) at any post-baseline visit in the double-blind phase were each experienced by two subjects in the OROS-MPH arm.

Discussion

Results from this long-term open-label study show that adults with ADHD receiving long-term treatment with OROS-MPH continue to experience small but statistically significant improvement in their condition. Improvements from baseline in the open-label

Table 5. Efficacy parameters during the double-blind phase

Parameter ^a (mean ± s.d.)	OROS-MPH (n = 23)	Placebo (n = 22)
CAARS:O-SV total score		
Baseline	12.1 ± 5.3	16.5 ± 7.5
Endpoint	16.2 ± 9.4	23.0 ± 10.4
Change	4.0 ± 7.6	6.5 ± 7.8
Treatment difference ^b	2.89	
CAARS:O-SV hyperactivity/impulsivity subscale		
Baseline	5.3 ± 2.8	7.0 ± 3.8
Endpoint	7.8 ± 4.9	10.5 ± 5.1
Change	2.5 ± 3.8	3.4 ± 4.6
Treatment difference ^b	1.16	
CAARS:O-SV inattention subscale		
Baseline	6.8 ± 3.9	9.5 ± 5.3
Endpoint	8.4 ± 5.7	12.5 ± 6.9
Change	1.6 ± 4.6	3.1 ± 5.3
Treatment difference ^b	2.14	
CAARS:S:SV		
Baseline	18.7 ± 11.1	27.2 ± 12.5
Endpoint	23.4 ± 13.9	31.8 ± 15.6
Change	4.4 ± 11.9	4.0 ± 12.0
Treatment difference ^b	2.39	
Clinical Global Impression – Severity		
Baseline	2.3 ± 0.7	2.6 ± 0.9
Endpoint	3.0 ± 1.3	3.6 ± 1.4
Change	0.6 ± 1.1	1.0 ± 1.2
Q-LES-Q		
Baseline	66.2 ± 9.0	53.2 ± 12.0
Endpoint	60.8 ± 15.2	51.1 ± 13.6
Change	-6.5 ± 11.4	-2.7 ± 12.4
Treatment difference ^b	2.24	
Sheehan Disability Scale		
Baseline	9.5 ± 6.6	13.2 ± 5.9
Endpoint	11.5 ± 7.6	15.1 ± 4.9
Change	2.2 ± 6.1	1.6 ± 8.3
Treatment difference ^b	2.30	

CAARS, Conners' Adult ADHD Rating Scale; CAARS:O-SV, CAARS Observer-rated – Short Version; CAARS:S-SV, CAARS Self-rated Short Version; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.

^a A reduction in score represents an improvement for all scales except Q-LES-Q.

^b Least-squares mean difference between treatment arms.

phase were observed for the level of ADHD symptoms, disease severity, and impairment of functioning, as reflected in the investigator-rated CAARS:O-SV and CGI-S scales, and the self-reported CAARS:S-S and SDS scales. There was also a numerical improvement in quality of life (Q-LES-Q score), although this was not statistically significant.

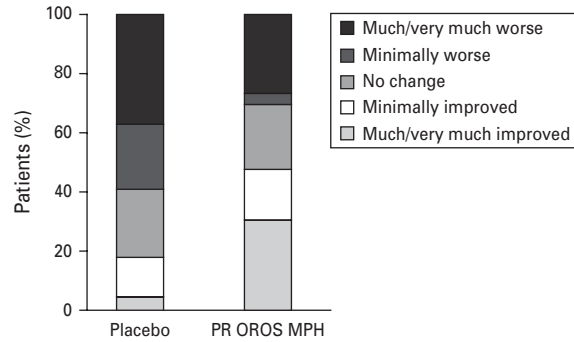


Fig. 5. Clinical Global Impression – Change score at double-blind endpoint. PR, Prolonged release.

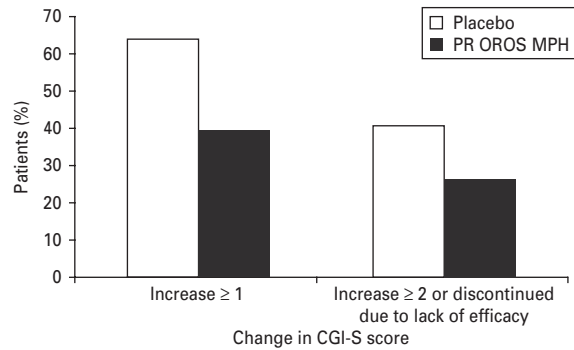


Fig. 6. Loss of treatment effect (pre-specified analysis of increase in Clinical Global Impression – Severity (CGI-S) score during double-blind treatment). PR, Prolonged release.

Furthermore, OROS-MPH was well tolerated during the long-term open-label phase, with an adverse-event profile similar to other studies of MPH in adults with ADHD (Adler *et al.* 2011; Bouffard *et al.* 2003; Kooij *et al.* 2004; Medori *et al.* 2008; Spencer *et al.* 2005) and no new or unexpected adverse events were reported with long-term exposure. Overall, 12 (7.7%) subjects had a serious adverse event in the open-label phase, but none was considered to be related to trial medication, and there were no deaths in the study. Cardiovascular and psychiatric adverse events of special interest occurred in 12% and 4% of subjects, and were mainly mild or moderate in severity. Changes from baseline to endpoint in mean blood pressure, pulse rate and body weight were minimal.

The completion rate in the open-label phase (mean duration 437 d) was 64%, which is higher than that observed in a recent open-label study of OROS-MPH in adults with ADHD (Rösler *et al.* 2011), in which 44% of 129 subjects completed 1 yr of treatment (median duration 213 d). The higher completion rate and longer median duration in the present study may relate to the

Table 6. Summary of adverse events occurring during the randomized, double-blind withdrawal phase

Adverse event, <i>n</i> (%)	OROS-MPH (<i>n</i> = 23)	Placebo (<i>n</i> = 22)
Any adverse event	7 (30.4)	8 (36.4)
Discontinued because of adverse event	0	0
Serious adverse event	0	1 (4.5)
Treatment-related adverse event ^a	3 (13.0)	5 (22.7)
Most common adverse events ($\geq 4\%$ of subjects in either arm)		
Hypertension	2 (8.7)	0
Irritability	1 (4.3)	1 (4.5)
Nasopharyngitis	1 (4.3)	1 (4.5)
Pyrexia	1 (4.3)	1 (4.5)
Restlessness	1 (4.3)	1 (4.5)
Somnolence	1 (4.3)	1 (4.5)

^a Adverse event considered by the investigator to be possibly, probably, or very likely to be related to study medication.

Table 7. Cardiovascular parameters during the randomized, double-blind withdrawal phase

Parameter (mean \pm s.d.)	OROS-MPH (<i>n</i> = 23 ^a)	Placebo (<i>n</i> = 22)
Systolic blood pressure (mmHg)		
Baseline	126.7 \pm 11.9	125.7 \pm 13.5
Endpoint	125.5 \pm 13.0	121.5 \pm 13.4
Change	-1.5 \pm 10.0	-4.2 \pm 11.6
Diastolic blood pressure (mmHg)		
Baseline	78.0 \pm 9.9	78.4 \pm 9.6
Endpoint	80.1 \pm 8.4	73.9 \pm 8.9
Change	1.7 \pm 8.3	-4.5 \pm 8.1
Pulse rate (bpm)		
Baseline	79.9 \pm 10.0	76.7 \pm 10.1
Endpoint	77.1 \pm 9.7	71.9 \pm 7.6
Change	-2.9 \pm 10.4	-4.8 \pm 9.6
Met clinically relevant criteria, <i>n</i> (%)		
Systolic blood pressure > 140 mmHg	0	0
Diastolic blood pressure > 90 mmHg	2 (9.1)	0
Pulse rate > 100 bpm	2 (9.1)	0

^a *n* = 22 for assessment of clinically relevant criteria at any visit.

fact that this was an extension study in subjects who had previously completed 12 wk of treatment with OROS-MPH. In a 1-yr open-label study that only enrolled subjects who responded to MPH in a 2-wk placebo-controlled crossover trial, the completion rate was even higher (73%) (Wender *et al.* 2011). The completion rate in the present study is consistent with a previous 2-yr study of MPH or dexamphetamine in adults with ADHD, in which the completion rates after 6 months and 2 yr were 83% and 50%,

respectively (Bejerot *et al.* 2010). The completion rate in the present study compares favourably with those reported in long-term studies with other treatments in adults with ADHD. In a 1-yr study of lisdexamfetamine dimesylate, for example, the completion rate was 55% (Weisler *et al.* 2009). Interim analysis of a 3-yr open-label study of atomoxetine reported a completion rate of 43% after mean treatment duration of 40 wk (maximum 97 wk) (Adler *et al.* 2005), while in a 1-yr open-label study of adults with

ADHD who had responded to a 10-wk course of atomoxetine ($n=10$), only one subject completed the trial (Johnson *et al.* 2010). The most common reason for withdrawal in the present open-label study was an adverse event, followed by withdrawal of consent. The most frequent modal doses of OROS-MPH in the open-label phase were 36 and 54 mg, with a median dose of 54 mg (range 18–90 mg). Dosing was generally stable over time.

In the double-blind withdrawal phase, the level of ADHD symptoms appeared to increase in both treatment arms, with numerically greater increases in ADHD symptoms (CAARS:O-SV) in the placebo arm *vs.* the OROS-MPH arm. Similarly, there was a trend to better outcomes in terms of functioning and quality of life with OROS-MPH compared to placebo. The results on the three pre-specified outcome measures (CAARS:O-SV, percentage of subjects with a ≥ 1 -point increase in CGI-S score from double-blind baseline, percentage of subjects with a ≥ 2 -point increase in CGI-S from double-blind baseline or discontinuation due to lack of efficacy) were not statistically significant for the difference between OROS-MPH and placebo. It seems likely that this is the result of the relatively small sample size. Of the 99 subjects who completed the open-label phase, only 45 consented to participate in the withdrawal phase, compared with the planned enrolment of 80. An additional reason for the observed lack of maintenance of effect may be that subjects were not required to meet pre-specified criteria for clinical response as a condition for randomization. Thus, not all subjects randomized showed a stable clinical presentation at the end of the open-label phase, usually a prerequisite for a formal randomized, placebo-controlled withdrawal study to show maintenance of therapeutic effect. Further, the observed response during the open-label phase may have been the result, in part, of non-treatment-specific or 'placebo' effects. The possibility of long-term and robust placebo effects has recently been described in another long-term efficacy study of OROS-MPH (Biederman *et al.* 2010). Such robust placebo responses may complicate and limit the detection of significant differences between active medication and placebo after randomized withdrawal after long-term, open-label treatment. In addition, it is possible that effective medication for ADHD symptoms over a longer period of time may provide patients with the opportunity to develop better coping and adaptive skills. This may result in further stabilization of the clinical condition and continued benefits, even when active medication is withdrawn (Biederman *et al.* 2010). It is tempting to speculate on the possible neural underpinnings of

such an effect, such as adaptive changes in brain chemistry and synaptic plasticity.

In the double-blind phase, OROS-MPH was well tolerated, with no clinically important differences between the treatment arms and no signal of rebound or withdrawal reactions in subjects assigned to placebo.

The major contribution of the present study was its duration, as long-term (≥ 1 yr) data on treatment of adults with ADHD with MPH are currently limited. Results should, however, be interpreted with caution, as patient populations in open-label extension trials are often 'selected' for efficacy and tolerability of treatment, as they comprise subjects who completed earlier randomized, controlled studies (Maguire *et al.* 2008). The patient population in the present study was, however, similar in terms of its baseline demographics and disease characteristics to the cohort in the initial LAMDA double-blind study (Medori *et al.* 2008). In the double-blind withdrawal phase, the primary efficacy endpoint failed to show a statistically significant difference between the treatment arms. A number of limitations must, however, be taken into account, such as the small sample size resulting from attrition during the course of the study; the lack of pre-specified criteria for clinical response for the randomized withdrawal phase; and the imbalances between the continued OROS-MPH and placebo arms in terms of symptom severity at double-blind baseline and previous OROS-MPH dose during open-label treatment. Overall, these limitations suggest that data from this randomized withdrawal phase are neither conclusive for maintenance of effect after long-term treatment, nor do they call into question the potential benefit of long-term treatment in adults with ADHD.

In conclusion, the short-term benefits of OROS-MPH in subjects with ADHD continue during long term (>1 yr), open-label treatment, with efficacy and functional outcome parameters showing a small improvement at endpoint compared to baseline. Withdrawal of OROS-MPH after long-term treatment leads to a worsening of subjects' ADHD symptoms; further research in a larger cohort is needed to establish this clearly. Flexibly dosed OROS-MPH (18–90 mg) was well tolerated by adults with ADHD during long-term treatment. There was no signal of rebound or withdrawal in subjects assigned to placebo during the double-blind phase after randomized withdrawal.

Appendix. Study investigators

Odd Auglænd; Jan K. Buitelaar; Miguel Casas; Michael Colla; Dominique Eich; Luis Ferreira; Carlos

Filipe; Markus Gastpar; Andreas Heinz; Maria Hofecker Fallahpour; Lothar Imhof; Martin Klein; Eric Konofal; Sandra Kooij; Johanna Krause; Sunhee Lee; Wolfgang Niemczyk; Thomas Nissen; Hans Jørgen Nyrerød; Alexandra Philipsen; Michael Rösler; Esther Sobanski; Götz-Erik Trott.

Acknowledgements

The authors thank Camille Orman (Johnson & Johnson Pharmaceutical Research & Development, LLC) for help with the statistical analyses and Pat Calaiaro (Johnson & Johnson Pharmaceutical Research & Development, LLC) for help with project management. This study was funded by Janssen–Cilag EMEA. Editorial support with the drafting and completion of the manuscript was provided by Daniel Booth, Ph.D. (Bioscript Stirling Ltd, London, UK) and funded by Janssen–Cilag EMEA. The authors are entirely responsible for the scientific content of the paper.

[Study registered at ClinicalTrials.gov (ID no.: NCT00307684) (<http://www.clinicaltrials.gov/ct2/show/NCT00307684>).]

Statement of Interest

J. K. Buitelaar has, in the past 3 years, been a consultant, a member of an advisory board and/or a speaker for Janssen-Cilag BV, Eli Lilly, Bristol-Myers Squibb, Organon/Schering Plough, UCB, Shire, Medice, Servier. G. E. Trott has, in the past 3 years, been a consultant, a member of an advisory board and/or a speaker for Janssen-Cilag BV, AstraZeneca, Medice, Novartis, Pfizer, Bristol-Myers Squibb, Shire, and Lilly. M. Hofecker has been an advisory board member and speaker for Janssen-Cilag, Switzerland for 5 years, and is also an advisory board member for Eli-Lilly, Switzerland. S. Wachter and B. Schäuble are employees of Janssen-Cilag EMEA. J. Berwaerts is an employee of Johnson & Johnson Pharmaceutical Research & Development. J. Dejonckheere is a consultant working on behalf of SGS-Life Science Services, a company employed by Janssen-Cilag EMEA to provide statistical analysis.

References

- Adler LA, Orman C, Starr HL, Silber S, et al.** (2011). Long-term safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: an open-label, dose-titration, 1-year study. *Journal of Clinical Psychopharmacology* **31**, 108–114.
- Adler LA, Spencer TJ, Milton DR, Moore RJ, et al.** (2005). Long-term, open-label study of the safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: an interim analysis. *Journal of Clinical Psychiatry* **66**, 294–299.
- Adler LA, Zimmerman B, Starr HL, Silber S, et al.** (2009). Efficacy and safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. *Journal of Clinical Psychopharmacology* **29**, 239–247.
- Bejerot S, Rydén EM, Arlinde CM** (2010). Two-year outcome of treatment with central stimulant medication in adult attention-deficit/hyperactivity disorder: a prospective study. *Journal of Clinical Psychiatry* **71**, 1590–1597.
- Biederman J, Mick E, Surman C, Doyle R, et al.** (2010). A randomized, 3-phase, 34-week, double-blind, long-term efficacy study of osmotic-release oral system-methylphenidate in adults with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychopharmacology* **30**, 549–553.
- Bouffard R, Hechtman L, Minde K, Iaboni-Kassab F** (2003). The efficacy of 2 different dosages of methylphenidate in treating adults with attention-deficit hyperactivity disorder. *Canadian Journal of Psychiatry* **48**, 546–554.
- Buitelaar JK, Michelson D, Danckaerts M, Gillberg C, et al.** (2007). A randomized, double-blind study of continuation treatment for attention-deficit/hyperactivity disorder after 1 year. *Biological Psychiatry* **61**, 694–699.
- Buitelaar JK, Ramos-Quiroga JA, Casas M, Kooij JJ, et al.** (2009). Safety and tolerability of flexible dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Neuropsychiatric Disease and Treatment* **5**, 457–466.
- Conners C, Erhardt D, Sparrow E** (1999). *Conners' Adult ADHD Rating Scales (CAARS): Technical Manual*. North Tonawanda, NY: Multi-Health Systems.
- Endicott J, Nee J, Harrison W, Blumenthal R** (1993). Quality of life enjoyment and satisfaction questionnaire: a new measure. *Psychopharmacology Bulletin* **29**, 321–326.
- Faraone SV, Biederman J, Mick E** (2006). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine* **36**, 159–165.
- Johnson M, Cederlund M, Rastam M, Areskoug B, et al.** (2010). Open-label trial of atomoxetine hydrochloride in adults with ADHD. *Journal of Attention Disorders* **13**, 539–545.
- Kooij JJ, Burger H, Boonstra AM, Van der Linden PD, et al.** (2004). Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. *Psychological Medicine* **34**, 973–982.
- Kooij SJ, Bejerot S, Blackwell A, Caci H, et al.** (2010). European consensus statement on diagnosis and treatment of adult ADHD: the European network adult ADHD. *BMC Psychiatry* **10**, 67.
- Maguire MJ, Hemming K, Hutton JL, Marson AG** (2008). Reporting and analysis of open-label extension studies of anti-epileptic drugs. *Epilepsy Research* **81**, 24–29.

- Medori R, Ramos-Quiroga JA, Casas M, Kooij JJS, et al.** (2008). A randomized, placebo-controlled trial of 3 fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry* **63**, 981–989.
- Michelson D, Buitelaar JK, Danckaerts M, Gillberg C, et al.** (2004). Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry* **43**, 896–904.
- Mick E, Faraone SV, Spencer T, Zhang HF, et al.** (2008). Assessing the validity of the quality of life enjoyment and satisfaction questionnaire short form in adults with ADHD. *Journal of Attention Disorders* **11**, 504–509.
- National Collaborating Centre for Mental Health** (2009). *Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults*. London: National Institute for Health and Clinical Excellence.
- National Institute of Mental Health (NIMH)** (1985). CGI (Clinical Global Impression Scale). *Psychopharmacology Bulletin* **21**, 843.
- Rösler M, Ginsberg Y, Arngrim T, Adamou M, et al.** (2011). Correlation of symptomatic improvements with functional improvements and patient-reported outcomes in adults with attention-deficit/hyperactivity disorder treated with OROS methylphenidate. *World Journal of Biological Psychiatry*. Published online: 26 April 2011. doi:10.3109/15622975.2011.571283.
- Sheehan DV, Harnett-Sheehan K, Raj BA** (1996). The measurement of disability. *International Clinical Psychopharmacology* **11** (Suppl. 3), 89–95.
- Social and Health Directory** (2010). *Diagnosis and Treatment of Hyperkinetic Disorder/Attention Deficit Hyperactivity Disorder (ADHD) in Children, Adolescents and Adults* [in Norwegian]. Oslo: Sosial-og helsedirektoratet.
- Spencer T, Biederman J, Wilens T, Doyle R, et al.** (2005). A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry* **57**, 456–463.
- Weisler R, Young J, Mattingly G, Gao J, et al.** (2009). Long-term safety and effectiveness of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *CNS Spectrums* **14**, 573–585.
- Wender PH, Reimherr FW, Marchant BK, Sanford ME, et al.** (2011). A one year trial of methylphenidate in the treatment of ADHD. *Journal of Attention Disorders* **15**, 36–45.