Two-Year Outcome of Treatment With Central Stimulant Medication in Adult Attention-Deficit/Hyperactivity Disorder: A Prospective Study

Susanne Bejerot, MD, PhD; Eleonore M. Rydén, MD; and Christina M. Arlinde, PhD

Background: Given that adults with ADHD continue to use stimulants for extended periods of time, studies on the long-term effectiveness and adverse events are warranted. The aims of this study were to investigate factors associated with persistence in treatment in an exploratory manner and to document side effects and reasons for discontinuation.

Method: The current study describes the systematic follow-up of 133 psychiatric patients with *DSM-IV*–diagnosed ADHD treated with central stimulants at a specialized outpatient unit between January 1, 2001, and August 31, 2006. A standardized questionnaire, derived from the Targeted Attention-deficit Disorder Symptoms Rating Scale, was used in order to measure improvement of the following target symptoms: hyperactivity, impulsivity, irritability, distractibility, structure/organization problems, inattention, and restlessness.

Results: Eighty percent of the patients were successfully treated with stimulants at the 6- to 9-month follow-up. Fifty percent remained in treatment after 2 years or more. Forty-five percent were treated for comorbid anxiety and/or depression during the study period. Only 15% dropped out because of lack of efficacy. The amount of clinical response over the first 6 to 9 months (but not at 6 weeks) predicted adherence to treatment at 2 years. The patients' heart rate increased from a least squares mean ± SE of 70 ± 2.2 to 80 ± 2.1 bpm ($P = .00003$) while blood pressure remained unchanged at the ≥ 2-year follow-up. Severe side effects or drug abuse were not detected in this cohort.

Conclusions: The long-term treatment outcome shows that stimulants are effective in adult ADHD and side effects tend to be mild.

J Clin Psychiatry 2010;71(12):1590–1597

Submitted: *February 24, 2009; accepted July 13, 2009.*
Online ahead of print: *June 1, 2010 (doi:10.4088/JCP.09m05168pur).*
Corresponding author: *Susanne Bejerot, MD, PhD, Northern Stockholm Psychiatry, St Göran's Hospital, SE-112 81 Stockholm, Sweden (susanne.bejerot@sll.se).*

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder with onset in childhood. A substantial proportion of affected children will have a chronic course. Although hyperactivity and impulsivity may decrease with age, 3.4% of the adult population fulfill the diagnostic criteria for ADHD.[1] Notably, symptoms of inattention tend to persist into adulthood.[2,3]

Adults with ADHD are at risk for developing anxiety disorders, major depressive disorders, and alcohol and drug dependency.[4] In addition, attention deficit is often reported by persons with autism spectrum disorder (ASD) or obsessive-compulsive disorder,[5,6] disorders that are not characterized by impulsivity.

Pharmacotherapy with central stimulants (CS; eg, methylphenidate or dexamphetamine) is the most effective treatment for ADHD. The short-term efficacy of pharmacotherapy for ADHD in adults is well established,[7,8] and controlled studies have demonstrated effect over 6 months.[9–11] However, studies of efficacy and safety after the first year of treatment are few and primarily carried out on children. These studies show that every second child treated with CS had stopped medication at the 2-year follow-up, and the number remaining in treatment was further decreased after 5 years.[12–14] In adults, evidence from a large-scale treatment program, including 840 patients in Norway and from an American open-label extension of a 4-week, multicenter, placebo-controlled trial, suggests survival rates of only 21%–34% at the ≥ 2-year time point.[15,16]

Therefore, long-term follow-up studies on adults treated with CS are warranted. The aim of the present study was to explore clinical factors associated with adherence to central stimulant treatment in a natural setting, to document side effects, and to investigate reasons for discontinuation of stimulant therapy.

METHOD

This study describes the systematic follow-ups of 133 adults with ADHD who were treated or started their treatment with CS between January 2001 and August 2006. Effects from treatment, adverse events, and reasons for discontinuation of stimulant therapy were documented. All patients had a physical check-up in which blood pressure and heart rate were measured before starting medical treatment. Treatments for comorbid depression, anxiety, or other psychiatric or somatic disorders were accepted.

The treatment was given at an outpatient tertiary psychiatric clinic for assessment and treatment of adult ADHD, situated in northern Stockholm. The catchments area has a population of nearly 320,000 inhabitants over 18 years of age.

In Sweden, medical treatment for childhood ADHD has been generally accepted only since the mid-nineties, and it was not until around 2000 that it was available for adult

ADHD. However, only selected psychiatrists were allowed to prescribe CS for adults, and the approval for each individual patient had to be decided by the Swedish Medical Products Agency. The legislation around the treatment was extensive, and the approval lasted for only 1 year at the time. The regulation was simplified in 2005, and methylphenidate was then allowed to be prescribed by specially licensed psychiatrists. Individual permissions were necessary only if dexamphetamine was prescribed. Thus, methylphenidate became the first choice of treatment thereafter, although initially, when dexamphetamine and methylphenidate were equally available for prescription, dexamphetamine was often preferred as it was viewed as more effective. When osmotic-release oral system methylphenidate (OROS-MPH) was introduced on the Swedish market, the patients taking short-acting methylphenidate were often switched to that.

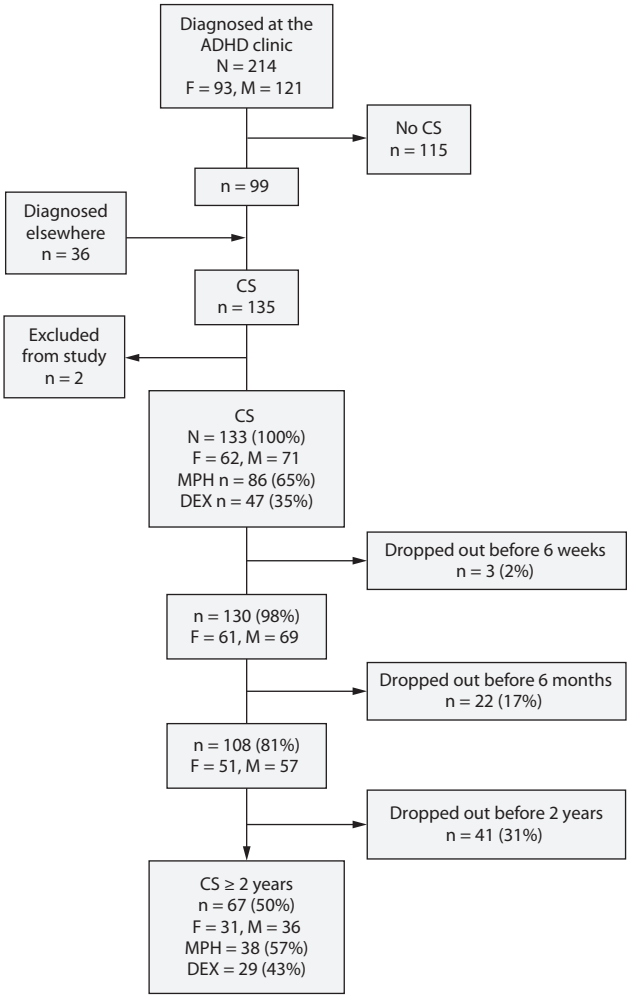
Given that only a small portion of the Swedish psychiatrists were allowed to prescribe CS in Sweden at the time of the study, prescriptions of CS outside the ADHD clinic were extremely rare. Thus, almost every prescription for CS in the catchment area originated from the ADHD clinic.

The study was approved by the Regional Ethics Committee in Stockholm. All patients were asked to consent to participate in the study, and only 1 patient refused to participate.

Subjects

All patients in this study were referred to a specialized ADHD and ASD outpatient tertiary psychiatric clinic at the Northern Stockholm Psychiatry at St Göran's Hospital, Stockholm, Sweden, by a licensed psychologist or physician for assessment for diagnoses and possible treatment for adult ADHD or ASD. All patients without obvious drug or alcohol abuse or dependence were accepted. No other exclusion criteria were used. Regardless of whether a patient attended an appointment or not, his or her medical record could be found in the Northern Stockholm Psychiatry database, which contains all psychiatric medical records in the catchment area. Only those who moved out of the catchment area or declined further contact with their psychiatrists were lost to follow-up. In all, 214 patients (93 women and 121 men) were assessed and diagnosed with ADHD at the neuropsychiatric unit during the time period of January 1, 2001, to August 31, 2006 (Figure 1). Eighty-nine of these patients had received psychiatric care in childhood, but only 1 had a prior diagnosis of childhood ADHD. Thirty-six patients (16 women and 20 men) were assessed elsewhere during this time period and referred to the specialized unit for medication only. Of the total number of 214 patients diagnosed with ADHD in the specialized unit, 115 were not included in this study due to the following reasons: (1) never medicated, (2) treated with atomoxetine, or (3) not treated at the neuropsychiatric unit but referred back to the nonspecialized outpatient unit for pharmacologic treatment and lost to follow-up. Two patients were excluded in this study due to a number of complicating factors. Both had severe comorbid obsessive-compulsive disorder and discontinued the stimulant medication for long periods of time.

Figure 1. Flow Diagram of ADHD Subjects' Progress[a]



[a]Percentage given as % of patients in the study.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CS = central stimulants, DEX = dexamphetamine, F = females, M = males, MPH = methylphenidate.

ADHD Assessments

All patients were assessed for childhood ADHD retrospectively and current adult ADHD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria. The assessments were conducted by board-certified psychiatrists and licensed psychologists. Diagnosis of ADHD was given by consensus between the psychiatrist and the psychologist and according to *DSM-IV* criteria.

The assessment procedure took 12–18 hours to complete over a period of 2 weeks. A parent, or another significant person who knew the patient since childhood, was interviewed in person about early ADHD symptoms with a semistructured instrument (Five to Fifteen [FTF]).[17] This instrument includes neuropsychiatric symptoms noted by parents when the child was between 5 and 15 years of age. It was completed by a parent prior to the first visit, and the results were discussed with the parent and patient together

© Copyright 2010 Physicians Postgraduate Press, Inc.

at the consultation. Also, a semistructured protocol covering childhood symptoms, social factors, educational level, employment status, and alcohol and drug use was administered. All patients were assessed with a structured interview for ADHD, the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), which covers attention difficulties, hyperactivity and/or restlessness, temper, affective lability, emotional overreactivity, disorganization, and impulsivity relating to present difficulties.[18,19] The WRAADDS is administered as an interview and has acceptable psychometric properties. It differs from other ADHD rating scales by its coverage of emotional dysregulation.

Treatment Protocol

The treatment was individualized, but initially most patients were treated with short-acting methylphenidate or dexamphetamine. The doses were slowly increased by 2.5 mg of dexamphetamine or 5 mg of methylphenidate every third day for 8 days; thereafter, the increase was approximately 5 mg of dexamphetamine or 10 mg of methylphenidate for another 3 days. On day 12, the target doses were 25 mg of dexamphetamine or 50 mg of methylphenidate. This protocol was modified if the patients developed problematic side effects or if there was a satisfactory effect at a lower dosage, and, conversely, the dosages were raised if the effect was unsatisfactory. Methylphenidate was generally administered tid, and dexamphetamine was administered either bid or tid. The patient came for weekly visits to a nurse assistant during the first month; thereafter, monthly during the first 6 months and, thereafter, every third month. During the second year, the patient came in twice yearly. If one stimulant proved ineffective, the other agent was tried. When long-acting methylphenidate was introduced on the market, most patients were switched to OROS-MPH, which was administered once daily or, in some cases, bid around breakfast and lunch. The maximum dosages were 100 mg/d for methylphenidate and 70 mg/d for dexamphetamine. Nonresponders to CS and patients with a history of alcohol or drug dependence were treated with atomoxetine.

Follow-Up Assessments

All patients were regularly called for follow-up measurements of blood pressure, heart rate, response to medication, and side effects by a trained nurse's assistant or psychiatrist. At 3 selected follow-up time points—short-term (ie, 6–12 weeks), long-term (ie, 6–9 months), and after treatment for at least 2 years (ie, 2–5 years)—data were collected for assessment of long-term outcomes of pharmacologic treatment.

A standardized questionnaire, derived from the Targeted Attention-deficit Disorder Symptoms Rating Scale[18] and administered in a large Norwegian treatment program for adult ADHD,[15] was used in order to measure improvement of the following target symptoms: hyperactivity, impulsivity, irritability, distractibility, structure and/or organization problems, inattention, and restlessness. The level of improvement was rated 0–4, reflecting "no improvement" = 0, "little improvement" = 1, "definite improvement" = 2, "large improvement" = 3, or "very large improvement" = 4. Ratings of 2.5 or more, ie, better than definite improvement, were regarded as a "good response." Adverse events were assessed with a specially developed questionnaire addressing 21 items of possible side effects (early insomnia, early awakening, interrupted sleep, increased need for sleep, headache, abdominal pain, diarrhea, constipation, dry mouth, nausea, nervousness, tics, low mood, elevated mood, tachycardia, dizziness, anorexia or decreased appetite, increased appetite, hallucinations, tremors, impaired dexterity). The patient could score each side effect as "not present" = 0, "seldom" = 1, "occasionally" = 2, or "often" = 3. There was also an open-ended question about the presence of other side effects than suggested in the questionnaire.

Statistics

The computer software STATISTICA 7 (StatSoft, Inc, Tulsa, Oklahoma) was used in the statistical analyses.

Frequencies and percentages for nominal values were calculated using standard descriptive statistics and frequency tables. For continuous values, least squares mean or median and standard deviation (SD) or standard error (SE) were used. For comparisons of continuously scaled values between and within sexes or other variables, analysis of variance (ANOVA) and Unequal N HSD post hoc analysis were used. The Mann-Whitney *U* test, the Wilcoxon matched-pairs test, and the median test (χ^2) were used for nonparametric data. Statistical significance was set at the 2-sided, 95% confidence interval ($P \leq .05$). When testing for medication effect on heart rate or target symptoms, or to predict adherence to treatment, adequate variables were taken into consideration as a potential influencing factor (sex, type of stimulant, earlier psychiatric diagnoses, etc).

RESULTS

This study includes 133 adult patients with ADHD (71 men and 62 women) who received treatment with CS while attending the clinic between the years 2001 and 2008. See Table 1 for a detailed description of the patient population. Mean age when medication was initiated was 31.1 years, and only 1 patient had started treatment before the age of 17 years. Forty-five percent of the patients were prescribed psychotropic agents for treatment of depression and/or anxiety at the time of the referral, and the stimulant was added on top of the current medication (see Table 1). Median intelligence quotient (IQ) was 98 for verbal and 97 for nonverbal (measured in 62 patients; verbal IQ SD ± 18.4; range, 60–138; and nonverbal IQ SD ± 17.4; range, 58–135). The total WRAADDS median score was 83 (SD ± 23.0; range, 13–123) without significant differences between men and women (Table 2).

Stimulant Therapy and Discontinuation Rate

At the first time point, the dosages were undergoing titration. The mean ± SD dose at 6–12 weeks was 39.3 ± 16.2 mg/d (range, 15–80; n = 81) for methylphenidate and 22.2 ± 10.3

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1. Population Characteristics

Population Characteristic	Men (n = 71)	Women (n = 62)	All (N = 133)
Age at start of stimulant therapy, mean ± SD, y	29.5 ± 9.4	31.8 ± 8.7	31.1 ± 10.9
Height, mean ± SD, cm[a]	182.9 ± 5.0	166 ± 5.4	NA[b]
Weight before central stimulant start, mean ± SD, kg[c]	83.3 ± 16.1	68 ± 19.0	NA[b]
BMI before start of stimulant therapy, mean ± SD[d]	25.3 ± 5.3	25.7 ± 7.7	NA[b]
DSM-IV ADHD diagnosis, n (%)			
With hyperactivity	56 (78.9)	49 (79.0)	105 (78.9)
Without hyperactivity	15 (21.1)	13 (21.0)	28 (21.1)
Civil status, n (%)			
Single	50 (70.4)	35 (56.5)	85 (63.9)
Divorced	2 (2.8)	5 (8.1)	7 (5.3)
Married/cohabiting	16 (22.5)	21 (33.9)	37 (27.8)
Missing data	3 (4.2)	1 (1.6)	4 (3.0)
Children, n (%)			
Yes	11 (15.5)	22 (35.5)	33 (24.8)
No	57 (80.3)	38 (61.3)	95 (71.4)
Missing data	3 (4.2)	2 (3.2)	5 (3.8)
Highest educational level, n (%)			
University	13 (18.3)	11 (17.7)	24 (18.0)
Upper secondary school	21 (29.6)	15 (24.2)	36 (27.1)
Vocational training	6 (8.5)	9 (14.5)	15 (11.3)
Compulsory school	23 (32.4)	18 (29.0)	41 (30.8)
Did not finish compulsory school	3 (4.2)	1 (1.6)	4 (3.0)
Missing data	5 (7.0)	8 (12.9)	13 (9.8)
Working or studying			
Yes, n (%)	38 (53.5)	25 (40.3)	63 (47.4)
Full-time[e]	34 (47.9)	17 (27.4)	51 (38.3)
To a lesser degree	4 (5.6)	8 (12.9)	12 (9.0)
No, n (%)[f]	30 (42.3)	35 (56.5)	65 (48.9)
Missing data	3 (4.2)	2 (3.2)	5 (3.8)
History of other psychiatric diagnosis	35 (49.3)	44 (71.0)	79 (59.4)
Other psychiatric medication at start with central stimulant, n (%)			
SRI[g]	21 (29.6)	25 (40.3)	46 (34.6)
NRI	1 (1.4)	3 (4.8)	4 (3.0)
Other antidepressants	2 (2.8)	4 (6.5)	6 (4.5)
Mood stabilizer	3 (4.2)	1 (1.6)	4 (3.0)
Neuroleptics only	0	2 (3.2)	2 (1.5)
Hypnotics only	8 (11.3)	4 (6.5)	12 (9.0)
Without other psychiatric medication	36 (50.7)	23 (37.1)	59 (44.4)

[a]34 men, 28 women.
[b]Height and weight data not computed for total sample due to different reference ranges for men and women.
[c]47 men, 40 women.
[d]31 men, 27 women.
[e]Full-time working/studying in Sweden = 40 h/wk.
[f]Living costs provided by taxes or health insurance.
[g]Both selective and nonselective.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BMI = body mass index, *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, SRI = serotonin reuptake inhibitors, NA = not applicable, NRI = norepinephrine reuptake inhibitor.

Table 2. Scores in the Wender-Reimherr Adult Attention Deficit Disorder Scale

Wender-Reimherr Adult Attention Deficit Disorder Scale	Men (n = 47), Median ± SD	Women (n = 43), Median ± SD	All (N = 90), Median ± SD
Attention difficulties	12 ± 3.4	10 ± 2.8	11 ± 3.1
Hyperactivity/restlessness	13 ± 5.3	13 ± 5.6	13 ± 5.4
Affective lability	10 ± 3.5	10 ± 3.6	10 ± 3.5
Temper	10 ± 5.5	9 ± 5.9	10 ± 5.7
Disorganization	20 ± 6.3	17 ± 6.4	19 ± 6.3
Emotional overreactivity	8 ± 2.9	9 ± 2.5	8 ± 2.7
Impulsivity	12 ± 6.8	12 ± 6.2	12 ± 6.4
Total	87 ± 24.4	80 ± 21.7	83 ± 23.0

mg/d (range, 6–55; n = 43) for dexamphetamine. At the second time point, the 6- to 9-month follow-up, the mean ± SD dose was 48.9 ± 15.8 mg/d (range, 18–90; n = 60) for methylphenidate and 28.4 ± 12.1 mg/d (range, 15–70; n = 36) for dexamphetamine. At the ≥ 2-year time point, the dosages were mainly unchanged, with mean ± SD doses of 48.9 ± 21.0 mg/d (range, 18–100; n = 37) and 27.8 ± 10 mg/d (range, 5–50; n = 29) for methylphenidate and dexamphetamine, respectively. Forty-eight percent of the patients initially treated with methylphenidate and 53% of the dexamphetamine group remained in the study; however, 4 patients taking methylphenidate had switched to dexamphetamine prior to the ≥ 2-year time point.

Around 80% of the patients entering the study were successfully treated with stimulants at the 6- to 9-month follow-up. After 2 years or more, 50% still adhered to treatment. There were no sex differences in the reasons for discontinuation. The reasons for discontinuation because of side effect or lack of efficacy were not related to the choice of CS. The reasons for dexamphetamine versus methylphenidate discontinuation are given in Table 3, which shows data from all discontinued patients in the study (n = 66). Thirty-eight percent of the discontinued patients ended central stimulant therapy before the 6- to 9-month time point and the rest before the ≥ 2-year time follow-up.

Medication Efficacy on ADHD Target Symptoms

The target symptoms hyperactivity and distractibility decreased between the 6- to 12-week and the 6- to 9-month time points, while the medication effect on other target symptoms remained unchanged. Interestingly, this increased effect of medication was observed only in the group that continued central stimulant treatment for more than 2 years. They improved in nearly every target symptom between the 2 time points: hyperactivity (Wilcoxon matched-pairs test; $T = 17.5$, $Z = 2.4$, $P = .016$, n = 24), impulsivity ($T = 25.5$, $Z = 2.4$, $P = .016$, n = 27), attention ($T = 63$, $Z = 2.3$, $P = .022$, n = 37), and distractibility ($T = 22.5$, $Z = 2.7$, $P = .006$, n = 35). When the patients were divided into definite responders, ie, having good treatment response on the target symptoms (ratings of 2.5 or more), and partial responders (with none, few, or moderate effects on target symptoms, ie, ratings of 0–2), we found that being a definite responder on the target symptoms attention ($\chi^2 = 8.8$, $P = .0029$, n = 82), impulsivity ($\chi^2 = 5.4$, $P = .020$, n = 73), restlessness ($\chi^2 = 4.1$, $P = .042$, n = 78), and irritability ($\chi^2 = 4.2$, $P = .040$, n = 70) at the 6- to 9-month time point predicted adherence to treatment at 2 years; however, no such predictions could be made at the 6- to 9-week time point.

Lower scores on temper in the WRAADDS predicted adherence to treatment at the ≥ 2-year time point in men (Mann-Whitney $U = 166$, $Z = 2.1$, $P = .033$, n = 46),

Table 3. Discontinuation Causes for Stimulant Therapy

Reason for Discontinuation	Patients Taking Methylphenidate (n = 44), n (%)	Patients Taking Dexamphetamine (n = 22), n (%)	All Discontinued Patients (N = 66), n (%)
Unknown, lost to follow-up	12 (27.3)	3 (13.6)	15 (22.7)
Anxiety and/or depression	7 (15.9)	4 (18.2)	11 (16.7)
Lack of efficacy	7 (15.9)	3 (13.6)	10 (15.2)
Patient decision, not specified	5 (11.4)	3 (13.6)	8 (12.1)
Side effects too bothersome	3 (6.8)	2 (9.1)	5 (7.6)
Does not want central stimulant treatment	3 (6.8)	1 (4.5)	4 (6.1)
Personal circumstances	2 (4.5)	2 (9.1)	4 (6.1)
Patient changed clinic, moved, or terminated contact	2 (4.5)	1 (4.5)	3 (4.5)
Alcohol or cannabis abuse	1 (2.3)	1 (4.5)	2 (3.0)
Epileptic seizures	1 (2.3)	0	1 (1.5)
Hyperactivity, aggression	1 (2.3)	0	1 (1.5)
Paranoia	0	1 (4.5)	1 (1.5)
Pregnancy	0	1 (4.5)	1 (1.5)

while the results on all other WRAADDS subscales were nonsignificant.

Cardiovascular Effects

There was a statistically significant elevation in heart rate (HR) from baseline to the ≥ 2-year time point (least squares means ± SE: baseline HR = 70 ± 2.2 bpm; 6- to 9-week HR = 79 ± 2.0 bpm; 6- to 9-month HR = 79 ± 1.9 bpm; ≥ 2-year HR = 80 ± 2.1 bpm [ANOVA $F = 8.8$, $P = .00003$, n = 38]). A post hoc analysis revealed that the women already had elevated heart rates at the 6- to 12-week time point (n = 15, $P = .048$), which was maintained over the course of the study (at 6–9 months [$P = .009$] and ≥ 2 years [$P = .037$]). A similar trend was observed in the men, but reached statistical significance only at the ≥ 2-year time point (n = 23, $P = .032$).

From baseline to the 6- to 9-month time point, an elevated heart rate was shown for both men and women (n = 66; least squares means ± SE: baseline HR 71 ± 1.7 bpm, 6- to 9-week HR 78 ± 1.6 bpm, 6- to 9-month HR 77 ± 1.7 bpm; $F = 10.6$, $P = .00006$, n = 67). Blood pressure remained stable during the course of the study. Blood pressure for the whole group was as follows: at baseline, systolic = 125 ± 14.2 mm Hg, diastolic = 76 ± 10.9 mm Hg, n = 114; at 6–9 weeks, systolic = 127 ± 13.9 mm Hg, diastolic = 80 ± 9.8 mm Hg, n = 102; at 6–9 months, systolic = 127 ± 13.7 mm Hg, diastolic = 79 ± 9.0 mm Hg, n = 89; at the ≥ 2-year time point, systolic = 127 ± 12.5 mm Hg, diastolic = 80 ± 9.2 mm Hg, n = 54). Men had higher systolic blood pressure at baseline than women (131 versus 119, $F = 25$, $P = .000002$), at 6–12 weeks (131 versus 121, $F = 14.8$, $P = .00022$), and at ≥ 2 years (131 versus 122, $F = 9.4$, $P = .0034$). There were no statistical differences in diastolic blood pressure between men and women. At baseline, 12% had a diastolic blood pressure of 90 mm Hg or above, at 6–12 weeks 19%, at 6–9 months 13%, and at the ≥ 2-year time point 13%.

Adverse Events

Side effects occurring "occasionally" or "often" at the 6- to 9-month time point were dry mouth (46%) and decreased appetite (34%). There were no differences in appetite between dexamphetamine and methylphenidate at the 6- to 12-week time point, although at the 6- to 9-month time point, methylphenidate more often resulted in decreased appetite compared to treatment with dexamphetamine (Mann-Whitney $U = 552.5$, $Z = -2.4$, $P = .017$, dexamphetamine n = 31, methylphenidate n = 49). Also common, but less frequently reported, were initial insomnia (25%), sleep disturbances (21%), and tachycardia (21%). Side effects reported by 15%–20% of the patients, but regarded as rare, were dizziness, early awakening, headache, nausea, tremors, and increased need for sleep. Other reported side effects were not expressed as being common. In total, 68 patients (76%) reported at least 1 side effect, and 21 patients (24%) reported no side effects at all. Similar adverse events were described already at the 6- to 12-week time point. Twenty-four patients reported the following additional side effects: muscle related (tension, pain, cramps), increased affective incontinence, decreased libido, and tiredness and/or drowsiness. These side effects were mainly reported during the first months of treatment and were not regarded as frequently occurring (Table 4).

Of the patients that discontinued before 6 months due to side effects and/or lack of efficacy, 5 patients were switched to atomoxetine, but only 1 continued this medication for 2 years. Of the 6 patients with more spectacular reasons for discontinuation reported in Table 4, the following was noted: 1 woman, aged 33 years with an IQ score of 94, who had recurrent depression and panic disorder and a history of inpatient care in childhood, was treated with methylphenidate. She reported hallucinations at the 6-month time point, and the treatment with CS was terminated. During approximately 18 months, she was without CS, but deteriorated. Therefore, in the spring of 2008, central stimulant treatment was reinstated, and dexamphetamine (20 mg/d) has been prescribed in combination with olanzapine and escitalopram since then. She is diagnosed as having bipolar II disorder and possibly as having a mitochondrial disturbance. The second patient, a female aged 27 years with an IQ score of 73, became paranoid as a result of treatment with dexamphetamine, and the treatment was terminated after only 9 weeks. The third patient, a man aged 44 years with an IQ score of 91, had a comorbid social phobia. He was treated with citalopram but became agitated and aggressive and terminated treatment with methylphenidate (50 mg/d) after 4 months. The

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 4. Summary of Adverse Events Among Reporting Patients at the 6- to 9-Month Time Point (n = 89)

Side Effect	Patients Reporting Side Effect (%)	Frequency, n		
		Seldom	Occasionally	Often
Dry mouth	46	18	17	6
Decreased appetite (anorexia)	34	15	10	5
Initial insomnia	25	9	6	7
Interrupted sleep	21	8	9	2
Tachycardia	21	11	6	2
Dizziness	17	12	1	2
Headache	17	10	3	2
Early awakening	16	9	4	1
Increased need for sleep	16[a]	5	5	4
Nausea	15	9	3	1
Tremors	15	10	1	2
Low mood	13[a]	5	5	1
Nervousness	12	6	4	1
Abdominal pain	11	5	2	3
Diarrhea	10	4	4	1
Elevated mood	10	5	2	2
Constipation	9	3	3	2
Increased appetite	9[a]	2	3	3
Impaired dexterity	8[a]	5	0	2
Hallucinations	1	1	0	0
Tics	1	0	1	0

[a]n = 88.

fourth patient, a male aged 19 years with an IQ score of 95, had comorbid Asperger syndrome and developed a seizure after 10 months of methylphenidate treatment (50 mg/d). Methylphenidate was not believed to cause the seizure, but the treatment was nevertheless terminated. Two additional patients were found to be abusing alcohol, and, consequently, the central stimulant was discontinued. One of them, a 19-year-old man, was also a cannabis smoker prior to treatment, and the second patient, a 32-year-old man, had a long history of recurrent major depression since childhood.

DISCUSSION

This study demonstrates the efficacy and side effects of long-term treatment with CS in adult psychiatric patients with ADHD who were treated in a natural setting. As far as the authors know, this is the longest prospective study published so far. We have shown that in the short term, most patients perceive the pharmacologic treatment as effective, but adherence at the ≥ 2-year time point could be predicted by large effects on attention problems, impulsivity, restlessness, and irritability.

In line with previous studies, an elevated heart rate was demonstrated early in treatment and continued to be elevated at the ≥ 2-year time point. The blood pressure was not affected by central stimulant treatment, contrary to earlier reports,[8] but approximately 12% of the patients had hypertension at baseline. However, no patient discontinued treatment for cardiac reasons.

The dropout rate was 50% at the ≥ 2-year time point, which is markedly lower than reported from other studies of corresponding lengths.[8,15] Possible reasons for this favorable outcome are—according to our experience—measures for reminding the patients to show up for appointments and offers to participate in support groups on a regular basis. The support groups provide opportunities to discuss problems with others and facilitate the establishment of a stable relationship between the patient and the caregivers. In fact, the caregivers may learn a lot from the patients about shortcomings related to adult ADHD, and, in turn, patients can learn simple strategies to use in their daily lives. The results from the Norwegian study[15] support this interpretation. They showed that the dropout rate varied vastly between very high in cites without structured models for follow-up, while other cites had high compliance rates corresponding to ours. In other words, in order to achieve high compliance rates, the caregivers must be engaged and have knowledge about the needs of the adult patients with ADHD. If the caregivers are understanding and supportive toward the patient, the probability for compliance is most probably enhanced. The typical adult patients with ADHD are forgetful, procrastinate, are susceptible to depression and extremely vulnerable to stress, and have problems at work or finding a job, and chaos is usually a part of their every day lives. Their problems tend to end up in the lap of the caregiver, which, according to our view, indicates that the psychiatric team should include not only doctors but also nurse assistants, social workers, occupational therapists, and psychotherapists, which has been the setting at our clinic.

Almost one-quarter of the patients terminated medication for unknown reasons. Anxiety and depression were the most often reported reasons for discontinuation. Seventeen percent discontinued treatment due to adverse events, but overall, the side effects were generally mild and showed no progression over time. Fifteen percent of the cases reported lack of efficacy as the main reason for termination, which indeed could be explained by the low dosages prescribed in this study (median dose of methylphenidate was 50 mg/d [0.55 mg/kg] and for dexamphetamine 30 mg/d [0.38 mg/kg] at the ≥ 2-year follow up). We were concerned about putting patients in a vicious circle in which higher doses were required to maintain the treatment effect, but, in retrospect, we may well have been too cautious. Earlier studies have shown that dosages around 1.3 mg/kg/d of OROS-MPH with a median dose of 81 mg/d were more effective than a lower dose.[8] On the other hand, Reimherr and colleagues[20] reported that nonresponders ended up with a significantly higher dose than responders (75 mg/d versus 57 mg/d). Naturally, the only way to go with nonresponders is to raise the dose and hope for a response, but this approach will automatically lead to higher prescribed doses in nonresponders than in responders.

The thorough assessments administered at the unit originate from a research model developed for childhood onset neuropsychiatric disorders by Gillberg and Rasmussen[21] and are widely used across psychiatric clinics in Sweden. Although the comprehensive investigation is time consuming, it provides an excellent basis for diagnosis and insights into how ADHD affects living conditions, relationships, studies,

working life, and life choices during a life span. We believe these insights are of importance for the acceptance of the diagnosis among both patients and professionals, for future planning and for compliance to treatment.

The high educational level of the patients in this study can be explained by the nature of the catchment area. When the unit started in 2001, adult ADHD was viewed as a rare occurrence. Only patients with well-educated parents or who themselves were knowledgeable about ADHD pushed to have an ADHD assessment made. In addition, the area was initially characterized by residents with a high socioeconomic status, and only later was the catchment area expanded to include poorer areas. Our patients were nonetheless severely disabled, and only 51% were in full-time work or studies, despite average intelligence within the group.

Nearly half of the population in this study received additional treatment for depression or anxiety, and they were all psychiatric outpatients. It could be debated whether the many comorbidities obscured the data, but this does, in fact, reflect real life practice. Typical adult patients with ADHD will most certainly have various psychiatric problems.

In contrast to a recent finding,[22] we did not find any sex differences in emotional dysregulation, a factor derived from WRAADDS. On the other hand, more women than men were receiving treatment for emotional problems in our study. It is a well-known fact that patients with ADHD often suffer from various psychiatric symptoms in adulthood.[23] Attention-deficit/hyperactivity disorder frequently goes unrecognized in childhood even though many of those with ADHD have been child psychiatric patients. Only 1 of our patients with ADHD was diagnosed and treated in childhood despite the fact that 38% had been assessed for psychiatric problems as children. An increasing proportion of the adult psychiatric patients are now correctly diagnosed for the first time in their lives, and it remains a challenge to provide good treatment options. Although stimulants are effective and relatively safe, a multimodal treatment model is required in order to reach treatment success. Moreover, the definition of treatment success needs to be further discussed among both patients and researchers.

Study Limitations

This study has several limitations. First, although this study has a naturalistic setting, the study group is not representative of the entire ADHD population, as it only represents the outcome of a subset of the total patients seen, ie, those treated with CS at the clinic. Half of the sample was either treated by doctors outside the ADHD clinic, nonpharmacologically, or taking other drugs and not reported here. However, we have scrutinized every patient computerized record and know that an overwhelming proportion of these subjects were not treated with CS, or any other drug, for their ADHD. Second, patients with known alcohol and drug abuse, which is believed to be common in ADHD, were not included in this study group. In Stockholm, there is a special psychiatric clinic for treating adults with ADHD combined with drug or alcohol abuse, and we subsequently referred all of those patients. Third, the patients overall had a higher level of education and higher socioeconomic status than could be expected among persons with ADHD in the general population. This could hypothetically affect the relatively low dropout rate in our study. Fourth, we do not know why a large portion of the responders stopped the central stimulant treatment. A possible reason is lack of insight of the benefits from treatment. Typically, when the patient feels "well," he/she may be reluctant to continue to take medication, and, in case of relapse, procrastination and disorganization may hinder the patient from making a new appointment with the doctor. Fifth, it is always difficult to differentiate the impact of various forms of treatments. The treatment outcome in this study could, in fact, have been affected by the participation in support groups. However, there is no evidence that support groups have any major impact on the target symptoms of ADHD. Finally, we did not assess whether the lessening of target symptoms resulted in improved living conditions, studies and/or work, or relationships. Our impression is, however, whatever it is worth, that it had such an impact. Future effectiveness studies in this area would benefit from systematic measurement as well as clinical measurement of quality of life and functioning in treated patients and in the dropouts.

CONCLUSIONS

In this study, we showed that clinical response predicted adherence to treatment with central stimulants. The strongest predictor was improvement in attention over time during the first year of treatment. Long-term treatment with moderate doses of central stimulants increased heart rate but did not induce hypertension in adults with ADHD. About half of the adults with ADHD terminated stimulant treatment before 2 years even though side effects were mild.

Drug names: atomoxetine (Strattera), citalopram (Celexa and others), escitalopram (Lexapro and others), methylphenidate (Ritalin and others), olanzapine (Zyprexa).

Author affiliations: Department of Clinical Neuroscience, Section of Psychiatry, Karolinska Institutet, Stockholm, Sweden.

Potential conflicts of interest: **Dr Bejerot** is an employee of Stockholm County Council and has received grant/research support from Karolinska Institutet. **Drs Rydén** and **Arlinde** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: Financial support was provided through the regional agreement for support for research between Stockholm County Council and Karolinska Institutet (ALF agreement).

***Acknowledgment*:** The authors would like to thank nurse assistant Gunilla Björk and the rest of the staff at the former neuropsychiatric unit at the St Göran Hospital for their kind assistance; Drs Kristiina Westberg, MD, Ylva Ginsberg, MD, Kai Bruno, MD, and Daniel Stråth, MD, for diagnosing patients; and Professor Anna Åberg Wistedt, MD, PhD, for making this kind of work possible. The acknowledged persons report no personal affiliations or financial relationships with any commercial interest relative to the article.

REFERENCES

1. Fayyad J, De Graaf R, Kessler R, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *Br J Psychiatry*. 2007;190(5):402–409.
2. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms

  © Copyright 2010 Physicians Postgraduate Press, Inc.

of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry*. 2000;157(5):816–818.
3. Larsson H, Lichtenstein P, Larsson JO. Genetic contributions to the development of ADHD subtypes from childhood to adolescence. *J Am Acad Child Adolesc Psychiatry*. 2006;45(8):973–981.
4. Davidson MA. ADHD in adults: a review of the literature. *J Atten Disord*. 2008;11(6):628–641.
5. Rydén E, Bejerot S. Autism spectrum disorder in an adult psychiatric population: a naturalistic cross sectional controlled study. *Clinical Neuropsychiatry.* 2008;5:13–21.
6. Mancebo MC, Garcia AM, Pinto A, et al. Juvenile-onset OCD: clinical features in children, adolescents and adults. *Acta Psychiatr Scand*. 2008;118(2):149–159.
7. Weisler RH, Biederman J, Spencer TJ, et al. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. *CNS Spectr*. 2006;11(8):625–639.
8. Biederman J, Mick E, Surman C, et al. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2006;59(9):829–835.
9. Friedman R. Adults benefit from drug treatment for ADHD. *Medscape Medical News*. http://www.medscape.com/viewarticle/456007. May 21, 2003. Accessed February 24, 2009.
10. Spencer T (speaker). *Preliminary Results of a Six-Month Trial of Methylphenidate in Adults With ADHD* (cassette recording no. 03APA–S54B). Valencia, CA: Mobiltone Company, Inc; 2003.
11. Weiss M, Hechtman L; Adult ADHD Research Group. A randomized double-blind trial of paroxetine and/or dextroamphetamine and problem-focused therapy for attention-deficit/hyperactivity disorder in adults. *J Clin Psychiatry*. 2006;67(4):611–619.
12. Charach A, Figueroa M, Chen S, et al. Stimulant treatment over 5 years: effects on growth. *J Am Acad Child Adolesc Psychiatry*. 2006;45(4):415–421.
13. Miller AR, Lalonde CE, McGrail KM. Children's persistence with methylphenidate therapy: a population-based study. *Can J Psychiatry*. 2004;49(11):761–768.
14. Thiruchelvam D, Charach A, Schachar RJ. Moderators and mediators of long-term adherence to stimulant treatment in children with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):922–928.
15. Aanonsen NO, Lensing MB, Prietz R, et al. *De sakkyndig team for hyperkinetisk forstyrrelse/ADHD for helseregionene sør og øst. Rapport til Statens helsetilsyn. Utprøvende behandling med sentralstimulerende legemidler till voksne med hyperkinetisk förstyrrelse/ADHD [The expert team for the hyper-kinetic disorder/ADHD for health regions South and East. Testing treatment with stimulant drugs to adults with hyper-kinetic disorder/ADHD. Report to the Norwegian Board of Health Supervision]. Avd. For voksenhabilitering*. Oslo, Norway: Ullevall University hospital; 2005.
16. Biederman J, Spencer TJ, Wilens TE, et al. SLI381.304 study group. Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. *CNS Spectr*. 2005;10(suppl 20):16–25.
17. Kadesjö B, Janols LO, Korkman M, et al. The FTF (Five to Fifteen): the development of a parent questionnaire for the assessment of ADHD and comorbid conditions. *Eur Child Adolesc Psychiatry*. 2004;13(suppl 3):3–13.
18. Wender PH. *Attention-Deficit Hyperactivity Disorder in Adults*. Oxford, England: Oxford University Press; 1995:252–253.
19. Reimherr FW, Marchant BK, Strong RE, et al. Emotional dysregulation in adult ADHD and response to atomoxetine. *Biol Psychiatry*. 2005;58(2):125–131.
20. Reimherr FW, Williams ED, Strong RE, et al. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. *J Clin Psychiatry*. 2007;68(1):93–101.
21. Gillberg C, Rasmussen P. Perceptual, motor and attentional deficits in six-year-old children: screening procedure in pre-school. *Acta Paediatr Scand*. 1982;71(1):121–129.
22. Robison RJ, Reimherr FW, Marchant BK, et al. Gender differences in 2 clinical trials of adults with attention-deficit/hyperactivity disorder: a retrospective data analysis. *J Clin Psychiatry*. 2008;69(2):213–221.
23. Stahlberg O, Soderstrom H, Rastam M, et al. Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *J Neural Transm*. 2004;111(7):891–902.