

Long-Term Tolerability and Safety of Pharmacological Treatment of Adult Attention-Deficit/Hyperactivity Disorder

A 6-Year Prospective Naturalistic Study

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Abstract:

Background: Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder typically treated with stimulants and atomoxetine. Data on long-term tolerability and safety of such pharmacological treatment in subjects diagnosed in adulthood are limited.

Methods: A cohort of adults diagnosed with ADHD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria was followed-up on an average of 6 years after first evaluation. Of 168 adults, 112 (67%) who initiated medication were available for follow-up. Data were obtained from patient record data, self-report forms, and a telephone interview.

Results: Of the 112 participants assessed, 57 (51%) were still on treatment with methylphenidate (MPH) at follow-up and 55 (49%) had discontinued. The 3 leading reasons for discontinuing treatment with MPH were lack of effect (29%), elevated mood or hypomania (11%), and losing contact with the prescribing physician (9%). The most common adverse effects in subjects still on treatment with MPH were decreased appetite (28%), dry mouth (24%), anxiousness/restlessness and increased pulse frequency (19% each), decreased sexual desire (17%), and perspiration (15%). Subjects still on treatment reported increased quality of life, a higher level of functioning, and a greater understanding of their way of functioning from those being close compared with nonmedicated subjects.

Conclusions: The high attrition rate underscores the need for further research to identify possible modes to increase retention to treatment. Those diagnosed with ADHD and on long-term treatment with stimulants experience mild and tolerable adverse effects.

Key Words: attention-deficit/hyperactivity disorder, methylphenidate, stimulants, atomoxetine, long-term, tolerability, adverse effects

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Attention-deficit/hyperactivity disorder (ADHD), initially considered a childhood condition, has now been shown to persist into adulthood. It is associated with functional impairment and decreased quality of life.¹ The global prevalence has been estimated to about 5%.²

Adult ADHD has a high lifetime prevalence of general psychiatric comorbidity. The treatment goal is not only temporary relief of symptoms but also to support a more positive long-term functional development. Stimulants (eg, methylphenidate [MPH])

as part of a multimodal treatment strategy have been suggested as first-line treatment. Atomoxetine (ATX), classified as a nonstimulant, is an alternative treatment to stimulants.¹ The effectiveness of current pharmacological treatment is often reduced because of low treatment adherence and discontinuation of medication.

There are only a few randomized controlled trials (RCTs) of stimulants and ATX in which efficacy and safety have been assessed over longer periods (24 weeks or more) in adults with ADHD.^{3–6} Actually, in a meta-analysis of 44 such RCTs, the mean treatment duration was only 10.2 weeks.⁷ Only 1 study has reported safety-related results over a period as long as 4 years.⁸ In addition, some short-term trials have been supplemented with open-label extensions confirming a pattern of relatively mild adverse effects.^{9–13} To our knowledge, there are few prospective or naturalistic studies. In a 1-year study, 30% of the participants experienced at least 1 adverse effect of MPH and 12% terminated treatment on any ADHD drug because of adverse effects.¹⁴ Another study, including subjects with a high degree of psychiatric comorbidity, reported that only half continued treatment with stimulants after 2 years.¹⁵ Furthermore, only 15% discontinued treatment because of lack of effect and 17% did so because of either anxiety or depression. This observation that about half continue drug treatment was corroborated in a recent study.¹⁶ Finally, a 4-year outcome questionnaire study of pharmacologically treated adults with ADHD reported a 37% discontinuation rate at the 4-year follow-up. Adverse effects were the most frequent reason to end medication, followed by a perceived lack of efficacy and misuse.¹⁷

This observational follow-up study aimed to evaluate tolerability and treatment safety in adults with ADHD over a longer period as compared with previous reports. This was done in a cohort of subjects with current long-term treatment. We also assessed baseline predictors for adherence to treatment. Finally, we evaluated the subjects' perceived outcome since being diagnosed with ADHD and subsequently treated with stimulants and ATX.

MATERIALS AND METHODS

Subjects and Design

The study was based on 168 subjects previously evaluated and diagnosed with ADHD as adults at an outpatient clinic for neuropsychiatric disorders at Uppsala University Hospital between 2002 and 2010. The diagnostic procedure and psychiatric comorbidity at the time of the evaluation have been presented elsewhere.^{18,19} The study was approved by the Uppsala Regional Ethics Committee, and written informed consent was obtained from each participant.

Treatment Routines

At the start of this observational study, there was a rigid national control of medication of ADHD, a requirement for an individual prescription for each patient authorized by the Swedish Medical Products Agency, a limited number of prescribers, and considerable uniformity of treatment routines. At that time, only

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short-acting stimulants (eg, dexamphetamine [DEX] and MPH) were available and in general treatment started with doses of 5 mg (DEX) and 10 mg (MPH) per day. Depending on effect and duration, dosage and number of single daily doses were increased on a weekly basis. After the introduction of long-acting MPH, most subjects were either switched to or first introduced to OROS[®] MPH administered once daily, or, in some subjects who had a too short duration of effect, with an additional dose at lunch time. In parallel, other extended-release formulations of MPH and ATX were later available as treatment options. Long-acting lisdexamfetamine dimesylate was not on the market at the time.

The subjects were generally granted visits on each or every other week for dose titration until an optimal effect was obtained. On these visits, blood pressure, pulse frequency, and adverse effects were monitored. If one stimulant proved ineffective, subjects were offered treatment with another stimulant or another stimulant formulation. In some subjects, ATX was initiated. The targeted maximum dosages, with few exceptions, were 100 mg/d for MPH and 50 mg/d for DEX.

Follow-Up Assessment

Assessment was performed in 2013 (mean follow-up, 77 months) and carried out in 2 steps. First, data were extracted from the patient record, either as a computerized record or as a paper record. The participants were then administered an ADHD symptom questionnaire. This questionnaire was later supplemented by a structured telephone interview performed by a research nurse with extensive experience of the patient group. The interview covered demographics as well as detailed information about current and previous periods of ADHD medication.

Subjects' self-reports on previous medication periods and reasons for discontinuation were validated against data in their patient medical records. A medication period was defined as being of at least 1 month and with an intervening period of nonmedication of 1 month or longer before another attempt at pharmacological treatment. In case of contradictory data, we choose to rely on patient record data. If there were several medication periods, the final reason for discontinuation was registered.

In participants who had ongoing medication, current adverse effects were assessed by a form that was used as part of the clinical routine and contained 31 adverse effect symptoms. The frequency of adverse symptoms was categorized as *never*, *sometimes* (corresponding to 1–2 times/wk), *often* (corresponding to 3–6 times/wk), and *very often* (corresponding to daily/always). There were also questions on the subjects' perception of the effect of current medication and on adherence and dosage pattern.

Finally, participants were asked to respond to 5 statements related to how their status had changed since baseline: "My quality of life has improved," "My level of functioning has improved," "My understanding of my way of functioning has increased," "I have a greater understanding of my way of functioning from those close to me," and "I find it worthwhile having been evaluated for ADHD." Answers to the first 4 statements were categorized using a 4-point scale from *not at all* to *exactly correct*; the last statement ("...worthwhile having been evaluated...") was categorized in the opposite order from *yes*, *indeed* to *not at all*.

Data on deceased subjects' cause of death and their ongoing pharmacological treatment at the time of death were supplied by The Swedish National Board of Health and Welfare.

Statistics

Dichotomous data were analyzed using χ^2 test statistics or Fisher exact test when applicable. For ordinal data or when continuous data departed from the normal distribution, the Mann-Whitney *U*

test was used to analyze group differences; otherwise, the *t* test was performed for continuous data. Potential predictors of ongoing pharmacological treatment at follow-up were investigated by binary logistic regression analysis. Values are given as mean \pm SD or median with range within brackets when appropriate. All statistical analyses were performed using IBM SPSS Statistics, version 23.

RESULTS

Of the 168 subjects eligible for inclusion, 5 were reported dead at follow-up. Only 1 had died from natural causes, 3 had died of intoxication of illegal drugs, and 1 of a self-inflicted gunshot wound. Of the remaining 163 subjects, 18 rejected participation, 21 could not be traced or contacted, and 12 were not medicated for diverse reasons. Thus, the final sample consisted of 112 subjects for the follow-up evaluation. The total sample and its long-term clinical outcome are described elsewhere.¹⁸

Table 1 presents participant baseline and follow-up characteristics. The sample had lower ADHD scores at follow-up than at baseline (26 ± 11 vs 37 ± 8 , $P < 0.001$). There was no difference in living conditions over time. Both education ($P < 0.01$) and work status ($P < 0.05$), however, improved over the mean period of 6 years after the first evaluation.

Fifty-seven subjects (51%) were currently on treatment, and 55 had discontinued. There were no significant differences between the current treatment and the discontinued groups in age, sex, ADHD scores, ADHD severity, or axes I and II comorbidity at baseline (data not shown). Follow-up data on age, sex, ADHD score, living conditions, education, work status, or time that elapsed since the diagnostic evaluation did not differ between the groups (data not shown).

Subjects Who Had Discontinued Treatment

The total treatment time of the 55 subjects who had discontinued treatment was 24 ± 22 months (range, 1–75; median, 15) corresponding to $31 \pm 27\%$ (range, 2–93; median, 26) of the time since the subjects were diagnosed with ADHD as adults. All had been treated with MPH in periods, whereas 11 had been treated with DEX and 15 with ATX (Table 2). The total time on treatment with stimulants was 22 ± 21 months (range, 1–75; median, 15), that is, MPH or DEX; the medication period for ATX was 6 ± 12 months (range, 1–48; median, 3). The number of medication periods for stimulants was 2 ± 1 (range, 1–8; median, 2); none had been treated with ATX more than once. The dosage at the time of discontinuation was 68 ± 42 mg (range, 18–220; median, 60) for MPH, 47 ± 18 mg (range, 25–90; median, 45) for DEX, and 57 ± 28 mg (range, 20–100; median, 40) for ATX.

The 3 most common reasons for discontinuation of treatment with MPH were lack of clinical effect (29%), elevated mood or hypomania (11%), and lost contact with the prescribing physician (9%). Those who discontinued because of poor response had higher doses of MPH at discontinuation than those who discontinued for other reasons, which does not corroborate the view that they were suboptimally treated (88 ± 59 vs 56 ± 23 mg/d, $P = 0.04$). The reasons for discontinuation were found to vary in those 15 subjects who had been treated with ATX. In addition to lack of clinical effect, they were related to psychiatric adverse effects in almost half of the subjects. Of the 40 subjects not given treatment with ATX as an option, 19 had not been informed of the possibility, 16 actively refused and 5 were considering treatment.

Subjects Currently On Treatment

The total treatment time in the 57 currently medicated subjects reached 63 ± 24 months (range, 10–110; median, 62) corresponding to $84 \pm 19\%$ (range, 16–100; median, 88) of the time since the subjects

TABLE 1. Baseline and Follow-Up Characteristics of 112 Subjects Diagnosed With ADHD as Adults and Given Subsequent Pharmacological Treatment

	Baseline	Follow-Up	
Age, mean ± SD, y	35 ± 9	42 ± 9	
Time since evaluation, mean ± SD, mo (range)		78 ± 24 (31–133)	
Time on treatment, mean ± SD, mo (range)		44 ± 30 (1–110)	
ADHD score*	37 ± 8	26 ± 11	<i>P</i> < 0.001
Sex, females, n (%)	57 (51)	57 (51)	
Ongoing medication with stimulants or ATX, n (%)		57 (51)	
ADHD subtype [†]			
Predominantly inattentive	42 (38)	30 (27)	
Combined	66 (60)	19 (17)	
Predominantly hyperactive/impulsive	3 (3)	5 (5)	
No subtype fulfilled	—	22 (20)	
Remission [‡]		35 (32)	
Psychiatric comorbidity	52 (46)		
Mood disorder	14 (13)		
Anxiety disorder	31 (28)		
Eating disorder	2 (2)		
Adjustment disorder	2 (2)		
Psychotic disorder	1 (1)		
Substance use disorder	5 (5)		
Autism spectrum	11 (10)		
Tourette syndrome	5 (5)		
Any personality disorder [§]	45 (40)		
Number of fulfilled personality disorder criteria	8 ± 8		
Living conditions			
Living alone	51 (46)	55 (49)	
Living with partner	53 (47)	51 (46)	
Living with parent/relative	5 (4)	0 (0)	ns
Supported housing	3 (3)	6 (5)	
Education			
Incomplete compulsory school	6 (5)	2 (2)	
Compulsory school	36 (32)	36 (32)	
High school/upper secondary school	35 (31)	27 (24)	<i>P</i> < 0.01
Incomplete university	19 (17)	26 (23)	
University degree	16 (14)	21 (19)	
Work status			
Full-time	34 (30)	36 (32)	
Part-time	11 (10)	29 (26)	
Student	11 (10)	5 (5)	<i>P</i> < 0.05
Unemployed	21 (19)	17 (15)	
Sick leave/pension	35 (31)	25 (22)	

**n* = 107.[†]*n* = 111.[‡]No subtype fulfilled + GAF value ≥70 last year.[§]Diagnostic criteria for a personality disorder fulfilled (general criteria not considered).

ns indicates not significant.

had received their diagnosis of ADHD as adults. Of those 57 subjects, 46 (81%) were on treatment with MPH, 8 (14%) on DEX, and 3 (5%) on a combination of MPH and ATX (Table 3). Fifty-six subjects had a lifetime history of treatment with MPH, 13 with DEX, and 8 with ATX. The total treatment time with stimulants, that is, MPH and DEX, was 61 ± 24 months (range, 10–110; median, 61). The

number of stimulant medication periods was 2 ± 1 (range, 1–5; median, 1). The total time of treatment for the first medication period with ATX was 9 ± 17 months (range, 1–54; median, 3).

The maximum dosage during treatment was 84 ± 37 mg (range, 18–240; median, 73) for MPH, 43 ± 10 mg (range, 25–65; median, 40) for DEX and 68 ± 23 mg (range, 25–100; median, 72) for ATX.

TABLE 2. Reasons to Discontinue Pharmacological Treatment in Subjects Diagnosed With ADHD as Adults (n = 55)

	MPH	DEX	ATX
No. subjects, n (%)	55	11	0. 15
Reason/adverse effects			
Lack of clinical effect	16 (29)	4	3
No perceived need for further medication	1 (2)	1	
Lost contact with prescriber	5 (9)		1
Psychiatric			
Elevated mood or hypomania	6 (11)	1	
Depressed mood	4 (7)		2
Aggressiveness	2 (4)	1	2
Insomnia	2 (4)	1	1
Fatigue	1 (2)		1
Lethargy	1 (2)		
Increased obsessive-compulsiveness	1 (2)		
Drug abuse		1	
Mentally affected by drugs			1
Dermatological			
Rash	1 (2)	1	
Loss of hair	1 (2)		
Perspiration			1
Pruritus			1
Gastrointestinal			
Nausea	3 (6)		1
Weight gain	1 (2)		
Unspecific gastrointestinal symptoms		1	
Cardiovascular			
Hypertonia	3 (6)		
Palpitations/arrhythmia	3 (6)		
Neurological			
Headache	2 (4)		
Dyskinesia	1 (2)		
Amnesia	1 (2)		
Unspecific pain			1

The current dose was 60 ± 32 mg (range, 10–154; median, 54) for MPH, 42 ± 9 mg (range, 25–55; median, 40) for DEX, and 38 ± 13 mg (range, 25–50; median, 40) for ATX.

Forty-five subjects were treated with medium- or long-acting MPH, 4 with short-acting tablets in monotherapy, and 5 used medium-acting or a combination of long- and short-acting tablets. All subjects treated with DEX were on short-acting tablets. Thirty-nine percent of the subjects took their medication once a day and another 39% twice daily. The remaining 22% had an intake ranging from 3 to 6 times per day. Eighty-four percent stated that they took their medication in the exact dosage as prescribed and 16% reported using a lower dosage. No patient abused medication by taking a higher dosage than prescribed. Eighty-eight percent reported daily adherence to treatment, and 10% reported adherence to treatment 5 of 7 days a week.

The most common adverse effects during treatment with MPH were decreased appetite (28%), dry mouth (24%), anxiousness/restlessness and increased pulse frequency (19% each), decreased sexual desire (17%), perspiration (15%), and depressed mood (11%) (Table 2).

Finally, 81% reported a pronounced beneficial effect of their ongoing medication for ADHD and 16% reported a

moderate beneficial effect. Only 2 participants declared minimal or no effect.

Prediction Analyses

All baseline variables recorded in Table 1 were tested for possible inclusion in a regression model with ongoing pharmacological treatment at follow-up as the dependent variables. None of those baseline variables, however, were significantly related to ongoing pharmacological treatment.

TABLE 3. Current Self-Reported Adverse Effects During Pharmacological Treatment of 57 Subjects Diagnosed With ADHD as Adults

Adverse Event*	MPH	MPH + ATX	DEX
No. subjects, n (%)	46	3	8
Psychiatric			
Anxiousness/restlessness	9 (19)		
Decreased sexual desire	8 (17)		1
Depressed mood	5 (11)		
Elevated mood	3		
Difficult getting to sleep	4		
Increased need for sleep	3		
Hyperactivity	3		
Increased sexual desire	2		
Apathy	1		
Irritability	1		
Dermatological			
Perspiration	7 (15)	1	2
Skin heating	3		
Sensitive/dry mucous membranes	1		1
Pale skin	1		
Cold hands/feet	4	1	
Sensitive skin			1
Gastrointestinal			
Decreased appetite	13 (28)	1	1
Dry mouth	11 (24)		1
Constipation	3		
Nausea/vomiting	3		
Abdominal pain	2		
Diarrhea	1		
Cardiovascular			
Increased pulse frequency	9 (19)	1	
Hypertonia	4		1
Palpitations	2		1
Hypotonia	1		
Neurological			
Headache	3		
Sexual function problems	1		1
Vertigo/unsteadiness	1		
Tics	1		
Clumsiness	1		
Difficult to accommodate (vision)			1

More than 1 symptom could be reported from each patient.

*Only those with symptom frequencies classified as *often* (3–6 times/wk) or *very often* (daily/always) are included.

Perceived Outcome

Participants in the current treatment group scored significantly higher on the statements, “My quality of life has improved” ($P = 0.002$), “My level of functioning has improved,” ($P < 0.001$) and “a greater understanding” ($P = 0.017$) as compared with those who discontinued medication (data not shown).

DISCUSSION

The main finding is that long-term pharmacological treatment of patients diagnosed with ADHD in adulthood and who have a high degree of general psychiatric comorbidity at the time of the diagnostic evaluation is tolerable after a mean follow-up of 6 years after first evaluation, at least for most patients.

Half of the subjects were still on medication at follow-up, which is consistent with previous findings.^{15,16} Baseline characteristics did not predict which subjects would still be on medication at follow-up. Most of those on medication perceived a pronounced or moderate beneficial effect on their ADHD, with a mean stimulant dosage within recommended limits. Adherence to treatment was excellent in this group in terms of dosage and regularity of intake. Self-reported adverse effects during treatment with stimulants demonstrated a broad spectrum of symptoms like those reported in previous studies. Decreased appetite, dry mouth, anxiousness, increased pulse frequency, and decreased sexual activity and desire were the 5 most frequent complaints. Our results point to the importance of a broad and systematic evaluation of adverse effects when treating adults with ADHD.

Most of the subjects were on medium- or long-acting agents, except for DEX in which all treated subjects were on short-acting tablets (DEX was the only available option at the time of the study). In fact, in a systematic literature review, long-acting formulations and DEX in general were associated with longer persistence of treatment than short-acting formulations and MPH.²⁰

Most importantly, our data do not indicate tolerance or a need to increase the dosage over time (an issue discussed in the literature). Possibly, long-term medication increases the possibility to profit from other nonmedical interventions, which may even have a reduced dosage as a potential result.

Half of the subjects in our study had discontinued treatment at follow-up. The mean treatment time in this group was 2 years, enough time to evaluate treatment and individualized adjustment of doses to obtain a clinical effect. The observation raises the question of whether the efficacy of treatment diminishes over time, as reported previously,⁷ or whether, once again, the nonpharmacological interventions that run concurrently with medication affect the perceived need for pharmacological support. Furthermore, poor response to treatment was the most common cause of discontinuation.

The second most common reason for discontinuation of treatment was affective symptoms (reported by almost one fifth of the subjects treated with MPH). Notably, none of the subjects who had reported elevated mood or hypomania had been diagnosed with a bipolar disorder (BD) at baseline, whereas those 2 who had been diagnosed with a BD at baseline discontinued treatment because of depressed mood. This finding is in accordance with previous results, suggesting that comorbidity of BD and ADHD is more frequently associated with depressive episodes than to BD per se.²¹ Another noteworthy finding is that nearly 10% of the participants had discontinued treatment because they could not maintain contact with the prescribing physician. Whether this finding was due to the subjects' own difficulties or to a suboptimal health care organization, or both, was not answered by this study.

As presented in a previous publication, those on current medication did not report lower ADHD symptom load and better function than those who had discontinued treatment as assessed by

validated instruments.¹⁸ Nevertheless, the subjects did report an increase in quality of life, level of functioning, and understanding of their way of functioning from those close compared with subjects who were not currently medicated. This discrepancy may suggest that there are medication-related improvements not adequately reflected in the symptom profile of ADHD disorder but still sensed by the subjects and those close to them. Another possibility is that the subjects' subjective ratings contain a placebo-related mechanism in those who are compliant with the medication and pursue treatment over time.

A limitation of this study is that psychiatric comorbidity was not evaluated at follow-up. At baseline, however, there was no difference in general psychiatric comorbidity between those who had continued and those who had discontinued medication. Second, differences in nonpharmacological treatment or supporting interventions since baseline could have potentially biased the results. Third, because this was a naturalistic and primarily a descriptive study with a limited number of participants, no power analysis was performed to assess adequate sample size. Finally, the present study cannot rule out the risk for rare adverse events. A major strength is that it is one of the longest prospective studies of subjects diagnosed as adults and medicated because of ADHD. Being based on a clinical sample with no exclusion criteria attached, in contrast to RCTs, the results can be considered representative of a typical patient sample from an outpatient clinic for adult persons with neuropsychiatric problems.

Our study underlines the need to increase retention to pharmaceutical treatment, which over time is only about 50% in this patient group, in part because of a perceived poor clinical response. A close surveillance and strategy to change drugs, drug combinations, and dosages are ways to achieve this goal. Those who continue treatment experience relatively mild and tolerable adverse effects.

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