Four-Year Outcome in Psychopharmacologically Treated Adults With Attention-Deficit/Hyperactivity Disorder: A Questionnaire Survey

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ABSTRACT

Objective: In adults with attention-deficit/hyperactivity disorder (ADHD), pharmacotherapy is a recommended treatment option. However, research on long-term outcome with such treatment has been scarce.

Method: A questionnaire survey was completed by adults with ADHD, diagnosed according to *ICD-10/DSM-IV* criteria and approved for pharmacotherapy during 2003 to 2005, living in southeastern Norway. The questionnaire was conducted from November 2008 to April 2009. Of an eligible number of 1,096 subjects, 1,080 remained at follow-up; 371 subjects (34.4%) agreed to participate, and 368 of these reported having ever been treated with ADHD medication. Baseline characteristics and self-reported outcome were studied by time on psychopharmacologic treatment. Primary outcome measures were the Adult ADHD Self-Report Scale version 1.1 (ASRS) Screener and the Mental Health Index–5 (MHI-5). Based on cutoff scores for these instruments, 2 groups (favorable outcome vs others) were created to study possible predictors of outcome status.

Results: Self-reported baseline ADHD symptoms and impairment did not differ between participants and nonparticipants. Mean observation time was 4.5 years (range, 3.5–6.0 years). At follow-up, mean age was 36.5 years. Altogether, 270 patients (73.4%) had been treated for more than 24 months. They reported better outcome on all measures compared to those treated for 24 months or less (mean values: ASRS Screener score: 12.8 vs 15.3; MHI-5 score: 63.7 vs 57. 7). The favorable outcome group consisted of 79 participants (21.5%). Comorbidity at baseline predicted poorer outcome than did no comorbid illness.

Conclusions: In adults with ADHD, pharmacologic treatment for more than 2 years was associated with better functioning than treatment for 2 years or less. Comorbidity at baseline predicted poorer outcome.

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Attention-deficit/hyperactivity disorder (ADHD) is a well-established childhood disorder, which persists into adolescence and adulthood in about 40% to 60% of cases.[1–4] In a cross-national study, Fayyad et al[5] found an ADHD prevalence of 3.4% in adults. Outcome studies show that adults with ADHD have fewer years of education, lower occupational achievement, poorer self-esteem, more deficits in social skills, and higher rates of anxiety, mood, and substance use disorders when compared to the general population.[6–8]

Pharmacotherapy, mainly with stimulant medication, is one of the recommended treatment options.[9] Its efficacy on core symptoms of ADHD has been demonstrated in adults,[10] but most studies have so far been of short duration, and long-term outcome has been questioned.[11,12]

Recently, some relevant studies have been published. Bejerot et al[13] reported on a 2-year follow-up study of 133 adults with ADHD, mainly treated with stimulant medication and seen at a tertiary care outpatient clinic. Fifty percent of the sample remained in treatment for 2 years or more. Wender et al[14] studied a sample of 116 adults with ADHD in which only subjects with response on short-acting methylphenidate treatment and at least a 50% decrease of ADHD symptoms were included in a 1-year open study (N = 78). Among these, a marked improvement in ADHD symptoms and psychosocial functioning was found. However, as the majority of adults with ADHD differ substantially from subjects included in treatment trials from specialized university clinics, results from these studies cannot be generalized.[15,16]

Systematic chart reviews of patients with ADHD have shown that they often drop out of treatment very early[17] and are mostly compliant for less than 2 months.[18] High rates of attrition (50%–82%) have also been reported in recently published open–label treatment studies in adults with ADHD.[19–21]

As the impact on outcome of time on treatment before discontinuation still is an unresolved question, and long-term follow-up studies of naturalistic samples of adults with ADHD are warranted, we decided to study a fairly representative sample during an observation time of more than 4 years. Taking recent findings on long-term treatment into account,[13,14] we arbitrarily drew a line at 24 months of treatment or less on one hand and more than 24 months of treatment on the other to study the impact of time on treatment on outcome. The study aims were

(1) to investigate current use of ADHD pharmacotherapy,
(2) to measure ADHD symptomatology and mental health functioning at follow-up,
(3) to investigate the relationship between time on treatment and outcome, and
(4) to identify possible predictors of outcome.

To our knowledge this is the first study of long-term outcome of psychopharmacologically treated adults with ADHD in a naturalistic setting.

Clinical Points

- This is the first naturalistic outcome study of psychopharmacologically treated adults with attention-deficit/hyperactivity disorder (ADHD) after more than 4 years of observation.
- Among participants, a majority reported current pharmacologic treatment for ADHD. Adults with ADHD treated for more than 24 months reported more favorable outcome compared to those treated for 24 months or less.
- Comorbidity at baseline predicted poorer outcome.

METHOD

Design

A follow-up questionnaire survey was conducted from November 2008 to April 2009. The Regional Ethics Committee for Southeastern Norway and the Norwegian Data Inspectorate approved the study. Written informed consent was obtained from all included subjects. One reminder was sent.

Subjects

Treatment of adults with ADHD with stimulant medication in Norway was not permitted until 1997. Then, National Health Authorities appointed expert teams to secure assessment, diagnosis, and treatment for a period until spring 2005. The diagnoses by the expert teams were primarily based on written information provided by local specialists (psychiatrists or clinical psychologists) responsible for the assessment of ADHD, as well as psychiatric comorbidity and substance use. Treatment with stimulant medication provided by local specialists (psychiatrists or general practitioners) could only be started when (1) the diagnosis of ADHD was confirmed, (2) safety was secured with respect to medical and psychiatric concerns (eg, blood pressure, current substance use), and (3) health authorities had licensed its use.

From a defined region in southeastern Norway with an adult population of approximately 2,000,000 inhabitants, 1,096 adults with confirmed ADHD approved for psychopharmacologic treatment between autumn 2003 and spring 2005 were eligible for this study. None of these subjects had been included in earlier reports.[22,23] The mean observation time was 4.5 years (standard deviation [SD] = 0.5 years; range, 3.5–6.0 years). At follow-up, 16 persons were reported dead.

Baseline Assessment

The diagnoses hyperkinetic disorder and ADHD combined type were based *on International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) research criteria[24] and *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[25] criteria. For subjects with primarily inattention problems, criteria for ADHD predominantly inattentive subtype in *DSM-IV* were applied. Baseline diagnostic conclusions were reassessed by checking the interrater reliability for 2 independent raters (M.B.L. and P.Z.) of records from 54 randomly selected subjects. Cohen κ for ADHD combined and predominantly inattentive subtypes was 0.94 and 0.87, respectively. For diagnoses of anxiety and depression Cohen's κ was 0.58 and 0.59, respectively.

Psychiatric symptoms at baseline were assessed with the Symptom Checklist 90-Revised (SCL-90-R).[26] This instrument consists of 90 statements scored on a 5-point scale from 0 (not at all) to 4 (very much). Scoring yields 9 subscales and a Global Severity Index (GSI), which is the mean of all 90 statements.

ADHD symptoms at baseline were initially assessed with the General Adult ADD Questionnaire.[27] While the original form consists of 77 questions, a short version with 29 questions was used that yielded 5 subscales (inattention, restlessness, impulsivity, organization difficulties, and procrastination). In 2004, a pilot version of the Adult ADHD Self-Report Scale (ASRS)[28] was introduced, and the ASRS was subsequently used to assess baseline ADHD symptoms. This version of the ASRS consists of 18 questions (9 for inattention and 9 for hyperactivity/impulsivity). All items were scored on a 5-point scale from 0 (never) to 4 (very often).

Follow-Up Assessment

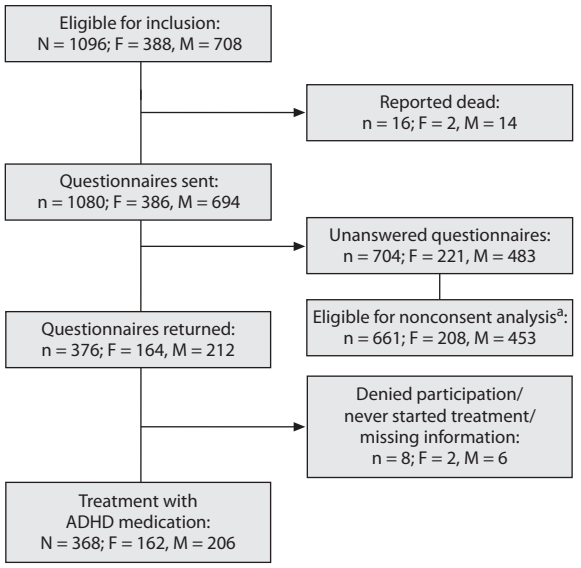
The follow-up questionnaire contained sections on ADHD treatment (pharmacologic and nonpharmacologic), self-reported symptoms, and functioning.

Current symptoms were assessed with the ASRS Screener.[29] It consists of 4 items on inattention and 2 items on hyperactivity/impulsivity. Symptom frequency was rated on a 5-point scale from 0 (never) to 4 (very often) with a cutoff score of 14.[30] Subjects with 3 or more missing items were excluded. Missing item values were otherwise replaced by the mean of the available item values. Cronbach α of the ASRS Screener in our study was 0.79.

Current mental health status was assessed with the Mental Health Index-5 (MHI-5), which is one of 8 subscales of the Short Form 36 (SF-36).[31] In the Norwegian validation study of the SF-36,[32] Cronbach α for the MHI-5 was 0.84, while in our study it was 0.87. Items are scored on 6 possible alternatives from "all of the time" to "not at all," with a score between 5 and 30, which is transformed linearly to a scale from 0 to 100.[31] Higher scores indicate better mental health. Subjects with 3 or more missing items were excluded. Otherwise, missing item values were replaced by the mean of the available item values. The MHI-5 is found to be especially sensitive for anxiety and depression, 2 conditions that occur frequently in adults with ADHD. Moreover, the questionnaire has been widely used in general health surveys.[33,34] Recently, Kelly et al concluded that a score below 77 indicated the presence of common mental disorders.[35]

ADHD-related improvement during psychopharmacologic treatment was assessed with a self-reported improvement question (SRIQ) (ie, "Have you experienced improvement during treatment for ADHD?"). The question

Figure 1. Study Flowchart



[a]Insufficient information for 43 subjects.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, F = female, M = male.

Table 1. Population Characteristics of 368 Adults With ADHD at Baseline[a]

Population Characteristic	Value
Age, mean ± SD, y	31.9 ± 10.7
Sex	
Female	162 (44.0)
Male	206 (56.0)
Highest educational level	
Junior high school	168 (45.7)
Senior high school	119 (32.3)
College/university	46 (12.5)
Missing	35 (9.5)
Civil status	
Single	190 (51.6)
Married/cohabiting	133 (36.2)
Missing	45 (12.2)
Employment	
Employed/student or apprentice[b]	182 (49.5)
Unemployed/disability pension[c]	157 (42.7)
Missing	29 (7.9)
ADHD diagnosis, subtype	
Combined	155 (42.1)
Predominantly inattentive	132 (35.9)
Predominantly hyperactive-impulsive	22 (6.0)
Residual	28 (7.6)
Insecure	31 (8.4)
Diagnosis of ADHD during childhood/adolescence	87 (23.6)
One or more comorbid psychiatric disorders at baseline[d]	224 (60.9)
Substance use	142 (38.6)

[a]Data are presented as n (%) unless otherwise noted.
[b]Student or apprentice: n = 82.
[c]Disability pension: n = 126.
[d]Most frequent comorbid psychiatric disorders, excluding substance use: mood disorders (n = 146), anxiety disorders (n = 107), personality disorders (n = 44), other psychiatric disorders (n = 42).
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

is scored on a 10-point visual analog scale from 0 (no) to 1–3 (little), 4–6 (moderate), 7–9 (much) to 10 (very great) improvement.

Statistics

Statistical analyses were performed with the PASW statistics 18.0 for Windows (IBM, Armonk, New York). The interrater reliability for diagnostic categories was estimated by using Cohen κ. χ^2 statistics were calculated to assess pairwise associations between categorical variables. Associations between a binary and a continuous variable were assessed by independent samples *t* test. One-way analysis of variance with Scheffé post hoc analysis was performed to assess group differences. Binary logistic regression was performed to identify predictive factors. A significance level of 5% was used.

RESULTS

In Figure 1, the study flow is presented. Altogether, 376 persons (34.8%) answered the questionnaire, of whom 371 (98.7%) agreed to participate. Among these, 368 (99.2%) stated that they, at least at one time, had been treated with ADHD medication.

A comparison of participants (N = 368) versus nonparticipants with available information (n = 661) did not reveal statistically significant differences as to hyperactivity, impulsivity, or inattention scores at baseline. Participants were older (mean ± SD age = 31.6 ± 10.7 years vs 28.8 ± 10.1 years; $t_{1027} = -4.6$, $P < .001$), more often female (44.0% vs 32.0%; $\chi^2_1 = 16.2$, $P < .001$), and had a slightly higher mean ± SD score on the SCL-90-R depression subscale at baseline (1.6 ± 1.0 vs 1.5 ± 0.9; $t_{623} = 2.1$, $P < .05$) than nonparticipants. Scores on other subscales and the GSI showed no significant differences between participants and nonparticipants at baseline. Neither did self-reported ADHD impairment differ between groups.

Sample baseline characteristics for participants are presented in Table 1. In addition to these data, women had a higher mean age (33.5 ± 10.4 years vs 30.6 ± 10.4 years; $t_{366} = -2.7$, $P < .05$) and more often finished senior high school (46.2% vs 27.9%; $\chi^2_2 = 16.6$, $P < .001$) than men. For the entire sample (n = 368), the mean ± SD ADHD baseline number of inattentive and hyperactivity/impulsivity symptoms was 7.2 ± 1.6 and 5.6 ± 2.4, respectively. No statistically significant differences in ADHD subtype distribution were found between women and men and across age. More men than women had been diagnosed with ADHD before adulthood (30.1% vs 13.0%; $\chi^2_1 = 15.2$; $P < .001$). Comorbidity was significantly more frequent in women than men (82.1% vs 64.6%; $\chi^2_1 = 14.6$, $P < .001$), but substance use was reported more often in men than women (44.2% vs 31.5%; $\chi^2_1 = 14.6$, $P < .05$).

Current Use of ADHD Pharmacotherapy

At follow-up, 232 subjects (63.0%) reported current psychopharmacologic treatment, and, of these, 116 subjects (50.0%) reported use of long-acting methylphenidate, while 77 subjects (33.2%) were treated with short-acting methylphenidate. Thirty-nine subjects used other ADHD medications (mostly dextroamphetamine sulfate or

Table 2. Self-Report Measurement Scores for 124[a] Adults With ADHD in the Off-Medication Group by Time on Treatment Before Discontinuation[b]

	Time on Treatment Before Discontinuation, mo			Group Comparison Statistic			
Self-Report Measure	0.25 to 6.0 [A] (n = 43)	> 6.0 to ≤ 24.0 [B] (n = 43)	> 24.0 to 72.0 [C] (n = 38)	*F*	*df*	*P*	Scheffé Post Hoc
ASRS-v1.1 Screener	15.7 ± 4.6	14.9 ± 4.9	12.0 ± 4.9	6.7	2, 119	.002	C < A,B
MHI-5	55.9 ± 20.7	57.5 ± 21.2	65.9 ± 19.3	2.7	2, 121	.069	NS
SRIQ	2.5 ± 2.7	4.9 ± 2.7	6.2 ± 2.4	21.3	2, 120	< .001	B,C < A

[a]Insufficient information for 12 subjects.
[b]Data are presented as mean ± SD unless otherwise noted.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASRS Screener = Adult ADHD Self-Report Scale version 1.1 Screener, MHI-5 = Mental Health Index–5, NS = not significant, SD = standard deviation, SRIQ = self-reported improvement question.

Table 3. Follow-Up Data for 356[a] Adults With ADHD by Time on Treatment[b]

	Time on Treatment, mo				
Self-Report Measure	≤ 24 (n = 86)	> 24 to ≤ 72 (n = 270)	*t*	*df*	*P*
ASRS-v1.1 Screener (range, 0–24)	15.3 ± 4.7	12.8 ± 4.8	4.2	352	< .001
MHI-5 (range, 0–100)	57.7 ± 20.8	63.7 ± 21.0	−2.7	354	.007
SRIQ (range, 0–10)	3.7 ± 2.9	7.4 ± 2.3	−12.0	352	< .001

[a]Insufficient information for 12 subjects.
[b]Data are presented as mean ± SD unless otherwise noted.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASRS-v1.1 Screener = Adult ADHD Self-Report Scale Screener, MHI-5 = Mental Health Index–5, SD = standard deviation, SRIQ = self-reported improvement question.

atomoxetine). Self-reported treatment adherence, defined as not missing a single dose during the last week, was significantly higher when patients were treated with long-acting than short-acting stimulant medication (75.7% vs 42.9%; $\chi^2_4 = 28.0$, $P < .001$). Among patients taking atomoxetine (n = 13), 50.0% reported not having missed a single dose during the last week.

At follow-up, 136 subjects (37.0%) had discontinued drug treatment (off-medication group). Nearly half of this group had used short-acting methylphenidate as the last medication before discontinuation. Most frequent reasons for discontinuation were adverse events (55.1%), lack of efficacy (32.4%), and misuse of medication (16.9%, reported by men only). Eleven subjects (8.1%) reported remission as reason for stopping medication.

ADHD Symptomatology, Mental Health Functioning, and Self-Reported Improvement

The mean ± SD ASRS Screener score at follow-up for the entire sample was 13.5 ± 4.9. A comparison between the current-treatment and the off-medication group revealed a significant difference in favor of the first-mentioned group (13.0 ± 4.8 vs 14.4 ± 5.1; $t_{363} = -2.7$, $P = .008$). In the current-treatment group, 130 subjects (56.0%) had a score below cutoff, while the corresponding number was 47 subjects (34.6%) in the off-medication-group.

The mean ± SD MHI-5 score was 61.7 ± 21.4. The difference between the current-treatment and the off-medication group was not statistically significant (63.3 ± 21.3 vs 58.9 ± 21.2; $P = .052$). Altogether, 263 subjects (71.5%) reported below cutoff.

The mean ± SD SRIQ score for the entire sample was 6.4 ± 3.0. The current-treatment group had a more favorable score than the off-medication group (7.6 ± 2.3 vs 4.3 ± 3.0; $t_{366} = 2.0$, $P < .001$).

Time on Treatment in the Off-Medication Group

The off-medication group was divided into 3 subgroups based on time on treatment before termination. Mean time on treatment before discontinuation in the off-medication group was 23.6 months (median = 12.0 months; range, 0.3–72.0 months). Those treated for more than 24 months before discontinuation (n = 38) were younger (mean ± SD age = 26.4 ± 8.9 years vs 31.8 ± 10.2 years; $t_{122} = 2.8$, $P = .006$) and had more often been treated for ADHD before adulthood (52.6% vs 10.6%; $\chi^2_1 = 25.8$, $P < .001$) than those treated for 24 months or less (n = 86). They also reported more favorable outcomes with respect to ADHD symptomatology, mental health functioning, and self-reported improvement (Table 2).

Relationship Between Time on Treatment and Outcome

Two groups were created to further investigate the relationship between time on treatment and outcome. One group contained the current-treatment group and subjects treated for more than 24 months before discontinuation (n = 270). The mean ± SD time on treatment for this group was 53.5 ± 8.1 months (median = 52.9 months; range, 30.0–72.0 months) versus 9.7 ± 7.7 months (median = 6.5 months; range, 0.3–24.0 months) in the other group that had been treated for 24 months or less (n = 86). Significantly more subjects in the long-term treatment group had been treated for ADHD before adulthood compared to those treated for 24 months or less ($\chi^2_1 = 10.5$; $P = .001$). Otherwise, baseline characteristics did not differ significantly between groups. Those treated for more than 24 months showed most favorable outcome when compared to the group treated for 24 months or less (Table 3).

Prediction Analysis

Based on self-reported level of functioning on ASRS Screener and MHI-5, 2 groups (favorable outcome vs others) were created for a prediction analysis. *Favorable outcome* was defined with an ASRS Screener score below the cutoff of 14 and an MHI-5 score above the cutoff of 76.

We compared the favorable outcome group (n = 79, 21.5%) to the rest of the sample (n = 276, 75.0%; see Tables 2 and 3). Mean ± SD ASRS Screener and mean ± SD MHI-5 scores for the favorable outcome group and the other group were 8.2 ± 3.3 vs 14.9 ± 4.3 and 85.9 ± 5.5 versus 55.3 ± 19.1, respectively. Sixty-seven (84.8%) of the 79 favorable outcome subjects had been treated for more than 24 months versus 203 (73.6%) of the 276 ($P < .05$). Current use of ADHD pharmacotherapy (70.9% vs 61.5%) was not significantly different between groups. In a binary stepwise logistic regression analysis, the baseline variables sex, age, number of ADHD symptoms, ADHD treatment before adulthood, and comorbidity were selected as possible predictive factors. Only psychiatric comorbidity predicted poorer outcome (odds ratio = 0.34, 95% CI, 0.19–0.61, $P < .001$).

DISCUSSION

In this naturalistic follow-up study of adults with ADHD, one-third of eligible subjects agreed to participate. However, participants and nonparticipants did not differ on core ADHD symptoms nor substantially on mental distress as measured by SCL-90-R scores at baseline. Health services are publicly funded, and no selection of subjects referred for assessment was done. Baseline characteristics of the study sample are similar to other studies of adults with ADHD.[36–38] Therefore, we find the study to be fairly representative.

Our study has 4 main findings. First, among participants, a majority reported ongoing treatment with ADHD medication after more than 4 years. Second, current treatment was associated with fewer self-reported ADHD symptoms and better mental health functioning. Third, pharmacologic treatment for more than 2 years was associated with better outcome. Fourth, psychiatric comorbidity at baseline predicted poorer outcome.

One of the main challenges in treatment is that "drugs don't work in patients who don't take them."[39(p487)] In studies of ADHD samples, difficulties with compliance with drug treatment over time have been reported frequently.[40–43] Although based on self-report, the high percentage of current treatment among participants in our study is striking. However, in a study on medication adherence in outpatients with severe mental disorders, Jónsdóttir et al[44] found patients' self-report to be a fairly reliable method for measuring adherence. Possible explanations for our finding can be found in the Nordic welfare system, which is based on equal treatment conditions, eg, the availability of specialists for all inhabitants, and expenses for necessary medical treatment are mostly covered by the national welfare system.

The efficacy of short-term ADHD pharmacotherapy in adults on core symptoms is well documented.[10,45,46] Open-label studies of stimulant medication in adolescents and adults with ADHD lasting up to 24 months have, despite high attrition rates, underpinned this finding.[20,21,47] We found our results to be in line with this. Interestingly, Volkow et al[48] recently provided neurobiological findings that increase of dopamine enhancement in specific brain areas was associated with response to long-term treatment with methylphenidate. However, most subjects still on medication reported significant ADHD symptoms. Thus, the overall impact of ADHD pharmacotherapy on academic, occupational, or social functioning in adults with ADHD is uncertain in our sample, as it is in studies reported by others.[10] One possible way to improve outcome may be found in more individualized and optimized treatment of ADHD, which has been highlighted recently.[49]

The mean MHI-5 score of 62 for the entire sample was well below an optimized cutoff score of 76. Along with the relatively high symptom load, the high proportion of comorbidity may explain this finding. Indeed, a score of 62 is more in line with the mean MHI-5 score of 67, which was found for any anxiety disorder in a large population-based study among 7,000 adults.[33] Overall, the result underscores the importance of assessment of daily functioning and comorbid conditions. Only a minority of our patients reported a level of ADHD symptomatology and mental health functioning that is in line with remission as a proposed goal for treatment.[50,51]

We lack empirical data for making decisions about time on treatment for ADHD in patients at different ages. Earlier, the common opinion was that treatment should be lifelong. However, adherence to medication over time is challenging.[52] Our study provides some information suggesting that treatment of adults with ADHD in many cases should be continued for at least 2 years.

In keeping with the findings of our study, psychiatric comorbidity has been identified as an important factor for impairment and persistence of ADHD symptoms in other studies.[53,54]

Limitations

Several limitations of our study have to be considered. First, of the eligible patients, only a minority agreed to participate, which may have led to a selection bias. There was, however, no difference in main sample characteristics between participants and nonparticipants. Second, the cross-sectional nature of the study does not permit causal conclusions. Third, unlike other studies, our study sample comprised a quite balanced gender distribution, which may have influenced the findings. However, as documented by others, sex differences as to severity of symptoms and clinical presentations are limited in adults with ADHD.[55,56] Fourth, our finding regarding current use of ADHD medication is cross-sectional, and we have not been able to investigate continuous use or switch of medication during the observation period. Fifth, study results are based on self-report alone, and the reliability can be questioned. However, other studies have documented that adults with ADHD are reliable reporters of their current symptoms[57] and even are at risk to underestimate their own ADHD-related impairment.[58]

Strengths

The naturalistic design, length of observation time, and the fairly representative study sample reflect common clinical challenges with respect to follow-up of adults with ADHD.

CONCLUSION

Pharmacologic treatment of ADHD for more than 2 years was associated with better functioning. Comorbidity at baseline predicted poorer outcome.

Drug names: atomoxetine (Strattera), methylphenidate (Concerta, Ritalin LA, and others).

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