Is Age-at-Onset Criterion Relevant for the Response to Methylphenidate in Attention-Deficit/Hyperactivity Disorder?

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Objective: Since DSM-IV criteria for attention-deficit/hyperactivity disorder (ADHD) require that some symptoms causing impairment must be present before 7 years of age, clinicians are faced with a diagnostic and treatment dilemma on how to proceed with late-onset ADHD patients. We aimed to compare the response to methylphenidate between a group of patients fulfilling all DSM-IV ADHD criteria (full ADHD diagnosis) and a group of patients fulfilling all DSM-IV criteria except the age-at-onset criterion (late-onset ADHD).

Method: We evaluated 180 children and adolescents (4–17 years old) and 111 adults from our ADHD unit. All ADHD diagnoses were assessed using DSM-IV criteria. Methylphenidate was administered twice daily (8 a.m. and noon), but an extra dose was allowed between 5 and 6 p.m. for children and adolescents needing extra coverage in the evening. The minimum dose was 0.30 mg/kg/day. Response to treatment was assessed in methylphenidate-naive subjects using the Swanson, Nolan, and Pelham Scale-version IV (SNAP-IV) at baseline and after 1 month of treatment. Data were collected from January 2000 to January 2006.

Results: In both samples, subjects with the full ADHD diagnosis did not have a better response to methylphenidate at doses around 0.5 mg/kg/day than the late-onset ADHD subjects. In fact, adults with late-onset ADHD with a better response to methylphenidate than adults with the full diagnosis, even after adjustment for confounders (baseline SNAP-IV total score and ADHD types) (children and adolescents: F = 0.865, p = .354; adults: F = 5.760, p = .018).

Conclusion: These results concur with recent literature questioning the validity of the DSM-IV age-at-onset criterion for the diagnosis of ADHD and suggest that clinicians should consider implementing methylphenidate treatment for subjects with late-onset ADHD.

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Although it is widely accepted that attention-deficit/hyperactivity disorder (ADHD) often begins in early childhood, defining an age-at-onset criterion for symptoms still generates much debate. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) states that some of the core ADHD symptoms that cause significant impairment must be present before the age of 7 years. In the International Classification of Diseases, Tenth Edition (ICD-10), criteria for hyperkinetic disorder require that symptoms must begin before the age of 6 years, with no mention of age for impairment.

Although the age-at-onset criterion for ADHD has been used for over 2 decades, its implementation and retention were based on the clinical experience of the committees formed to create diagnostic criteria, not on empirical research. Clinically, it is believed that the
age-at-onset criterion facilitates differential diagnosis between real ADHD and late-onset behavior and inattentive problems related to school stress or feelings of inadequacy. In this regard, Wolraich et al. suggest that previous school reports should be reviewed to help in documenting problems before the age of 7 years. In addition, the age-at-onset criterion seems to increase the homogeneity of samples for research. There is, however, much to be said against these apparently logical arguments. Green et al. showed that the recall of the exact age at onset of symptoms by parents has only moderate reliability after a 1-year period. This issue poses dilemmas for the diagnostic process that are even greater when assessing ADHD in adults. However, the most solid argument against the inclusion of this criterion in the classification system is that no systematic research had been done to validate the age-at-onset criterion until the publication of the DSM-IV.

More than 30 years ago, Robins and Guze proposed a strategy for assessing the validity of diagnostic constructs in psychiatric disorders that has been used in several investigations. Regarding psychiatric disorders of childhood and adolescence, Jensen et al. adapted the strategy including the following 8 criteria: clinical phenomenology; demographic, psychosocial, and biological factors; family genetics and environmental factors; natural history; and intervention response.

Several investigations assessed some of these parameters to determine the validity of the ADHD age-at-onset criterion. Regarding clinical phenomenology, Applegate et al. examined the validity of the age-at-onset criterion through the analysis of 380 youths aged 4 through 17 years using data from the DSM-IV field trials. They found that 18% of those having the combined type, 2% of those having the hyperactive/impulsive type, and 43% of those having the inattentive type had an age at onset after 7 years of age. The comparisons between the group having an age at onset after 7 years and the group with an age at onset before 7 years did not reveal significant differences in comorbid conditions or degree of impairment, possibly refuting the argument that a later onset of symptoms might be due to other disorders. Moreover, those who initiated symptoms after 7 years of age had more functional impairments than children who did not have ADHD symptoms. In a subsequent study, Rohde et al. found that subjects who fulfilled all DSM-IV ADHD criteria, except the age-at-onset criterion, showed patterns of symptomatology, comorbidities with disruptive behavior disorders, and global impairment more similar to youths with ADHD than to non-ADHD adolescents in a school sample of 191 Brazilian adolescents. Willoughby et al. assessed interviews of 1422 subjects (9 to 16 years old). In subjects with ADHD inattentive and combined types, elevated levels of symptoms, independent of their age at onset, were associated with more impairment.

There was no difference between the early- and late-onset groups in comorbidity in the inattentive group. However, early-onset subjects from the combined type were at higher risk for comorbidity with disruptive behavior disorders and more likely to receive treatment and to use mental health services. The findings from this study suggest that there are different clinical implications for the age-at-onset criterion depending on the ADHD subtype. Rucklidge and Tannock preliminarily compared 4 groups of adolescents: 6 subjects with adolescent-onset ADHD, 6 with childhood-onset but persisting ADHD, 6 with ADHD in remission, and 6 non-ADHD controls. The adolescents with childhood-onset ADHD showed more cognitive deficits than the group with adolescent-onset ADHD. The authors suggested that strictly observing the age-at-onset criterion is valid in the assessment of patients. In a referred sample of adults with ADHD, Hesslinger et al. found 50 patients into early-onset and late-onset ADHD subgroups. They found that late- and early-onset subjects both displayed similar psychiatric comorbidities and severity of current symptoms.

Regarding psychological factors, Faraone et al. compared 127 adult subjects meeting all DSM-IV criteria for childhood-onset ADHD with 79 adults meeting all ADHD criteria except the age-at-onset criterion using an extensive neuropsychological battery for the assessment of executive functioning deficits. Besides similar psychiatric comorbidity and functional impairment, they did not find significant differences between late-onset and full ADHD subjects in neuropsychological impairment.

Regarding family history, Faraone et al. assessed the same sample of adults with ADHD mentioned above. Trained interviewers extensively evaluated family psychiatric history through structured interviews. Again, no significant differences emerged in the comparison between late-onset and full ADHD subjects in patterns of family transmission.

Regarding response to interventions, we were able to find just 1 previous article that addressed response to methylphenidate in a small sample of adults with late-onset ADHD. Biederman et al. assessed 36 patients in an open-label trial using monotherapy with oral release osmotic system (OROS) methylphenidate at a daily dose up to 1.3 mg/kg/day. They found a statistically and clinically significant reduction in ADHD symptoms relative to baseline. However, no comparison was made against subjects with the full ADHD diagnosis.

Thus, the main objective of this study was to compare the response to methylphenidate treatment between a group of patients who fulfilled all DSM-IV ADHD criteria (full ADHD diagnosis) and a group of patients fulfilling all DSM-IV criteria except the age-at-onset criterion (late-onset ADHD). On the basis of the lack of significant differences between late-onset and full ADHD subjects on clinical phenomenology and psychosocial and family
factors in the majority of previous investigations, we hypothesized that no significant difference would exist between these 2 groups regarding response to intervention (methylphenidate).

METHOD

Design

This was a naturalistic study (noncontrolled cohort) assessing the efficacy of methylphenidate between early- and late-onset ADHD patients in 2 samples: 1 comprising children and adolescents and the other comprising adults.

Subjects

Subjects enrolled in this study came from 2 different samples collected in the ADHD Outpatient Clinic at the Hospital de Clínicas de Porto Alegre (HCPA). The first sample comprised children and adolescents with ADHD; the second comprised adults with ADHD. The HCPA is the university hospital of the Federal University of Rio Grande do Sul, Brazil. Data were collected from January 2000 to January 2006.

Inclusion/exclusion criteria were (1) age between 4 and 17 years for the child and adolescent sample and 18 years or older for the adult sample; (2) diagnosis of ADHD based on DSM-IV criteria; however, for the purpose of this study, we included those who did not fulfill DSM-IV age-at-onset criterion; (3) use of methylphenidate as the primary medication for the disorder in doses equal to or higher than 0.30 mg/kg/day; and (4) patients who were drug naive for methylphenidate.

The diagnosis of ADHD in children and adolescents was achieved in our clinic through a 3-stage process: (1) diagnostic procedures, the patient's current and past ability to function in areas of life activity was also assessed using a subset of the Swanson, Nolan, and Pelham Scale-version IV (SNAP-IV),26 (2) review of each diagnosis derived from a direct questionnaire formulated to the patients: “What was your age when you first experienced inattentive, hyperactive, or impulsive problems?” In order to improve reliability, whenever possible, a close member of the family who knew the patient since childhood was also asked about the age at onset of symptoms. The earliest reported age at onset of symptoms was considered in the analysis. Regarding impairment, the patient’s current and past ability to function in areas of life activity was also assessed using a subset of the Barkley ADHD Rating Scale.32

Measures

The primary outcome measure for assessing effects of treatment on ADHD symptoms was the total score of the SNAP-IV in both samples. The SNAP-IV is based on a 0 to 3 rating scale and has been frequently used in ADHD investigations, including those designed to assess clinical interventions.33 The internal consistency of the SNAP-IV varies from good to excellent.34 In a previous study, we obtained a Cronbach’s α coefficient of .74 for the complete scale (26 items) in a different sample.15 The scale was completed using information gathered from the subjects’ parents for the sample of children and adolescents and from the patient for the adult sample. Patients were evaluated for ADHD symptoms at baseline and after 1 month of treatment.

Demographic characteristics (gender, ethnic background, and age) were collected by direct interview. Intellectual functioning was measured in children and adoles-
cents by the Wechsler Intelligence Scale-Third Edition,36 administered by a trained psychologist to assess full-scale IQ score. In adults, intellectual functioning was estimated by vocabulary and block design subtests of the Wechsler Adult Intelligence Scale-Revised,37 also applied by a trained psychologist.

Pharmacologic Intervention

Patients were treated according to the program’s protocol. Doses of short-acting methylphenidate were augmented until there was no further clinical improvement or there were limiting side effects.23 Methylphenidate was administered preferentially twice daily (8 a.m. and noon), but an extra dose between 5 and 6 p.m. was allowed for children needing continuous coverage during the evening. The minimum dose of methylphenidate accepted in this protocol was 0.30 mg/kg/day. Concomitant use of other medications was allowed.

Data Analyses

Baseline patient demographic characteristics, IQ scores, ADHD subtype, comorbid conditions (current disruptive behavior disorders, anxiety and mood disorders), baseline SNAP-IV scores, doses of methylphenidate, and use of a second medication were compared between the 2 groups (full ADHD diagnosis and late-onset ADHD) in the 2 samples using the 2 groups (full ADHD diagnosis and late-onset ADHD) use of a second medication were compared between the 2 samples (baseline total score – total score at 1 month of treatment) was assessed through analysis of covariance with baseline scores and potential confounders as covariates. A 5% significance level was accepted in all these comparisons (2-tailed).

For both the child/adolescent and adult samples, an unbiased estimate of the endpoint versus baseline effect size was also computed for the total score of the SNAP-IV. An effect size greater than 0.80 is considered large, between 0.50 and 0.80 is considered moderate, and less than 0.20 is considered small.38

RESULTS

From a total sample of 238 children and adolescents with ADHD fulfilling our inclusion/exclusion criteria, we were able to include 180 subjects (75.6%). Reasons for exclusion were (1) lost at follow-up: 46 patients (19.3%); (2) lack of adherence to methylphenidate use: 10 subjects (4.2%); and (3) missing data for the baseline SNAP-IV scores: 2 patients (0.9%). From a total sample of 123 adults with ADHD fulfilling our inclusion/exclusion criteria, we were able to include 111 subjects (90.3%). Reasons for exclusion were (1) lost at follow-up: 10 patients (8.1%) and (2) missing data for age at onset of symptoms: 2 patients (1.6%) (Figure 1).

We compared patients included in and excluded from analyses in both samples on demographic characteristics, IQ scores, ADHD subtype, comorbid conditions (current disruptive behavior disorders, anxiety and mood disorders), SNAP-IV scores at baseline, doses of methylphenidate, and use of a second medication. There was no significant difference between children and adolescents with ADHD included in the study compared with those excluded on any assessed variable. Regarding the adult sample, there was a trend for between-group difference in the prevalence of ADHD subtypes (p = .054). No other significant differences were found.
Demographics, clinical data, IQ scores, and final doses of methylphenidate in both groups of children/adolescents and adults can be found in Table 1. Among the 180 children and adolescents evaluated in this study, 145 met all DSM-IV ADHD criteria (full ADHD) and 35 met all DSM-IV ADHD criteria, except the age-at-onset criterion (late-onset ADHD). Among the 111 adults assessed in this study, 54 met all DSM-IV ADHD criteria (mean age at onset = 4.2 years, SD = 1.6) and 57 met criteria for late-onset ADHD (mean age at onset = 9.0 years, SD = 2.1). In the sample of children and adolescents, significant between-group differences were found in age (full ADHD: mean = 9.9 years, SD = 2.8; late-onset ADHD: mean = 12.1 years, SD = 2.59; p < .001), subtypes (full ADHD: combined was the most prevalent [66.9%]; late-onset ADHD: inattentive was the most prevalent [60.0%]; p < .001), and comorbidity with anxiety disorder (full ADHD: 27.6%; late-onset ADHD: 8.6%; p = .016). In the sample of adults, no significant difference was found between the full ADHD and late-onset ADHD groups.

In both samples, subjects with full ADHD did not respond better to methylphenidate than those with late-onset ADHD. In the sample of children and adolescents, no significant difference was found (F = 0.865, df = 1, p = .354; confounders included in the model: SNAP-IV score at baseline, IQ score, and ADHD type). In the adult sample, however, the late-onset patients had a significantly higher response to methylphenidate than did the full ADHD patients, even after adjusting for confounders (SNAP-IV score at baseline and ADHD type) (F = 5.760, df = 1, p = .018) (Figure 2). Endpoint versus baseline effect sizes were large in both groups of children and adolescents (ADHD full diagnosis: 1.05; late-onset ADHD: 0.91) and adults (ADHD full diagnosis: 1.27; late-onset ADHD: 1.73).

**DISCUSSION**

In 2 independent clinical samples of patients with ADHD across the life cycle, we were not able to detect a...
significantly better response to methylphenidate in subjects with the full diagnosis of ADHD compared with subjects with late-onset ADHD. In contrast, for adults, we found a better response to methylphenidate for the late-onset subjects. Although medication response cannot be viewed as a gold standard for validating diagnoses, these results viewed in the context of prior work provide converging evidence for the validity of late-onset ADHD. We are not aware of previous studies in children and adolescents investigating the role of age at onset of symptoms in response to methylphenidate in subjects with ADHD.

Similar to findings from other studies,13,14 we found many children (almost 20%) with impairing late-onset ADHD symptoms (age 7 years or later). In addition, a substantial proportion of adults (51%) with ADHD reported symptom onset after 7 years of age. Their age at onset of symptoms would exclude these subjects from full DSM-IV ADHD diagnosis, although they would qualify for the diagnosis of ADHD, not otherwise specified. This issue assumes an even more relevant perspective considering that Mannuzza et al.7 found, in a longitudinal study, that only 27% of adults with a confirmed childhood ADHD diagnosis would be correctly identified as having ADHD in childhood on the basis of an assessment in adulthood. Moreover, patients with full ADHD diagnosis and those with late-onset ADHD had a similar male/female ratio and comorbid profile in our samples of children/adolescents and adults. The only difference found regarding comorbidity was for anxiety disorders in the sample of children and adolescents. As expected, more ADHD inattentive type was found in late-onset ADHD.

Concerning response to methylphenidate treatment, we found large endpoint versus baseline effect sizes for both patients with full ADHD and those with late-onset ADHD in the 2 samples. The magnitude of effect in subjects with full ADHD was comparable with that found in previous short-term clinical trials (see Faraone et al.39 and Szobot et al.40). No significant difference in the response to methylphenidate was detected between full ADHD and late-onset ADHD in the sample of children and adolescents. Surprisingly, we found an even greater response to methylphenidate in late-onset ADHD compared with full ADHD in the sample of adults. This difference remained significant even adjusting for potential confounders (SNAP-IV score at baseline and ADHD subtype), and it cannot be explained by methylphenidate doses since adults with late-onset ADHD received similar mg/kg/day doses as those provided to adults with full ADHD (see Table 1). It is important to note that Biederman et al.20 evaluated response to OROS methylphenidate in a sample of 36 adult patients presenting with late-onset ADHD in the only previous noncontrolled open study assessing this issue. The authors also documented a robust reduction in ADHD symptoms.

The neurobiological model for ADHD suggests the implication of several genes in the etiology of the disorder, each of them with small effect.39 The genetic susceptibility of each individual with the disorder may vary greatly, and the expression of these genes into a definable disorder may also depend on the demand posed by environmental adversities. A child with low genetic vulnerability may manifest the disorder early in life if he or she was raised in a challenging environment, such as a more demanding school. Likewise, the same child may manifest the disorder later in life if he or she faces higher environmental demands only later in life. Thus, requiring an age at onset before the age of 7 years may not be in accordance with this etiologic model, since an absolute age does not take into consideration the child’s environmental demands.

Limitations of the Study

The results reported in this study must be interpreted in the context of some methodological limitations. First, since we performed a retrospective assessment of the age-at-onset criterion, findings are subject to recall biases, especially in the adult sample. Other investigations have suggested a low accuracy of adult recall regarding ADHD symptoms in childhood.73 However, it is important to note that there is no reason to expect that this assessment bias would differently affect the 2 groups (full diagnosis and late-onset ADHD) considering that impairment of ADHD symptoms was present in both groups. Moreover, prior work shows little evidence for reporter biases in the assessment of adult ADHD.42–44

Second, we did not have a placebo arm in this trial, so we did not have an internal control to correct for any effect of time or expectancy bias. However, the improvement of ADHD symptoms in both groups in the 2 independent samples of children/adolescents and adults was comparable with those previously reported in randomized clinical trials. Although a placebo response was likely present to some degree in our study and most likely decreased power by reducing precision of measurement of drug response, it is unlikely that placebo response has been systematically related to only one of the groups (full diagnosis or late-onset ADHD). Third, we assessed age at onset of impairment in the sample of children and adolescents and age at onset of symptoms in the sample of adults. Since these different measures (age at onset of impairment and age at onset of symptoms) might introduce bias in analyses, we ran separate analyses in samples of children/adolescents and adults. It is important to note that independent of the strategy used, patients with full ADHD diagnosis did not have a better response to methylphenidate than those without ADHD age-at-onset criterion or without ADHD age at onset of impairment criterion (late-onset ADHD). Moreover, the confusion between these 2 measures is implicit in the literature since
DSM-IV criteria emphasize age at onset of impairment, and ICD-10 criteria emphasize age at onset of symptoms in the diagnosis of ADHD.

Clinical Implications

Our results in independent samples of children/adolescents and adults have a direct clinical implication. They corroborate previous findings suggesting that patients with late-onset ADHD symptoms (age 7 years or older) might present similar symptomatology, comorbid profiles, and levels of impairment as those with early onset of symptoms. Moreover, our findings suggest that patients with late-onset ADHD symptoms do not have a poorer response to methylphenidate treatment. Thus, clinicians should consider not only a diagnosis of ADHD in these patients, but also the possibility of implementing methylphenidate treatment. This approach is even more important in adults for whom recall of age at onset of ADHD symptoms is extremely problematic, and evidence from this and a previous study document a robust response to methylphenidate for those presenting a late onset of symptoms.

In addition, our results add to previous findings suggesting that revisions of classification systems that are in progress should consider revising this restrictive non-empirically based criterion for ADHD.

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