

# Adaptive Changes Related to Medication Treatment of ADHD: Listening to Parents of Children in Clinical Trials of a Novel Nonstimulant Medication

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The DSM-IV diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) have proved useful in providing a common language for diagnosing, treating, and researching the disorder. Despite the utility of current ADHD diagnostic criteria, sophisticated theoretical conceptualizations of the etiology of ADHD have described a much more complex disorder that includes a range of neuropsychological impairments (such as working memory deficits and other executive dysfunction) and underlying structural and functional neuropathology (e.g., caudate nucleus volume, frontal lobe activity). Inattention, hyperactivity, and impulsivity, the hallmark triumvirate symptoms of ADHD, may be better viewed as some of the many meaningful symptoms with roots in executive-functioning impairment. Outcomes of brain-imaging studies, public skepticism about diagnosis and treatment, and a demand for meaningful clinical outcomes of treatment point to a considerable need to broaden treatment-outcome criteria beyond the DSM-IV domains. The wide-ranging decrements in adaptive function and quality of life reported by parents of children diagnosed with ADHD further support core executive dysfunction. Emerging findings concerning medication-related improvements in adaptive functioning (e.g., social, emotional, academic), as well as the rapid search for the neuropathology that may underlie these improvements, are fueling interest in the assessment of adaptive function in clinical trials. In a series of ongoing clinical trials of a novel nonstimulant medication for ADHD, many parents reported significant improvements in the lives of their children beyond the DSM-IV criteria. These parental reports, despite their inherent sources of error, underscore the importance of including broader and more meaningful clinical outcome assessment in clinical trials. Research protocols that omit parental interviews that assess adaptive and executive function may well overlook several meaningful and consequential medication-related improvements.

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**A**ttention-deficit/hyperactivity disorder (ADHD) is not caused by poor parenting, poor nutrition or food additives, too much sugar, or an unstable home life; it is most likely a disorder of behavioral inhibition mediated by neuropathology.<sup>1,2</sup> Although there is a general consensus

among experts<sup>2-4</sup> that the etiology of ADHD involves neuropathology, the precise mechanisms remain elusive.<sup>5,6</sup> The etiology of ADHD includes multiple influences (e.g., neurochemistry, neuroanatomy, genetics, prenatal complications) that determine its expression and course.<sup>2,4,5,7</sup> There is widespread agreement that stimulant medication, despite some of its limitations and drawbacks, is generally effective in treating ADHD symptoms.<sup>8-10</sup>

In other articles in this supplement, our colleagues review and discuss various ADHD topics related to these issues, including etiology, neuropathology, treatment outcomes, and promising research. Our contribution in this article discusses the common experience in a series of clinical trials (across raters and investigators) of parents who noticed exciting adaptive functioning changes in their children (Table 1) that were not being captured by DSM-IV rating instruments. This experience demonstrates the profound importance of these functional changes to families coping with ADHD and underscores the need for assessing and understanding the role of adaptive functioning within a conceptual or theoretical framework.

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**Table 1. Examples of Statements From Parents Concerning Additional Improvements in Their Children's Functioning**

Parents whose children were taking an investigational nonstimulant medication to treat ADHD reported the following:

My child:

- Is more concerned about people's feelings
- Is willing to go places he or she didn't want to go before
- Understands time and calendar; plans ahead
- Is more emotionally available now
- Gets along with siblings much better
- Is finally being invited to birthday parties
- Is much less bothered by things
- Cooperates when told to go to bed
- Is not a sore loser when he or she loses a game
- Is interested in having a conversation
- Remembers to do homework without my encouragement
- Is interested in learning; has frequent conversations about feelings, life, and so on
- Has a greater sense of pride; cares more about appearance
- Rarely interrupts; apologizes and then waits
- Is more enjoyable for the family to be around than ever before

### IMPROVING DIAGNOSIS AND TREATMENT OF ADHD

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),<sup>11</sup> has contributed to improvements in ADHD diagnostic clarity by emphasizing inattention and hyperactivity/impulsivity symptom clusters. However, the implementation of these criteria in clinical practice may often be imprecise.<sup>12</sup> That is, clinicians and researchers active in the study or treatment of ADHD commonly meet parents of children with ADHD who, despite perhaps numerous contacts with treatment providers, remain befuddled about how diagnostic conclusions are reached. In our experience, this confusion contributes heavily to the parents' perceptions about the murkiness of ADHD diagnostic and treatment decisions.

Parents of children with ADHD are commonly frustrated with diagnostic screening procedures that may not target the symptoms that parents consider the most troubling or impairing. A screening procedure that focuses on the DSM-IV criteria may not ask about the child's friendships with his or her peers, interactions with other children at school or in play, or the degree to which the child is included in social activities. Although inattention, impulsivity, and hyperactivity can have negative effects on these aspects of a child's life, these symptoms cannot account for all the impairments commonly seen in a child with ADHD.

One of the most common parental misconceptions about ADHD is that it is a "new" disorder, a product of the 1990s. In fact, ADHD has been documented for over a century under various names (e.g., postencephalitic behavior disorder, organic drivenness, brain-impaired child syndrome), and has likely been in existence throughout history. Diagnostic uniformity for the disorder did not occur until the advent of the DSM with its emphasis on

symptom-based descriptors for diagnosing all mental disorders. Even within the DSM, the disorder has been dynamic, evolving since DSM-II to its current diagnostic approach in DSM-IV, which requires identifying a specific subtype.

Making an ADHD diagnosis should be a complex process,<sup>13</sup> but parents commonly observe diagnosis occurring based exclusively on their answers on a checklist or unstructured conversation, rather than following a more thorough evaluation process.<sup>8</sup> To diagnose ADHD, DSM-IV requires that the ADHD subtype criteria must be met and specified.<sup>11</sup> Five subtyping options are used: ADHD primary inattentive, ADHD primary hyperactive impulsive, ADHD combined type, ADHD not otherwise specified (NOS; used for diagnoses that are somehow anomalous), and ADHD in remission. To meet diagnostic criteria, the current system requires that 6 of 9 criteria from either the inattentive (9 descriptors) or hyperactive/impulsive (6 hyperactive, 3 impulsive) symptom listings be met. Meeting requirements in only one or the other of the symptom listings denotes a diagnosis of a primary subtyping; meeting criteria in both symptom listings denotes a diagnosis of a combined subtyping. Symptoms must create impairment in at least 2 domains (e.g., academic and social) and must be present before 7 years of age. Symptoms must occur far more than expected for children of the same age and sex.

A recent study<sup>12</sup> of the prevalence of ADHD in the United States illustrates the diagnostic difficulties associated with the disorder. The diagnostic aberrations seen in the study illustrate how imprecision in diagnosis can contribute to the variable outcomes noted in key areas of study.<sup>14</sup> The study examined 5718 children in Rochester, Minn., and categorized them as having definite ADHD (clinical DSM-IV diagnosis confirmed by ADHD questionnaire results), probable ADHD (either clinical DSM-IV diagnosis not confirmed by ADHD questionnaire results or diagnosis via ADHD questionnaires even though DSM-IV criteria were not met), questionable ADHD (diagnosis via one ADHD questionnaire even though DSM-IV criteria were not met), or no ADHD. The results show how diagnostic imprecision occurs even when using diagnostic conventions that require "objective" assessment of specific symptoms. Only 7.4% of the children included were found to have definite ADHD, but when the incidence of definite ADHD was added to that of probable and questionable ADHD, the prevalence rate rose to 16%. Although the authors note that the variation in reported prevalence of ADHD may be due to differences in diagnosis (i.e., the more stringent the criteria, the fewer cases diagnosed), it should be noted that all diagnoses of ADHD should be made using the same criteria. In actual practice, differences may occur in the interpretation of the diagnostic criteria but should not occur in the use of the criteria per se.

Current ADHD diagnostic criteria insufficiently account for the types of problems children with ADHD

encounter.<sup>15,16</sup> For example, the inattention of children with ADHD does not typically signal a problem with the perception and processing of information; instead, inattention often reflects problems with motor inhibition and control. By focusing on inattention, impulsivity, and hyperactivity, the DSM-IV criteria do not recognize other behavioral or cognitive problems commonly seen in children with ADHD. Somewhat paradoxically, the criteria make no effort to connect the spectra of symptoms even though the hyperactive and impulsive symptoms often emerge first as precursors to the inattentive symptoms. In fact, the combined type and inattentive type are the most common forms of the disorder seen in school-aged children, and the 2 types are so distinct that they may be 2 different disorders.<sup>3</sup>

Controversy about the appropriateness of the diagnostic requirements,<sup>16</sup> particularly the age-at-onset restrictions and the number of symptoms required across the life span,<sup>17</sup> is contributing to important dialogue about the way ADHD should be diagnosed in light of new symptom descriptors emerging from a new theoretical framework.<sup>16</sup> The current dialogue is an important contribution to the overall dynamic process that accompanies reformulations of ideas and concepts.

Can diagnostic precision and treatment effectiveness for ADHD be improved by using a more broadly descriptive conceptual framework based on executive functioning that includes hyperactivity, impulsivity, and inattention as 3 of many descriptive symptoms? It is possible that casting a broader net of descriptive symptoms based on a new theoretical conceptualization may assist in diagnostic precision and in improving the public's perceptions about how diagnostic and treatment decisions occur.

### REDEFINING ADHD

The primary roles of executive functioning are initiating, sustaining, inhibiting, shifting, and directing and redirecting attention in combination with monitoring and regulating emotional responses. These executive functions are principal elements in the reexplanation and reconfiguration of ADHD as a disorder of behavioral inhibition resulting from underlying neuropathology. This emerging model posits that impairments in 4 areas of executive functioning (nonverbal working memory; internalizing self-directed speech; self-regulating mood, motivation, and arousal; and segmenting and recombining observed behaviors into component parts to form new behaviors) create cognitive and emotional impairments that result in compromised adaptive functioning.<sup>1,5,18</sup> The impairments seen are not, as once was believed, derived from attentional deficits, but rather from deficits in behavioral inhibition, which are explained by central impairments in executive functioning. In addition to producing the hyperactive and impulsive behaviors seen in ADHD, impaired

executive functioning is responsible for the myriad of additional cognitive and behavioral impairments noted in ADHD.<sup>16</sup> The underlying neuropathophysiology is explained in detail elsewhere,<sup>6,14,18</sup> but it is important to note that there are compelling neurochemical and neuroanatomical explanations for how executive function becomes impaired and why specific medications are effective. In addition to medication, Barkley's<sup>7</sup> conceptualization advocates specialized training for parents and teachers to promote understanding of ADHD and increase the effectiveness of treatment interventions at home and at school.

Knowing the distinction between the terms *executive function* and *ADHD* is helpful in understanding at least some of the frustration or confusion regarding the DSM-IV diagnosis of ADHD. ADHD is a medical diagnosis, which defines a subtype of the disorder based on meeting criteria for clusters of descriptive symptoms. Executive function is a neuropsychological construct inferred from observed behavior; it is not a construct that is in any direct way specified in the DSM-IV diagnostic criteria. To fully grasp both the semantic nuance and the frustration many parents report, it is also important to define adaptive functions, which are defined by performance, not ability; these are the everyday skills needed to interact with others and to be both self-sufficient and socially proficient. They include, for example, social fluency, performance at an age-appropriate level at school and among friends, physical expressions of affection, maintenance of family relationships and relationships with other adults, problem-solving ability, caring, and empathy. Although deficits in adaptive function are often discussed in the context of mental retardation or pervasive developmental disorder, children with ADHD exhibit developmental delays in this area as well. In fact, as with deficits in executive function, deficits in adaptive functions can also be seen as a core feature of the disorder, with inattention and hyperactivity/impulsivity as an outward expression of those deficits.

Stein and coworkers<sup>19</sup> examined adaptive skills in children with ADHD and pervasive developmental disorder/mental retardation (PDD/MR). They investigated whether IQ was linked to the level of adaptive skills dysfunction in children with ADHD as it is in children with PDD/MR. Adaptive skills were measured by the Vineland Adaptive Behavior Scales (VABS), and the discrepancy between IQ and VABS scores was calculated. One would expect little discrepancy since developmental problems in one often affect the other, and this expectation was confirmed in the PDD/MR group. However, in the ADHD group, a significant discrepancy was found on the socialization, communication, and daily living domains of the VABS, and a significant difference in the discrepancies in these areas was found between the ADHD group versus the PDD/MR group. Older age in the ADHD group was associated with a greater discrepancy—adaptive dysfunction increased as

the children got older. This pattern of dysfunction, if it persists into adulthood, could cause a high degree of impairment among adults with ADHD. The authors conclude by calling for more testing of adaptive function in children with ADHD and more treatments geared toward improving function as well as improving attention and alleviating hyperactivity.

Deficits in adaptive functioning usually alert parents and teachers that something may be amiss. These deficits often herald the diagnosis of and beginning of treatment for ADHD. Because the adaptive behaviors are meaningful (i.e., observable and relevant) to parents, they, and thus the executive functions, are often much more salient treatment targets than the symptom listings in the DSM-IV criteria.

The DSM-IV diagnostic criteria include a strong but implied connection between the descriptive symptoms listed and executive functioning. The DSM-IV criteria do not, however, include an exhaustive list of the possible (or even the most commonly expressed) descriptive symptoms seen in ADHD. Making the connection between descriptive symptoms of ADHD used in DSM-IV and executive functioning more central to the diagnosis and treatment of ADHD will greatly strengthen understanding and measurement of the impairments and the treatment-related improvements of the disorder.

Participants in our clinical trials attempted to convey this message during weekly visits to assess changes in ADHD symptoms as measured by the ADHD Rating Scale (ADHD-RS).<sup>20</sup> In response to questions about ADHD-RS items, parents asked repeatedly when we were going to assess other exciting changes they were noticing. Parents mentioned that although changes were occurring on the DSM-IV criteria reflected on the ADHD-RS, many more changes were also taking place. They reported changes in social functioning (e.g., having more friends, being invited to or included in events, receiving phone calls initiated by others), family interactions (e.g., greater patience in communicating, ability to play family games without “meltdowns,” greater affection), academic improvements, better sleep habits, increased ability to solve problems, and an often reported but intangible quality of “being available” or “being there.”

This same phenomenon took place across clinical trial sites; parents of subjects told research personnel at many sites that meaningful, adaptive changes were occurring. Because the quality of executive functioning is implied from observed behavior (i.e., adaptive functioning), we concluded that treatment-related changes in executive functioning might be occurring. Based on this possibility, we set about to identify existing tools that might capture the unfolding phenomenon being reported. This search eventually led to the development of a new tool, the Life Participation Scale for ADHD, to assess treatment-related changes in adaptive functioning in ADHD.

## DEVELOPING THE LIFE PARTICIPATION SCALE FOR ADHD

Most ADHD treatment outcome studies are unable to systematically assess many changes that are meaningful to parents, family members, teachers, and others. These efficacy studies primarily use scales that emphasize attention deficits, impulsivity, and hyperactivity, both for inclusion criteria and primary outcome measurement.<sup>5</sup> Examples of commonly used DSM-based assessments in these studies are the ADHD-RS,<sup>20</sup> the Diagnostic Interview Schedule for Children (DISC),<sup>21</sup> and the Kiddie SADS Behavioral Disorders Supplement for ADHD.<sup>22</sup> Many non-DSM scales in ADHD treatment outcome studies also emphasize the symptoms of inattention, hyperactivity, and impulsivity. Examples include SKAMP,<sup>23</sup> the Conners scales,<sup>24</sup> and Swanson, Nolan, and Pelham (SNAP).<sup>25</sup> Although many other scales could be included in clinical trials to assess adaptive functioning, social skills, executive functioning, and emotionality, it is not common practice to incorporate these measures into ADHD treatment outcome studies.

Recently, there has been increased dialogue among researchers about the importance of including the assessment of adaptive functioning, quality of life, social development, emotion regulation, and/or other variables that are more “meaningful” in the lives of children and parents in clinical trials and treatment.<sup>26</sup> Although it is not yet common practice to include such measures, clinical researchers have started to use assessments such as the Child Health Questionnaire,<sup>27</sup> the Social Skills Rating System (SSRS),<sup>28</sup> and the ADHD Impact Module (AIM)<sup>29</sup> to assess further effects of medication on the lives of children and their families.

During the course of recent clinical trial follow-up interviews, parents commented often about the positive impact of study medication. Questions and statements included, “When are you going to ask me about how his relationship with his brother has changed?” and “He seems so much more emotionally available now.” Parents noted improvements like, “He started using a scheduler all by himself! I never told him to use it.” Interestingly, these parental reports are similar to the executive functioning constructs hypothesized to be at the core of ADHD.<sup>3</sup> Parents’ statements (see Table 1) prompted conversations between other clinical investigators participating in studies on the same novel compound at other research sites; many parents at all sites were reporting similar information about exciting, yet not systematically assessed, changes in adaptive and executive functioning. Together, these parent reports and the apparent void in the outcome assessments highlighted a clear need to include measures of executive and adaptive functioning or other “broadband” measures such as quality of life or social functioning scales.

Before suggesting which additional scales might be included in future clinical trials, we explored further the



**Table 2. Sample Items From a New Instrument for Attention-Deficit/Hyperactivity Disorder: Life Participation Scale for ADHD<sup>a</sup>**

Parents are asked to think about the past week. Raters use the following 4-point scale: 0 = never/seldom, 1 = sometimes, 2 = often, 3 = very often

- During the past week, has your son or daughter:
- Gotten ready for bed without difficulty
  - Woken up in a good mood in the morning
  - Spoken at an appropriate volume
  - Been even-tempered, slow to anger
  - Looked happy (smiled and laughed)
  - Been affectionate (eg, given hugs, kisses, pats on the back) with you or others
  - Been fun and enjoyable for you to be around
  - Been included in activities by peers
  - Made socially appropriate comments
  - Started homework without being told to do so
  - Been aware of things going on around him or her without being distracted by them
  - Thought things through before taking action (when faced with a problem)

<sup>a</sup>This scale is still under development.

content of parents' statements made during follow-up interviews. We identified constructs and searched for existing instruments that might assess these constructs (e.g., self-efficacy and self-control scales, adaptive functioning measures, quality of life instruments, emotion regulation questionnaires, tests of executive function). Specifically, we searched for instruments that would (1) measure the constructs reported by parents, especially those related to adaptive and executive functioning; (2) include items that measure social skills and interpersonal functioning; (3) include items that measure frustration tolerance or emotion regulation; (4) establish respectable psychometric properties; and (5) be sensitive to change over time in a medication trial. We found many existing instruments but none that precisely and succinctly assessed the domains reported to us by parents; a new scale needed to be developed.

As a first step in developing a new instrument, we talked further with parents to ensure we were identifying the constructs they intended. After receiving approval from our institutional review board and consent from parents, we interviewed parents about the changes they have observed over the course of the medication trial, especially those related to meaningful social, emotional, and self-regulatory aspects of their daily lives. Using a series of open-ended and probing questions, parents reported a variety of improvements in relationships with peers and siblings, emotional stability, self-regulation, "availability," planning skills, and general insight. In general, parents' statements reflected changes in improved self-control, emotional regulation, and interpersonal skills or social development.

On the basis of the constructs identified in parent interviews, we created 110 items for a pilot questionnaire. Anchoring each item, we used a 4-point Likert frequency scale

(0 = seldom/never, 1 = sometimes, 2 = often, 3 = very often). To obtain expert panel validity, 4 other principal investigators reviewed and modified the pilot instrument. A second set of parent interviews was conducted to ensure that items were being interpreted as intended and that parents' reports of change were addressed and included in the interview. After these interviews, we removed items that were redundant, commonly misinterpreted, confounded, and ambiguous. The resulting interview of 34 items (Table 2) was included as a pilot instrument in the next (and still ongoing) clinical trial.

Life Participation Scale for ADHD (LPS) interviews conducted during this clinical trial generated useful feedback from raters about the "flow" of the interview. Several interviewers noted redundancy in items, an awkward ordering of items, and a desire to move toward a shorter interview. This feedback prompted a second revision, which produced a brief (i.e., 24 items) and unambiguous interview with a more logical flow. Additionally, items that appeared relevant to a narrow age group were removed so that both children and adolescents could be interviewed with the LPS. The LPS-24 is to be included in an upcoming atomoxetine clinical trial. The results of changes in adaptive functioning related to treatment will be forthcoming during the next several years.

## CONCLUSION

The nature of ADHD and the theory behind it have yet to be firmly defined. Although the DSM-IV criteria have been useful, newer conceptualizations of ADHD limit their scope and precision. Rating and screening measures based only on DSM-IV criteria frustrate parents, teachers, researchers, and clinicians because these measures omit many areas in which parents and teachers see the most difficulties and, with treatment, the most improvement. Expanding assessment strategies to include measures of adaptive behavioral improvements in clinical trials may further contribute to understanding, diagnosing, and treating ADHD.

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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