The Hard Work of Growing Up With ADHD

Attention deficit hyperactivity disorder (ADHD) had long fallen under the nearly exclusive purview of child psychiatry. The prevailing view had been that children outgrew the restless ways of the condition through some magical pubertal coincidence, much as they outgrow acne (the "persistent" type category of ADHD was but a half-hearted concession in DSM-III acknowledging that rare instances of the disorder might not always burn out by adulthood). Stimulants remained a medicine for children, a vice for adults, and diagnoses of ADHD in grown-ups about as common as those of porphyria.

Perceptions and practices around ADHD in adults have changed radically during the past decade, so much so that the condition now faces a potential risk almost as large as the previous one of going unrecognized, namely that of becoming fashionable. Evaluations for and diagnoses of ADHD in adults are steadily on the rise, although there is a long way to go before it becomes the most commonly diagnosed condition among outpatients (an unlikely eventuality anyway, although long the case among children). Whether ADHD in adults will be ultimately embraced by the public or not (and under the influence of direct-to-consumer advertising or not), the state of the science is that ADHD in adults not only exists and is more prevalent than we ever surmised, but that its impact and consequences are dire.

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In one of three papers devoted to ADHD in this issue of the *Journal,* McGough et al. provide one line of evidence quantifying the damage. In the largest study to date on the psychiatric comorbidity patterns of non-clinically-referred adults, parents of children with ADHD who themselves had the disorder (N=152) were compared with parents who did not (N=283). Affected parents had increased lifetime rates of disruptive behavior, substance use, mood disorders, anxiety disorders, and earlier ages at onset for major depression, dysthymia, and conduct disorder. Such patterns of comorbidity indicate not only personal suffering and maladaptation (as further reflected by lower educational and occupational achievement) but compound the familial impact of the disorder through parenting abilities burdened by disabling psychopathology. The study lays bare the large extent to which ADHD is a family affair.

The article by Hudziak et al. helps deconstruct the elements underlying such family matters. Using data from 1,595 7-year-old twin pairs from the Netherlands Twin Registry, the study provides a breakdown of the genetic architecture of ADHD. That ADHD is one of the more highly heritable psychiatric disorders is nothing new: heritability rates in the 80% range have been consistently documented in previous twin studies (1). The contribution of this study is less in the replication of a solid heritability finding than in separating it into a dominant component (referring to the interaction of effects at the same locus, and contributing 48% of the variance in this sample) and an additive one (contributing 30%.) Of note, the remaining 22% of the variance in the study was attributed to unique, or nonshared, environmental influences such as different parenting styles on each of the twins in a given sibship.

A separate and methodologically critical contribution of the same study is in making effective use of what it intelligently calls "a taxonomic middle ground." Rather than relying on the traditional DSM demarcations of ADHD—"You have it or you don't"—the authors approached nosology through a quantitative approach (based on the Conners'

Rating Scale—Revised ADHD Index) that was age-, gender-, and informant-normed. Phenotypic assessments that are valid and reliable are perhaps most crucial to gene finders, for whom classification errors can prove misleadingly promising yet often scientifically fatal.

Brain imaging holds great promise as a means of arriving at the phenotypic characterizations that have proven so elusive to psychiatry in general, and to ADHD in particular. In a third article in this issue, Vaidya et al. take a step toward understanding phenotypic variation based on the mapping of neural circuitry patterns. In their study, functional magnetic resonance imaging (fMRI) was used to compare 10 children (ages 7–11) with ADHD to 10 age- and gender-matched unaffected subjects on two distinct cognitive operations subserving attention. fMRI reliably differentiated children on tasks of interference suppression (where reduced frontal-striatal-temporal-parietal engagement was seen in those with ADHD) and response inhibition (where reliance on superior temporal engagement was seen in those with ADHD, and reliance on frontal-striatal circuits seen in those without.) Methodologically strengthened by the medication-naive status of its diagnosed children, this study's main contribution may be in documenting the multiplicity of abnormal functional neural patterns at play in ADHD—by showing that the disorder is more complex and textured than previously thought, and by suggesting more circumscribed brain functions as potential targets of study and intervention.

Three original research articles and an editorial devoted to ADHD in this issue of the *Journal* are all testament to the growth of the disorder into the mainstream of psychiatric research and practice. They prove that just as the diagnosis is no longer suitable only for children, its research contributions have outgrown subspecialty child psychiatric journals. All of this of course is welcome news and cause for optimism.

But not for complacency. These studies advance the field as much as they reveal its shortcomings. They remind us that the prevailing approach to comorbidity (and to nosology more generally) is too rigidly and unrealistically categorical; that structured interviews and paper-and-pencil questionnaires, rather than trustworthy biological metrics, are still our primary (if not only) diagnostic tools; that these and other limitations have conspired against our ability to make full use of the readily available riches of our age (foremost among them the Human Genome Project). And even though none of the three studies addressed treatment per se, treatment may be a telling place to look to, as the risks of the alluded complacency may be most evident there.

ADHD is one of the more pharmacologically targetable psychiatric conditions, with response rates to stimulants consistently above 70% of treated subjects, and with effect sizes very comfortably in the "large" category. Moreover, stimulants are brisk in their action, and clinical response can be usually ascertained within a few days—if not doses. Alternatives to stimulants abound and include tricyclic antidepressants, alpha-2 agonists, and now noradrenergic reuptake inhibitors. Many medical (let alone psychiatric) conditions could only wish for so many therapeutic avenues. With so many good options on hand, what could possibly warrant concern?

Quite a bit in fact, since it appears that we have collectively dozed while at the wheel of new drug development. The stimulants that we use today (methylphenidate and amphetamines) are mechanistically no different from the Benzedrine that Charles Bradley used in his classic study, published in these pages three score and eight years ago (2). The panoply of new stimulant preparations emerging these past few years is but the same molecules disguised under better pharmacokinetic cloaks. Once-daily administration is a very good thing indeed, but dashing forward progress it is not. Atomoxetine, a touted nonstimulant alternative, seems better conceptualized as a "tricylic-lite": a noradrenergic antidepressant morphing into an ADHD superhero because of its low potential for cardiotoxicity but, at best, quashing only its closest rival desipramine. Initial reports equating its short-term efficacy to methylphenidate notwithstanding (3),

atomoxetine is still a dark horse to do better than just place in the ADHD treatment algorithm.

The development of me-too drugs is the price we have paid (quite literally) for our complacency. We do not need yet another, perhaps cherry-flavored, long-acting stimulant preparation: we need novel compounds. We should be daring in the application of our science, going from mechanisms incrementally understood to truly new psychotropics. To the children, adolescents, and adults with ADHD who have not responded to (or tolerated) stimulants or their alternatives; to those with comorbidities (like bipolar or substance abuse disorders) jeopardizing or impeding their use of available agents—to all those who continue to be limited by ADHD we owe the development of a new generation of treatment alternatives. When we become capable of moving from serendipitously stumbling upon the next effective compound into developing it with foresight by putting to use the type of findings in these studies—when that day arrives we will have true cause for celebration and know that ADHD has finally grown up. For now, optimism and enthusiasm in the context of these studies, and awareness about the risky business of complacency, should together spur us to do more for the many with ADHD. Growing up is hard work: we look forward to seeing ADHD (as much as its patients) reach the maturity of their fully realized potentials.

References

1. Faraone SV, Doyle AE: The nature and heritability of attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Clin North Am 2001; 10:299–316, viii–ix
2. Bradley C: The behavior of children receiving Benzedrine. Am J Psychiatry 1937; 94:577–585
3. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, Newcorn JH, Casat C, Milton D, Michelson D: Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry 2002; 41:776–784

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