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Editorial
Where to with treatment for ADHD?

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One hundred years ago, a range of behavioral and psychotherapeutic treatments were used for children with behavioral and emotional problems; ADHD was not yet defined in its current form. Modern pharmacotherapy for what is now called ADHD was foreshadowed by Bradley's discovery in 1937 that an amphetamine, benzadrine, temporarily improved behavior and learning in troubled children, although it was not until the 1950s that regular clinical use of medications such as methylphenidate and d-amphetamine began[1]. Other pharmacological preparations followed, with perhaps the most significant recent pharmacological advance for ADHD being the introduction of prodrugs and other new delivery vehicles in the early 21st century[2] with noteworthy clinical benefits[3]. New molecular targets have emerged as well, notably the targeting of the noradrenergic alpha-2a receptor with new formulations in the past decade[4]. However, as the articles in this special section attest, the fundamental picture of pharmacological treatment for ADHD is still in many respects unchanged over the past half century. The good news in this picture is that ADHD has available to it safe and often effective medications.

The bad news is that we still face a situation in which (a) most children with ADHD are treated with and respond to pharmacotherapy with symptom reduction, but only so long as the medication is in their system, (2) long term outcomes remain disappointing[5], partly due to (3) poor compliance and poor treatment persistence[6], suggesting that even the new pharmacological preparations remain unsatisfactory in some manner to many patients.

As exemplified in the special section, progress in the meantime has centered on pharmacological applications to special patient populations, such as adults with ADHD[7], and new treatment targets including cognitive symptoms[8] and comorbid problems. Many patients (and even some clinicians) remain unaware that effective psychosocial treatments are available for ADHD[9], perhaps because few payers provide adequate funding for implementation of psychosocial treatments. Efforts have begun to examine pharmacogenetics, or individual differences in medication response due to genotype. As in most other diseases, progress on this front has proven more difficult than initially imagined and genetic profiling to predict drug (or other treatment) response in ADHD remains insufficiently effective for clinical use, though an important direction for continued investigation.

In light of all this, it remains fundamentally concerning that we lack a treatment that satisfies a majority of patients in the long term, a major breakthrough in treatment effectiveness, the ability to prevent the condition from developing in young children, or the ability to reduce symptoms permanently in sufferers.

Where might fundamental breakthroughs emerge if not in pharmacotherapy? Interest has continued in new cognitive training interventions that might target the core executive functioning problems in ADHD and develop the neural networks and cognitive skills believed to be lacking in children with ADHD, so that they can resume their full learning potential. Despite some encouraging

findings, particularly with very young children[10], to date these efforts are in the very early going and mostly unsatisfying with regard to major, generalizable changes for children with ADHD. Work in this area should continue, however, with combined and multimodal interventions (such as learning and motor tasks) as one current area of promise.

Although national survey data are lacking, small surveys consistently show that families continue to flock to complementary and alternative treatments for ADHD in large numbers[11]. These include new and potentially promising treatments such as refined versions of EEG or other biofeedback schemes, and a surprisingly consistent and resurgent interest in dietary interventions including both restriction diets[12] and supplementation trials[13]. Indeed, children's dietary intake in the developed world has changed dramatically in the past 100 years; a wide range of nutrients in addition to additives can be investigated. It is likely that dietary responses are also modulated by genotype[14].

Finally, and crucially in my view, insufficient investment has been forthcoming in attempting to identify ADHD's developmental origins so that early prevention can be undertaken. This may be due in part to uncritical acceptance of the idea that ADHD is an evolved, normally varying, genetically determined trait. Often forgotten is that ADHD may also reflect subtle, life-changing, but avoidable injuries to the nervous system. In groups of children with ADHD, on average the brain is developing abnormally already by age 5 years. Development of the human brain is exquisitely responsive to its early environment, so an array of events besides gene assignment could be relevant. Just to give some examples, in the modern world, environmental lead exposure – absent during evolutionary times – now almost universally begins in the womb, peaks at age 2 years, continues throughout neural development, alters striatal gene expression among many other effects in the brain, and still occurs in sufficient amounts even in the United States that it is still reliably associated with ADHD in both clinical and population samples in this country[15]. Lead is only one among dozens of neurotoxins that are insufficiently studied in relation to early neural development in children who go on to develop ADHD and other developmental disorders. This represents an unconscionable gap in our scientific and public health knowledge.

Furthermore, we know that some perinatal insults can lead to ADHD, as exemplified by predictive effects of low birth weight (nearly a three-fold increase in probability of clinically significant attention problems)[16]; when that occurs it is apparently associated with micro-ischemias[17]. Likewise, maternal prenatal diet – which can have a massive effect on offspring neural development at least when it goes awry – is a promising new direction for investigating the roots of temperament and early precursors to behavior and learning problems in children[18] but remains surprisingly neglected in the research portfolios of major American funding agencies.

The papers in this section underscore the likelihood that if we are to achieve exciting breakthroughs, in addition to maintaining incremental progress on the pharmacological front and looking to genetic modulation of effects, broadened conceptions of how to intervene with ADHD will need more energetic pursuit. In particular, dietary and other alternative lifestyle interventions for ADHD need to be taken far more seriously by our mainstream treatment and research communities. Further, fresh attempts to understand how ADHD develops, in the context of early neural development, and how it might be prevented in the early months and years is sorely needed. It is to be hoped that a focus on new treatment directions will stimulate this interest in the near future.

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