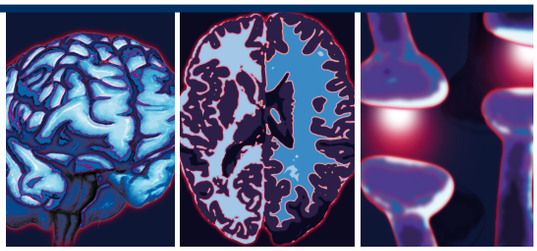
REVIEW



Adult ADHD and amphetamines: a new paradigm

Derick E Vergne[1,2], Elizabeth A Whitham[1,2], Sergio Barroilhet[1,3], Yuli Fradkin[4] & S Nassir Ghaemi*[1,2]

Practice points

- The diagnostic validity of adult ADHD is questionable.
- It typically co-occurs with mood disorders, raising the question of whether it is a reflection of mood disorders.
- The concept of a diagnostic hierarchy may be helpful to determine when distractibility symptoms are due to mood disorders versus possible ADHD.
- The long-term use of amphetamine stimulants has been shown in animal studies to be associated with neurotoxicity; similar human data are lacking.
- Social and economic, rather than biological, factors may be important risk factors for ADHD.
- Caution may be warranted in routinely diagnosing ADHD in adults with distractibility, and in routinely treating such adults with amphetamine stimulants.

SUMMARY This review examines the diagnostic validity of adult ADHD on the basis of phenomenology, genetics, course of illness and treatment response in the context of a diagnostic hierarchy. In addition, it examines ADHD treatment options, particularly amphetamine use, associated risks and the clinical and social factors that may influence treatment. Risks of neurotoxicity with amphetamines are discussed.

ADHD in adults has become an increasingly popular diagnosis in the past decade, correlating with the introduction of the first medication the US FDA indicated for adult ADHD, atomoxetine. Data from US pharmacies indicate the number of prescriptions for drugs commonly used to treat ADHD increased by 90% among adults between 2002 and 2005 [1]. Adults now receive approximately a third of all prescriptions for these drugs [2].

The rapid increase in diagnosis of ADHD in adults has not, however, been associated with a marked increase in evidence of the validity of this diagnosis based on scientific research. In this review, we will discuss the validity of the diagnosis of adult ADHD, and the risks and benefits of amphetamine treatments.

The first description of ADHD was in the early 1900s [3]. The first studies showing follow-up into adulthood did not appear until

[1]Tufts University Medical School, Boston, MA, USA
[2]Mood Disorders Program, Department of Psychiatry, Tufts Medical Center, 800 Washington St, Boston, MA 02111, USA
[3]School of Psychology, Universidad de los Andes, Santiago, Chile
[4]Yale Child Study Center, New Haven, CT, USA
*Author for correspondence: Tel.: +1 617 636 5735; Fax: +1 617 636 7795; nghaemi@tuftsmedicalcenter.org

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more than 60 years later [4], and included many patients with comorbidities. Later studies encountered the same diagnostic problems with mixed samples that were treated with combinations of methylphenidate (MPH) and other medications [5,6]. The DSM-III ADHD criteria of "childhood hyperactivity" was seen as inappropriate for adult patients [7], but inclusion of irritability was thought to improve the diagnostic validity [7,8]. DSM-III-R and DSM-IV added a "residual type."

The controversy surrounding the definition of cognitive impairment and adult ADHD exists in the context of western culture, where competition, achievement and productivity are important social values [9], and where cognitive enhancers [10] are increasingly used [11–13] and abused [1,14].

The scientific validation of any diagnosis in psychiatry is generally seen as following four basic lines of evidence: course of illness, treatment response, phenomenology and family history [15]. Since there is no gold standard in psychiatry for diagnostic validation, these multiple lines of evidence are used to validate a diagnostic entity. Where these lines of evidence point in one direction, one infers the presence of a definable and separate diagnosis, usually reflecting an underlying disease. Here, we review this evidence in relation to adult ADHD.

Phenomenology

The symptoms of adult ADHD reflect cognitive distractibility, or the inability to maintain attention; the objective behavioral expressions of hyperactivity seen in childhood ADHD are said to be infrequent in adults [16]. Therefore, the diagnosis hinges almost entirely on the core symptom of distractibility, with its cognitive and functional consequences (impairment in organization and executive functioning skills); ADHD in adults is essentially a monosymptomatic diagnosis. Distractibility, thus defined, is one of seven criteria for mania, hence the lack of phenomenological specificity to ADHD in adults.

A major phenomenological study of adult ADHD, the National Comorbidity Survey, assessed the prevalence of all DSM-IV axis I diagnoses in the US population. According to that study, approximately 3% of the US population was diagnosable with ADHD in adulthood (after also meeting ADHD criteria in childhood) [17]. In these individuals diagnosable with adult ADHD, 45% were diagnosable with bipolar disorder and approximately 40% were diagnosable with major depressive disorder. Thus, in those diagnosable with adult ADHD, over 80% were diagnosable with another mood disorder.

We suggest three possible explanations for these data: ADHD causes mood disorders; mood disorders cause ADHD-like symptoms; or whenever one gets ADHD as an adult, one also gets a mood disorder ('comorbidity'). The third possibility is statistically unlikely; of the other two options, some have suggested that the difficulties of coping with ADHD could cause depressive symptoms, but few have speculated about how ADHD could possibly cause mania. The second possibility seems the most logical to us. Put another way, it could also be that mood disorders are always present because their cognitive symptoms are being called ADHD.

This extensive overlap of ADHD with other psychiatric conditions, especially mood disorders, is also seen in family studies of parents of ADHD children. Among parents who have current adult ADHD, 87% had at least one psychiatric disorder and 56% had at least two other psychiatric disorders. Non-ADHD parents of ADHD children also showed a high frequency of psychiatric illness: 64% had at least one psychiatric disorder and 27% had at least two psychiatric disorders [18]. The authors proposed two hypotheses: increased psychopathology might result from independent biological susceptibilities associated with ADHD, or comorbid psychopathology could emerge as a developmental consequence of ADHD. A third hypothesis might be that this syndrome could be part of a different disease entirely; just as fever is part of pneumonia, attentional impairment might be part of mood disorders.

Genetics

A genetic basis for adult ADHD has been proposed by some investigators who claim quite high heritability for ADHD (reported to be 60–80%) [19]. This is quite a claim, given that this amount of heritability approximates schizophrenia and bipolar disorder [20,21], as well as highly inherited traits such as height [22]. All other psychiatric illnesses, including major depressive disorder and substance abuse, have heritabilities of approximately 50% or less [22]. Genetic studies that support this association do not correct for comorbid diagnoses; if patients

also have bipolar disorder, for instance, and a parent also has bipolar disorder, researchers may diagnose them with ADHD as well. The presence of ADHD in both the parent and adult offspring has been used as genetic evidence for ADHD, while the co-occurring presence of bipolar disorder in both individuals is not reported. Conducting genetic studies while not correcting for comorbidities would seem to raise questions of validity.

Course of illness

The studies that indicate that ADHD persists into adulthood are quite limited. For instance, in a 1996 review of nine prospective studies of ADHD in children followed from age 10 to 25 years (n = 718), only 10% could be diagnosed with ADHD in adulthood [23]. Reports of higher rates are limited to studies in the past decade, which report 30–40% persistence rates of ADHD from childhood into adulthood [24]. This definition of an increased prevalence in adulthood includes patients with subsyndromal ADHD. Even with this very broad definition of ADHD, it is notable that 50–60% of children with ADHD have no symptoms of it at all by 18–20 years of age [24]. In a later meta-analysis of outcome studies by the same group [25], it was estimated that DSM-defined ADHD persists at 25 years of age in only 15% of persons who were diagnosed with ADHD in childhood. However, subsyndromal symptoms were found to persist in approximately 65% by 25 years of age. Again, this estimate does not correct for any comorbidities, such as anxiety or mood disorders, that could cause these symptoms.

One might look at the problem from the other direction. One study examined 159 adult patients with bipolar disorder and found that slightly less than 10% had a history of childhood ADHD. Those with a history or childhood ADHD had significantly more mood episodes than patients who had bipolar disorder without prior childhood ADHD [26]. Thus, sometimes it appears that childhood ADHD may resolve and be a preliminary stage to other illnesses, such as bipolar disorder, in adulthood.

Treatment response

Some suggest that ADHD is a valid diagnosis because such individuals improve with amphetamine medication treatment, including MPH and its derivatives. However, this treatment response is not diagnostically relevant, since normal individuals without ADHD also improve with amphetamines (including MPH). In one study, for instance, amphetamines were given to patients with schizophrenia and normal controls; both groups improved for cognitive tasks, with schizophrenic patients improving more than the normal controls [27]. Some observers comment that even though amphetamines improve normal cognition, ADHD patients improve more than normal controls. But this could simply reflect a ceiling effect: those with ADHD have lower cognitive scores, and thus more room to improve, than normal persons. Amphetamines in fact are the most diagnostically nonspecific treatments because they are widely effective in the normal population for enhancing cognition. This is probably why 3–10% of the college-age population of the USA abuses amphetamines [28]. Approximately a third of those college-age students receive amphetamine prescriptions, and approximately two-thirds of those students share those medications with their friends.

Clinical implications

As described above, the validity of ADHD in adults is poorly established [7]. The widespread diagnosis of adult ADHD, potentially for the purpose of prescribing medications such as atomoxetine or amphetamines and their derivatives, has clinical implications. There is an unawareness on the part of the public and many clinicians as to the risks of amphetamine use, including MPH. The Drug Enforcement Agency (DEA) highly restricts the prescription of these medications by not allowing refills to be written, because the DEA views them as highly abused drugs. Physicians seem to have a resistance to this notion, but both the policy experience of government authorities and animal studies raise concerns. Biologically, these agents are direct dopamine stimulants, similar to but less potent than cocaine.

Besides abuse, these drugs have important side effects, the most common of which are the triad of anxiety [29], mania and insomnia [30]. Anxiety is an important side effect on its own, because it too is associated with cognitive impairment, including poor attention and executive dysfunction. Insomnia is itself problematic, and can also trigger the third side effect of mania.

Mania with amphetamines is not rare. This is shown in studies of children and adults. For

instance, in children with bipolar disorder and ADHD, stimulant use was associated with the occurrence of manic symptoms at approximately the same age that stimulant treatment began [31]. In adolescents hospitalized with mania, stimulant use was associated with an earlier age of onset of bipolar disorder [31,32]. In another study in children, 18% of 82 children with ADHD and bipolar disorder developed mania upon taking amphetamines [33]. Amphetamines were also associated with more mood episodes, suicidality and hospitalization in those children with bipolar disorder and ADHD [34]. In the largest of the studies of mania in adult ADHD, we examined 137 adult patients with bipolar disorder (72% bipolar disorder type 1; 28% bipolar disorder type II/not otherwise specified), 25% of whom had prior stimulant treatment for ADHD. Among those with prior stimulant treatment (21 with MPH, 17 with amphetamine and six with modafinil), 43% were treated with a concurrent mood stabilizer. The rate of stimulant-associated mania/hypomania was 40% [35].

The efficacy of amphetamines in adult ADHD is well established in multiple placebo-controlled studies, but again, this is not surprising given that amphetamines improve cognitive symptoms in individuals who do not have ADHD as well.

Neurotoxicity

Amphetamines have been shown to be neurotoxic in animal studies, a fact that is underappreciated and little discussed. Studies with rats show that amphetamines are associated with decreased responses to rewarding stimuli [36], decreased dopaminergic neuronal activity [37], increased corticosteroid responses to stress [36], increased depression-like behaviors into adulthood [38] and decreased long-term survival of newborn cells in the temporal hippocampus [39]. In some of these preclinical studies conducted on adult animals, the dose of MPH was 10–50 mg/kg given intraperitoneally, which brings into question the legitimate extension to clinical treatment in human children, as the human dose is usually 0.3–1.0 mg/kg given orally. Other studies, however, used lower doses of MPH in rats and are thus comparable with chronic exposure to MPH in children. In one rat study with MPH dosages in the therapeutic range (0.4–1 mg/kg), changes in behavior and function of brain dopamine cells were similar to those occurring in depression and anxiety [37]. These animal studies indicate that younger exposure to amphetamines produces greater abnormal biological effects, extending into adulthood. If these rat models can be translated to humans, the use of amphetamines in childhood may be partly responsible for depression and anxiety in adulthood.

It should be noted that contrary to the opinion of many experts and clinicians, MPH is an amphetamine. It is part of the pharmacological class of amphetamines, is listed as such in standard pharmacology texts [40] and shares their harms and benefits.

Clinicians often respond to some of these neurobiological data by stating that amphetamines have not been proven to be harmful in adult humans. The burden of proof is not that all drugs are safe until proven harmful, but rather that if there is evidence of harm in animals, drugs should be viewed as harmful in adult humans until proven safe. This philosophy is the driving force behind the current FDA guidelines, in which drugs that prove to be unsafe in animals are not approved for human consumption. However, when the new FDA rules for drug approval and safety trials were implemented in the late 1960s, amphetamines were grandfathered into treatment, since they have been on the US market since the 1930s and 1940s, long before these safety trials were required for the marketing of medications. Clinicians and patients have long been using amphetamines, not knowing that they are neurotoxic in animals.

Studies of amphetamine use in humans to date have been short term. Some indicate benefits with amphetamines, meaning increased size of some brain regions in treated children versus untreated children [41–43], but such studies do not assess long-term effects that would be analogous to the animal studies. For instance, one study was a 4-year prospective follow-up of 20 adolescents with ADHD, in which those not taking stimulants had thinner brain cortical volumes than those who did [41]. Besides the small sample size, this study did not follow children into adulthood. Two other analyses, based on a case–control study of 46 children with ADHD compared with 59 controls (aged 8–18 years), are cross-sectional and retrospective. One of them in fact found some evidence of harm: longer duration of psychostimulant treatment was associated with smaller cortical volumes [42]. The other analysis reported that

stimulant treatment appeared to reduce basal ganglia deformation, not volume loss, in ADHD [43]. These studies, all in the 50–100 sample range, are observational, not randomized, and thus liable to a large degree of confounding bias, especially confounding by indication (i.e., differences could have to do with why clinicians decided to treat some children with stimulants and not others). None of the studies even mention this potentially major confounding factor, much less try to adjust for it statistically.

This limited and poorly analyzed evidence stands in direct contrast to the well-analyzed, replicated evidence of neuroprotection with lithium [44]. Yet clinicians often avoid lithium because of the mistaken impression that it is toxic. One observes an unfortunate paradox: many clinicians believe that a drug that is neuroprotective, namely lithium, is toxic, while they believe that a drug class which is neurotoxic, namely the amphetamines (including MPH), is safe.

There is a very common viewpoint that is held by many clinicians, but it is a viewpoint that reflects a basic misunderstanding of the bedrock principle of clinical science: confounding bias. As described in detail in standard texts of statistics and epidemiology [45], as well as some of our work [46], all clinical observation is affected by many confounding factors that we cannot control and, more importantly, often do not even know exist. The bias that results – confounding bias – blurs our clinical vision so that we can never know, with much probability, whether we are wrong or right. Randomization was developed to solve this problem, and the power of randomization is key to remind us of the reality and profundity of confounding bias. For instance, based on a "wealth of safety data" from over half a century, most clinicians thought estrogen hormone-replacement therapy was safe and effective; a huge (16,000 patient) randomized clinical trial [47] proved hormone-replacement therapy was ineffective in many ways, and harmful in some ways, including carcinogenicity, which had completely eluded extensive clinical observation for decades [46].

Social factors

ADHD in children is the first psychiatric illness studied by the CDC in a large epidemiologic sample from the USA [48]. We would like to emphasize that this was an epidemiological study, not a clinical study. In other words, it was systematically conducted by CDC researchers applying diagnostic definitions to large, randomly collected samples. It does not reflect the vagaries of clinical practice, nor the diagnostic judgments of clinicians.

To underline the epidemiological nature of this study, we quote from the methods of this study as follows: in 2003 and 2007, the CDC researchers conducted "national, cross-sectional, random digit-dialed landline telephone surveys used to estimate the prevalence of health and well-being indicators among children aged <18 years in the USA. One child was selected randomly from each household to be the focus of the parent or guardian interview. During April 2007–July 2008, a total of 91,642 interviews were completed for the 2007 National Survey of Children's Health (NSCH; overall response rate = 46.7%; cooperation rate = 66.0%). In 2007, data, including complete information on ADHD and sex, were obtained for 73,123 children aged 4–17 years. Data were weighted to account for unequal probabilities of selection of households and children, nonresponse, and households without landline telephones, and to reflect the demographic distribution of noninstitutionalized children in the United States."

In the state-by-state study of the prevalence of ADHD using the most current epidemiologic diagnostic tools, the CDC found a wide variation in ADHD frequency, with the lowest range occurring in some of the wealthier states (such as Colorado and California: ~6% ADHD prevalence) and the highest occurrence in the poorest states (such as Alabama, Louisiana and West Virginia: ~10–11% ADHD prevalence). Why ADHD, if it was the most genetic illness in psychiatry, should be twice as common if you live in Colorado versus Alabama, is difficult to explain. Social factors would seem to be relevant, as is the case with diabetes and high blood pressure and heart disease, all of which have state distributions that correlate with socioeconomic status. In other words, state-based differences, such as poverty (including access to care), may be more relevant than biology.

Other research has shown that ADHD in children is increased in prevalence if those children have various behavioral patterns, notably watching television or playing video games [49]. Although not consistently replicated, this finding has some scientific support and raises the question, if true, of why a highly genetic illness would be influenced by television or video

games. Finally, psychosocial interventions appear to help children with ADHD. In one randomized clinical trial, parental and child psychosocial training was associated with remission rates comparable to what is found in many amphetamine treatment studies [50].

Hierarchy of diagnosis

This review of the concept of adult ADHD leads us back to the older notion of a diagnostic hierarchy [51]. This view, derived from classical European psychiatry, is that not all diagnoses are created equal. For instance, one should not diagnose schizophrenia when auditory hallucinations occur if a major depressive episode is present. Furthermore, one should not diagnose panic disorder when panic attacks occur if major depressive episodes or manic episodes are present. This kind of hierarchy is implicit in the DSM-IV for those conditions, but the makers of DSM-IV explicitly tried to avoid introducing a diagnostic hierarchy, leading to the problem of multiple comorbidities, which some psychiatrists have labeled nosologomania [52]. Psychiatric symptoms overlap; thus, without diagnostic hierarchy, patients are routinely diagnosed with multiple diagnoses, often leading to polypharmacy. ADHD in particular is prone to this kind of overdiagnosis, because it is a monosymptomatic illness, and its symptom of cognitive impairment with distractibility is present in anxiety and mood disorders. Since mood disorders, both bipolar and unipolar, can cause concentration impairment, as can anxiety conditions, it would seem rational not to diagnose ADHD unless anxiety and mood disorders are first ruled out. If we take this approach, we would not diagnose ADHD, based on the National Comorbidity Survey data, in the vast majority of individuals who currently meet adult ADHD diagnostic criteria.

Indeed, one might think of inattention (with or without impulsivity) as a pathophysiological common pathway for many different psychiatric diagnoses. Thus, it would seem simplistic to separately diagnose 'comorbid' ADHD whenever inattention/impulsivity occurs. This is not to say that inattention/impulsivity does not have a biological mechanism; yet such biological mechanisms do not validate the separate disease of ADHD. Instead, it could be that inattention/impulsivity represents a clinical syndrome that reflects a biological common pathway seen in many diagnoses. That biological pathway appears to involve frontal lobe dysfunction, probably of developmental origin. Early studies using functional MRI technology in randomized clinical trial designs have begun to show such mechanisms. For instance, atomoxetine improved control inhibition in ADHD-diagnosed subjects with activation of the right inferior frontal gyrus that correlated with plasma drug levels [53]. Similarly, in healthy subjects exposed to threatening stimuli, modafinil decreases prefrontal, anterior cingulate and amygdala activity, which is associated with less reactivity to threatening stimuli [54]. In summary, inattention can be caused by many conditions, and it may be improved symptomatically by many treatments, probably reflecting common biological mechanisms for inattention of any cause. The habit of diagnosing ADHD in most such cases seems questionable.

Conclusion

This review raises both diagnostic and treatment questions of public health importance. If adult ADHD is not validly separable from other disease entities, then caution will be needed in making such a diagnosis. If amphetamines are found to be harmful in humans, there would appear to be a need to re-educate both the public and clinicians to be more cautious in their use, especially long term.

Future perspective

The field of treatment of adult ADHD has been heavily influenced in the past 10 years by a great deal of pharmaceutical marketing. This has led to a new claim of validity for this concept and a widening of the belief in the long-term chronicity of ADHD from childhood into adulthood. This diagnostic widening is still continuing, and will likely continue in the next 5–10 years. Besides marketing, clinicians have long been comfortable with administering amphetamines, which led to their common use even before recent marketing efforts had increased. As patent lives end for some agents in the next decade, there may be some decline in use of amphetamines, but not greatly, since clinicians are still positively disposed toward these agents. If the biological data in this review lead to further studies in humans, and harmful effects are shown in humans, these data may lead to an eventual decline in use of these agents. Whether the future will take that course or not will depend on whether such scientific research is conducted, and what it eventually shows.

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