Affective Temperaments Misdiagnosed as Adult Attention Deficit Disorder

Prevalence and Treatment Effects

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Abstract: Adult attention-deficit disorder (ADD) is a common diagnosis, and amphetamine medications are increasingly used. Recent reports suggest high prevalence of affective temperaments, such as cyclothymia, in adult ADD. This study reexamines prevalence rates as reflecting misdiagnosis and reports for the first time on the effects of amphetamine medications on mood/anxiety and cognition in relation to affective temperaments. Among outpatients treated at the Tufts Medical Center Mood Disorders Program (2008–2017), 87 cases treated with amphetamines were identified, versus 163 non–amphetamine-treated control subjects. Using the Temperament Scale of Memphis, Pisa, Paris and San Diego–Autoquestionnaire, 62% had an affective temperament, most commonly cyclothymia (42%). In amphetamine-treated cases, mood/anxiety symptoms worsened notably in 27% (*vs.* 4% in the control group, risk ratio [RR] 6.2, confidence interval [CI], 2.8–13.8), whereas 24% had moderate improvement in cognition (*vs.* 6% in the control group; RR, 3.93; CI, 1.9–8.0). Affective temperaments, especially cyclothymia, are present in persons about one-half of persons diagnosed with adult ADD and/or treated with amphetamines.

Key Words: Adult ADD, affective temperaments, cyclothymia, hyperthymia, amphetamines, cognition

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Attention-deficit disorder (ADD), a diagnosis previously made in children, is being given frequently to adults in the last two decades (Chung et al., 2019; Kazda et al., 2021; Montejano et al., 2011). Commonly, it is accompanied by "stimulant" medication treatment, including amphetamines. The diagnosis typically is related to attentional impairment and/or executive dysfunction in adults (Huang et al., 2020). Comorbid diagnoses of mood or anxiety disorders are frequent (Huang et al., 2020). Clinicians frequently prescribe amphetamines or other stimulants for purported adult ADD, along with antidepressants and/or benzodiazepines for concomitant mood or anxiety symptoms (Olfson et al., 2014). Worsening of bipolar illness by such amphetamine treatment has been reported (Wingo and Ghaemi, 2008).

In the differential diagnosis of adult ADD from mood illnesses, it commonly is stated that mood conditions are episodic, whereas ADD symptoms are chronic. However, there is one category of mood conditions that also is chronic: affective temperaments, such as cyclothymia, hyperthymia, and dysthymia (Pompili et al., 2018; Rihmer et al., 2010).

The concept of affective temperaments also is poorly understood in contemporary American psychiatry (Akiskal et al., 1998). The original perspective, dating to Kretschmer and before him to Kraepelin and others, was that diseases like schizophrenia and manic-depressive illness (MDI) can have common mild variants that occur in relatives of persons who have the full diseases (Kraepelin, 1921; Kretschmer, 1925). Depressive personality, also termed "dysthymia," was mild, chronic, and biologically related to more severe depressive disease. Manic personality, termed "hyperthymia," similarly was a mild version of full manic episodes. Cyclothymia reflected a personality with both mood traits. These temperaments were not seen themselves as diseases but as variants of normal personality, but they were biologically related to their corresponding diseases. Furthermore, they were present in persons with MDI as the baseline personality in between mood episodes (Ghaemi and Dalley, 2014). Hence, someone could be manic all the time, with hyperthymia, and then have intermittent severe depressive episodes.

The concept of affective temperaments conflicts with the common belief that mood "disorders" should be episodic, not constant (Ghaemi and Dalley, 2014). Instead, affective temperaments are constant. These mood conditions have the same associated features as classic mood episodes, namely, anxiety and inattention, and cognitive impairment (poor executive function, impaired memory) can be present in affective temperaments of all kinds. Further manic traits include impulsivity and risky behavior; in hyperthymia, this behavior is constant, not episodic (Rihmer et al., 2010).

Recent studies have begun to address the possibility of affective temperaments presenting in the context of adult ADD (Landaas et al., 2012; Ozdemiroglu et al., 2018; Pinzone et al., 2019; Syrstad et al., 2020). However, prior studies have not addressed the specific question whether affective temperaments, causing attentional impairment and executive dysfunction as an effect of constant manic/depressive traits, are being misdiagnosed as adult ADD. Furthermore, the possible harmful effects of amphetamines on patients with manic traits as part of affective temperaments have not been reported.

In this report, we describe the prevalence of affective temperaments in persons with either ADD diagnosis or amphetamine treatment, compared with a non-ADD/nonamphetamine mood disorder control group. We also assess treatment effects of amphetamines in persons with affective temperaments, both for mood symptoms and for cognitive ADD-like symptoms, compared with mood disorder control subjects.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology statement (von Elm et al., 2007). Charts of all outpatients treated in the Tufts Medical Center Mood Disorders Program (2008–2017) were reviewed to identify all adult subjects (age 18 or more) treated with any amphetamine medications to treat ADD (methylphenidate, dextroamphetamine, dexmethylphenidate, and lisdexamfetamine). In addition, an inclusion criterion was presence of a completed Temperament Scale of Memphis, Pisa, Paris and San Diego–Autoquestionnaire (TEMPS-A), a validated research scale for temperaments (Akiskal et al., 1998, 2005). Except for these inclusion criteria above, no patients were excluded from this analysis.

In a total clinic population of 770 patients, 87 adult subjects were identified who had completed the TEMPS-A scale and had been treated with amphetamines in the past; and 163 control subjects were identified who had completed the TEMPS-A scale and had not been treated with

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amphetamines in the past. All charts were reviewed for the following clinical and demographic variables: age, sex, ethnicity, marital status, employment, education level, family history, psychosis and mania history, the average time of amphetamine use, and diagnosis after evaluation in the Mood Disorders Program. Furthermore, if prospective treatment was given, treatment outcomes were assessed for mood and cognition, as described below.

All patients received the same naturalistic treatment in the Mood Disorders Program, consistent with standard of care of mood disorders. If diagnosed with bipolar illness, they received mood stabilizers, and if with unipolar depression, standard antidepressants.

There is no general standard about the method of determining dominant temperament. One method used is choosing the highest subscale among the three temperaments. Another method to determine a dominant temperament is based on a *z*-score above the population mean. In this study, the dominant mood temperament was based on a cutoff of endorsement of 75% or more of items of the TEMPS-A, a threshold validated previously (Vohringer et al., 2012). Data on endorsement on 50% or more of items also are presented for comparison.

Treatment response was assessed in relation to cognition/attention and mood with the Clinical Global Impression improvement (CGI-I) rating scale (Guy, 1976). The CGI-I ratings were ascertained retrospectively at the time of chart review by two psychiatrist/researchers with expertise in mood disorders (S. M. and S. N. G.). After completing independent ratings, consensus was established for each patient for any ratings that differed. The CGI-I scale assesses the extent of clinical change in the patient at the point of assessment compared with baseline, using a 7-point range from "very much improved" to "very much worse." From May 2016 to April 2017, data were collected using REDCap, a research electronic data capture program. Statistical analyses included descriptive statistics, stratification, and relative risk to compare the treatment response between the two groups in both domains (mood and cognition). TEMPS-A was used as a dichotomous measure with 50% and 75% item endorsement cut offs. All analyses were made using "R" version 3.2.4 software.

RESULTS

Table 1 provides clinical and demographic characteristics of the total sample and stratified by amphetamine versus the nonamphetamine control group. Overall, the two groups were similar in many clinical and demographic features, including other past psychiatric diagnoses and concomitant psychiatric medications. They differed mainly in past ADD diagnosis and in mood temperament prevalence.

TABLE 1. Clinical, Demographic, and Treatment Characteristics of the Sample

	Amphetamine (n = 87)	Controls (n = 163)	Total (N = 250)
Age, mean ± SD, years	34.3 ± 14.1	39.5 ± 13.6	37.7 ± 13.9
Sex, male, %	53.3	43.9	47.6
Marital status, single, %	66.7	46.0	53.4
Ethnicity, White, %	78.9	80.9	80.2
Unemployed, %	61.1	43.2	49.6
Education level, bachelor's degree, %	23.3	27.0	25.7
Lives alone, %	26.7	22.4	23.9
Dysthymic 50, %	45.6	54.9	51.6
Cyclothymic 50, %	66.7	57.9	61.0
Hyperthymic 50, %	48.9	51.8	50.8
None, %	5.6	10.4	8.7
Dysthymic 75, %	20.0	17.2	18.2
Cyclothymic 75, %	42.2	30.7	34.8
Hyperthymic 75, %	24.4	22.1	22.9
None, %	37.8	44.8	42.3
Past ADD diagnosis, %	50.0	0	50.0
Family history of bipolar I, %	48.9	40.5	43.5
Unipolar depression, %	23.3	17.2	19.4
Schizophrenia, %	7.8	9.8	9.1
Past trauma, %	14.4	23.0	19.8
Past psychosis, %	18.9	18.6	18.7
Diagnosis BD, %	91.1	74.9	80.7
Manic episode with amphetamine use, %	5.7	0	5.7
Average time amphetamine use, mean ± SD, weeks	180 ± 185.7	0	180 ± 185.7
Mood stabilizers, %	47.5	41.7	43.6
Lithium, %	24.4	17.8	20
Valproate, %	8.5	11.6	10.4
Lamotrigine, %	19.5	21.4	20.8
Carbamazepine, %	2.5	0.6	1.2
Antidepressants, %	56	44.4	48.4
Neuroleptics, %	40.2	26.5	30.8

ADD indicates attention deficit hyperactivity disorder; BD, bipolar disorder; Cyclothymic 50, 50% criteria cutoff; Cyclothymic 75, 75% criteria cutoff; Dysthymic 50, 50% criteria were met as cutoff; Dysthymic 75, 75% criteria were met as cutoff; Hyperthymic 50, 50% criteria cutoff; Hyperthymic 75, 75% criteria cutoff; None, no temperament; SD, standard deviation.

In the amphetamine group, about one-half of the sample was diagnosed with ADD in the past, whereas about one-half received amphetamine treatment without clinical ADD diagnosis. Family history of bipolar disorder was present in about half of subjects in both groups. Average time of amphetamine use was more than double in those clinically diagnosed with ADD. After research-based diagnostic evaluation, about 92% of the amphetamine sample was diagnosed with bipolar illness. A total of 6% of subjects overall had amphetamine-related manic/hypomanic episodes.

Using the 50% item TEMPS-A endorsement threshold, affective temperaments were common in both groups, with high and similar prevalence for all three temperaments (about 46%–67%). Only about 9% of the sample was not diagnosable with any temperament. Using the 75% item TEMPS endorsement threshold, the most prevalent temperament in both groups was cyclothymia (42%), and 38% of the sample did not have any kind of temperament. Affective temperaments are not mutually exclusive; there is less overlap with higher cutoff thresholds.

Regarding treatment response in the amphetamine group, amphetamine treatment led to worsened mood symptoms in 27% (defined as much or very much worse; *vs.* 4% in the control group not treated with amphetamines; RR, 6.2, confidence interval [CI], 2.8–13.8; Fig. 1), whereas 24% of subjects had moderate improvement in cognition (*vs.* 6% with moderate or marked improvement in the control group not treated with amphetamines; RR, 3.93; CI, 1.9–8.0; Fig. 2). In the control group, which did not receive amphetamines, mood improved moderately to markedly in 51% (*vs.* 2% in the amphetamine group; RR, 22.2; CI, 5.6–87.9). No one in the control group experienced worsened cognition with treatment, which was the case as well in the amphetamine group. The most common cognitive outcome in both groups was no change after treatment, occurring in 87% of the control group *vs.* 63% of the amphetamine group (Fig. 2).

DISCUSSION

Affective temperaments, especially cyclothymia, were prevalent in patients diagnosed with adult ADD and/or treated with amphetamines. Amphetamine response was poor, with worsening of mood/anxiety in 27% and benefit for cognition/attention in 24%, versus a non–amphetamine-treated control group, with better mood/anxiety, but worse cognitive, outcomes. These results suggest that affective temperaments, such as cyclothymia, are misdiagnosed as adult ADD and that amphetamine treatments may improve cognitive symptoms but worsen mood/anxiety symptoms in those patients.

These data are consistent with a small and emerging literature. The first study on affective temperaments and adult ADD, conducted in Norway in 2012, found that 71% of adults diagnosed with ADD were diagnosed with cyclothymia using the TEMPS-A scale, *vs.* 13% of controls (Landaas et al., 2012). Only 11% of adult ADD subjects had been

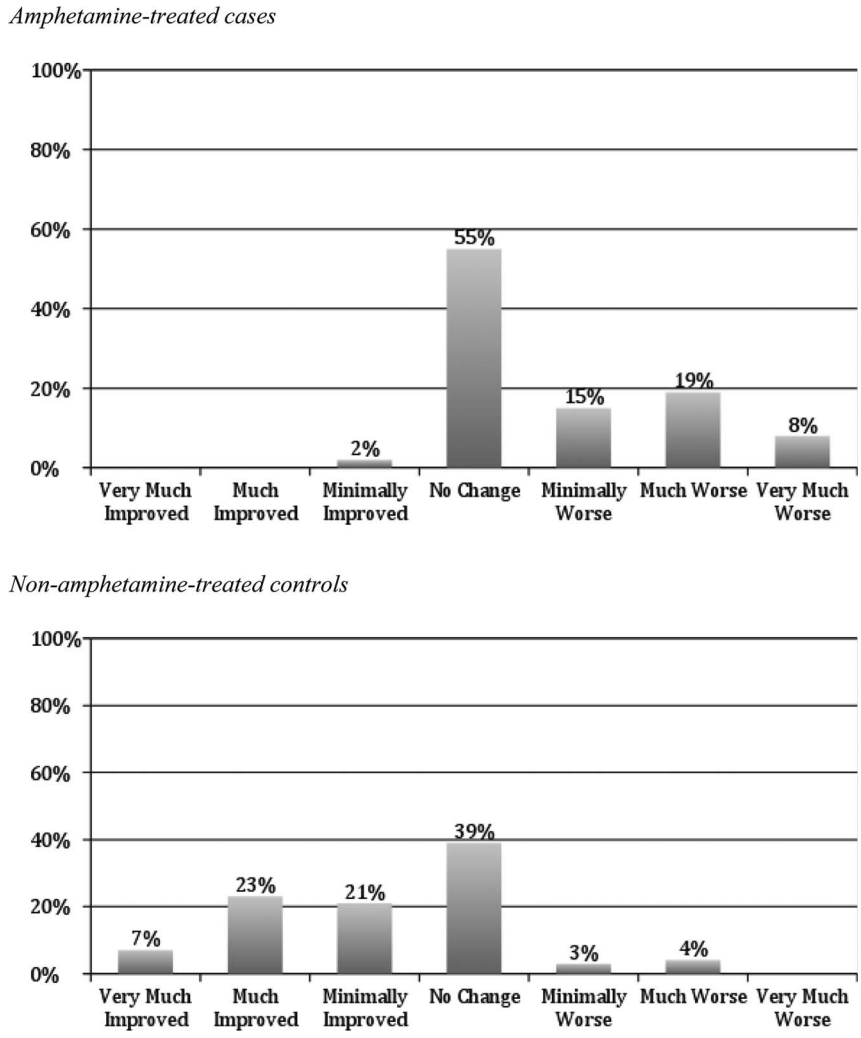

FIGURE 1. CGI-I mood/anxiety. Amphetamine-treated cases. Non–amphetamine-treated controls.

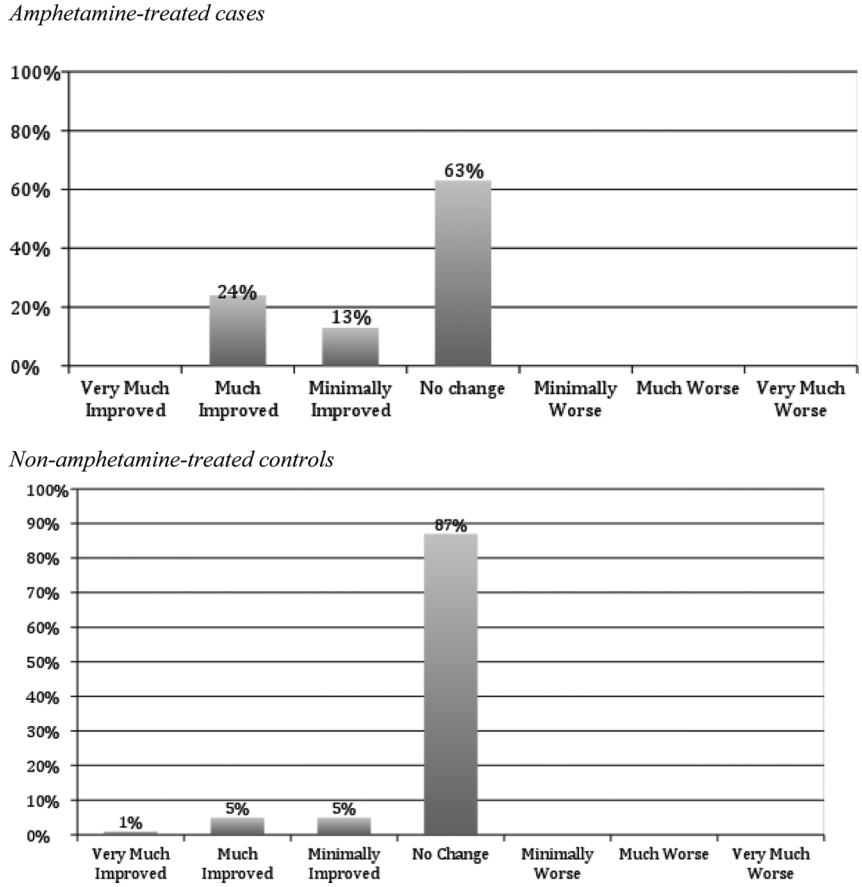

FIGURE 2. CGI-I cognition. Amphetamine-treated cases. Non–amphetamine-treated controls.

diagnosed with bipolar illness; hence, the sevenfold higher rate of cyclothymia occurred in the absence of clinically diagnosed bipolar illness. Another study found that 20% of patients with bipolar illness were diagnosable clinically with adult attention deficit hyperactivity disorder (ADHD), and in those patients, higher scores for cyclothymia were seen on the TEMPS scale compared with bipolar subjects without adult ADHD (Perroud et al., 2014). A third study from Turkey/Cyprus found that 48% of patients diagnosed with bipolar illness were also diagnosable with adult ADHD, compared with about half that amount with *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*)–defined major depressive disorder (25%); this study had a healthy control cohort, very importantly, which showed a half lower rate of adult ADHD than MDD (12%), and one-quarter the rate of diagnosed bipolar illness (Harmanci et al., 2016). Multiple ADHD scales were given along with the TEMPS scale. Again, the "comorbidity" of adult ADHD with bipolar illness was associated with higher temperament scores, most strongly for cyclothymia. High scores on anxiety traits also were highly associated with receiving the adult ADHD label. A recent study from Italy found that about one-quarter (23.8%) of *DSM-IV*–defined patients with adult ADHD could be diagnosed with *DSM-IV*–defined cyclothymia, and a similar number of *DSM-IV*–defined patients with cyclothymia could be diagnosed with *DSM-IV*–defined adult ADHD (29.4%) (Brancati et al., 2021). All told, these studies support an overlap between bipolar illness and cyclothymia with *DSM*-defined adult ADHD that is in the 20% to 50% range. These studies all assume the validity of the concept of "comorbidity" in this regard, which can be questioned, as discussed below. Finally, a recent systematic review identified five other studies using the TEMPS scale in patients with adult ADD, with overall replication of high prevalence of affective temperaments. Cyclothymia consistently had the highest prevalence, with lower association with hyperthymia (Pinzone et al., 2019). These studies include adult subjects with ADD with and without bipolar or unipolar mood comorbidities and find, in general, that affective temperament rates in adult ADD are similar to what are found in bipolar illness. In short, the prevalence of affective temperaments occurs in ADD separate from the comorbid diagnosis of bipolar illness.

A distinction should be made between misdiagnosis and comorbidity. One interpretation of these data would be that patients with adult ADD commonly have comorbid mood temperaments or vice versa. Another interpretation is that adult ADD may be misdiagnosed in persons with mood temperaments. Both interpretations are possible, although the first one depends on a prior acceptance of the diagnostic validity of adult ADD. The second concept should be considered, however, and not rejected out of hand, especially if mood temperaments are present in most patients (*i.e.*, the majority) with purported adult ADD diagnosis. In other words, comorbidity, defined as the random co-occurrence of two independent diseases, should not happen all the time, or most of the time, but only some of the time (Feinstein, 1970).

The clinical implications of this study include better understanding of affective temperaments in clinical practice, as well as better delineation of the use of the adult ADD construct and its treatments. One implication is that adult ADD is diagnosed when the *cognitive effects* of affective temperaments are viewed as diagnostically important, instead of diagnosing the mood condition underlying those cognitive effects. This interplay between mood illness and ADD-like symptoms is a

complex clinical issue that deserves greater attention. A few points will be made on these topics here.

First, regarding the validity of adult ADD, it is relevant that the diagnosis rate has markedly increased in the past two decades and likely now reflects overdiagnosis. With loosening of ADD criteria in the *DSM-5* in 2013, diagnostic rates have shot up. In one large database, adult ADD diagnoses more than doubled (0.43% in 2007 to 1.12% in 2017), a much larger increase than in children (2.96% in 2007 to 3.74% in 2016) (Chung et al., 2019). A new systematic review found a consistent increase in ADD diagnosis in youth between 1989 and 2017 and more ADD pharmacological treatment (Kazda et al., 2021). Another US database found that adult ADD diagnosis tripled in just 5 years (2002–2007) (Montejano et al., 2011), coinciding with the introduction of the first marketed drug for adult ADD, atomoxetine (Kratochvil et al., 2003). This increase in ADD diagnosis has been accompanied by large increases in amphetamine and stimulant medication prescription. In a standard national sample of US office-based medical practice from 1995 to 2010, the stimulant drug class increased in prescribing practices from about 4.77% to 17.29% (odds ratio, 4.29; 95% CI, 3.05–6.03), the largest increase in any psychotropic drug class (Olfson et al., 2014).

As can be seen from this description of the increasing prevalence rates for diagnosis and treatment, it seems that many clinicians take it for granted that ADD diagnosed in childhood or adolescence will persist into adulthood. This assumption is not well founded in data, however. Large prospective studies, some with decades of follow-up, indicate that around 80% of children or adolescents with ADD are no longer diagnosable in adulthood (Caye et al., 2016; Klein et al., 2012). A systematic review of 12 prospective studies between 1992 and 2016 found a range of persistence of ADD from childhood to adulthood of 4% to 77% (Sibley et al., 2016). When limited to those studies, which used the most valid forms of assessment (self and informant ratings, age-appropriate symptom thresholds, requiring presence of impairment), the authors concluded that the most valid persistence rates were in the 40% to 50% range.

Because of the widespread acceptance of the *DSM* nosology as valid, which has not been proven (Ghaemi, 2013), the assumption of many researchers is that adult ADD is a legitimate and valid diagnosis, and thus, its presence always is a matter of "comorbidity." Instead, so-called ADD symptoms may simply reflect the cognitive effects of mood conditions, and thus, it is not a matter of comorbidity but of misdiagnosis. Cyclothymia also is conceived by clinicians within its *DSM* definition, which never has been proven to be valid. In contrast, the diagnostic validity of cyclothymia in the empirical literature is as a temperament, not a "disorder," which is defined deliberately by the *DSM* system to be vague (Ghaemi, 2014). Cyclothymic temperament is not a "disorder" if by that term is meant a disease, equal to "bipolar disorder" or schizophrenia. Rather, it is part of the broad spectrum of manic-depressive illness, as a personality variant, closer in its ontology to personality traits rather than to a psychiatric disease (Ghaemi and Dalley, 2014).

Because mood symptoms can cause ADD-like cognitive symptoms and because these data indicate limited benefit and observable harm with amphetamines in affective temperaments, the question arises whether the diagnosis of affective temperaments, such as cyclothymia, should be given priority to the adult ADD diagnosis. A corollary would be that amphetamine treatment should be avoided in the majority of such subjects. It is notable that some patients in our study simply did not respond to amphetamines, whereas others worsened in their mood states, experiencing manic or mixed states or even worsening depression. Amphetamines are antidepressants, and the latter class is well known to cause mania and destabilize bipolar illness; hence, these results should not be surprising (Ghaemi, 2012). In general, they argue for avoiding amphetamines in patients overall, especially if diagnosed with bipolar illness and/or cyclothymia.

Readers will note a very high rate of diagnosis of bipolar illness in the adult ADHD sample in this study (91.1% *vs.* 74.9% of non-adult ADHD sample). The high rates of bipolar illness in our sample relate to the selection bias of our mood disorders program, which tends to be referred patients with bipolar illness. Nonetheless, it is notable that those who previously had been diagnosed with adult ADHD had not received mood stabilizers in about half the cases, suggesting that they simply had been misdiagnosed as having adult ADHD only, without bipolar illness even as a so-called comorbidity.

This study has several limitations. Although controlled, the sample was nonrandomized and analyzed retrospectively. Prior clinicians made the diagnosis of ADD clinically without using validated diagnostic interviews. The naturalistic context of treatment, especially concomitant use of other medications, could introduce confounding treatment effects in the assessment of amphetamine treatment response or side effect perception. Because most subjects were White European-Americans, these results may not be generalizable to other ethnic groups.

CONCLUSIONS

Affective temperaments, especially cyclothymia, are commonly present in persons diagnosed with adult ADD and/or treated with amphetamine medications. Amphetamine treatment response was either ineffective or harmful for mood/anxiety symptoms in these subjects, compared with a non–amphetamine-treated mood disorder control group. Cognition improved in a minority (about one-quarter) of amphetamine-treated subjects. The overall risk-benefit profile for mood and cognition in this setting would seem to be unfavorable for amphetamines.

DISCLOSURES

Ethical considerations: Tufts Medical Center Institutional Review Board approval to conduct this chart review was obtained. All authors have read and approved this article.

Author contributions: S. M.—conceptualization, methodology, formal analysis, and writing of the original and final draft; G. G.—data curation and writing of the original draft; S. N. G.—conceptualization, methodology, formal analysis, and writing of the original and final draft.

Terminology note: As it has been shown that hyperactivity is not a feature of reported ADD in adults, the term "attention deficit hyperactivity disorder (ADHD)" is not used in this article and is replaced with "ADD." The term "ADHD" is used in relation to titles of specific scales only.

S. N. G. was an employee of Novartis Institutes for Biomedical Research from October 2017 to June 2021. This research was conducted before that employment. G. G. and S. M. declare no conflict of interest.

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