Curr Psychiatry Rep (2017) 19: 109
https://doi.org/10.1007/s11920-017-0859-6

ATTENTION-DEFICIT DISORDER (A ROSTAIN, SECTION EDITOR)

ADHD and Anxiety: Clinical Significance and Treatment Implications

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Published online: 20 November 2017

Abstract In comparison to the DSM formulation of ADHD, we have proposed that ADHD in adults should be divided into Inattentive and Emotional Dysregulation Presentations. Under both systems, there is potential overlap with generalized anxiety disorder (GAD). We compared data from four distinct populations: ADHD clinical trials, GAD clinical trials, an ADHD clinic, and a forensic clinic. Approximately 25% of patients in each population had comorbid ADHD and anxiety. Comorbid subjects reported more childhood ADHD symptoms and higher scores on ADHD scales and were more likely to fit criteria for ADHD Emotional Dysregulation Presentation or DSM-IV combined type. Comorbid subjects did not drop out at a higher rate and showed significant drug-placebo differences on ADHD symptoms, including Emotional Dysregulation. Conversely, although symptoms of anxiety decreased, there was no drug-placebo difference in improvement.

Keywords ADHD · Anxiety · GAD · Treatment response · Emotional dysregulation · WRAADDS

This article is part of the Topical Collection on *Attention-Deficit Disorder*

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Introduction

The overlap between ADHD and generalized anxiety disorder has led to very productive investigations exploring both disorders and areas of intersection.

First, there is evidence that in adulthood, generalized anxiety disorder (GAD) and attention deficit hyperactivity disorder (ADHD) frequently occur together [1]. An association between ADHD symptoms and anxiety has been shown in community surveys [2•, 3]. Piñeiro-Dieguez [4•] found that in a sample of 367 adult outpatients with ADHD, 23% had an anxiety disorder. Van Ameringen [5•] examined the prevalence of ADHD in a sample of consecutive adult patients referred to an anxiety disorders clinic and found that 28% had ADHD. Consequently, while both disorders are relatively common, the observed rates of co-occurrence are higher than would be expected on this basis of chance alone.

This overlap maybe partially explained by the diagnostic overlap of the criteria for ADHD and GAD that resemble symptoms of the other Tannock [6]. For example, the fidgeting and restlessness of ADHD is similar to the physical restlessness of GAD. It has been suggested that certain forms of anxiety may be manifested as "anxious impulsivity" [7]. Milberger [8•] directly examined the overlap of ADHD and GAD in adults and found that 75% of the sample still met criteria for ADHD and 76% of the sample still met criteria for GAD after eliminating symptoms common to both disorders.

Second, the combined presence of ADHD and GAD leads to a more complicated, severely symptomatic presentation of each disorder. In a six-year follow-up of teenagers with ADHD, those subjects with ADHD persisting into adulthood had more anxiety than those with sub-clinical ADHD [9]. Some researchers have suggested that ADHD combined with anxiety might be regarded as a distinct ADHD subtype [10].

Third, there is concern that treating one disorder may complicate, or interfere with, treating the other. A major consideration in this regard is the US Food and Drug Administration label warning that stimulant medications may produce increased anxiety. Treatment of subjects with both ADHD and anxiety has been has been very carefully examined in children as part of the MTA study [11]. March showed that ADHD children with anxiety responded as well to methylphenidate as those with only ADHD, but that there was additional improvement with counseling. There have been other reports of improvement in comorbid anxiety with pharmacotherapy of ADHD [12–14]. However, in a small study of male children, Mosche [15] found that higher levels of anxiety were associated with a poorer methylphenidate (MPH) response, and findings by Ter-Stepanian [16] and Sciberras [17] regarding children are similar. Conversely, a review by Clemow [18] reported that atomoxetine, often used as an alternative to psychostimulants, was not associated with an exacerbation of anxiety.

In adults, there are reports of research subjects showing reductions in anxiety with ADHD treatment [19–21, 22•, 23]. However, Horrigan [24] in a small study of adults with ADHD treated with dextroamphetamine found that four of seven patients with an anxiety disorder diagnosis experienced acute anxiety as an adverse event. Similarly in several larger positive ADHD medication studies, anxiety did not improve with OROS MPH [25•], or atomoxetine [26]. In a study that is most confusing, Bilodeau [27] reported improvement in ADHD symptoms with duloxetine, but no change in anxiety.

Fourth, is the overlap between anxiety and ADHD associated with particular facets of ADHD? We have reported that adults with ADHD show two factor clusters that are the bases for defining two ADHD presentations, Inattentive Presentation and Emotional Dysregulation Presentation [28•]. A high emotional dysregulation factor defines a more severely impacted ADHD population. Conversely, in the DSM system, ADHD has been conceptualized as having two factors, inattention and hyperactivity/impulsivity. Is anxiety associated with one of these specific factors or with both of them?

A number of highly influential early papers dealing with conditions similar to what we now call ADHD (for example Bradley [29] and Wender [30]) noted such patients frequently reported a variety of emotional symptoms. In 2005, we provided an operational definition of "Emotional Dysregulation" that was present in many ADHD patients in the absence of any other DMS axis I diagnosis [31]. For research and clinical purposes, we have operationalized emotional dysregulation using three domains of the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS): temper, affective lability, and emotional over-reactive. These symptoms frequently occur in response to environmental stresses. The WRAADDS (both the self-report and investigator-rated versions are freely available) contains indicator questions to assist in identification of the presence and severity of these symptoms. Even in ADHD samples specifically selected to exclude comorbid anxiety or depression, at least 30% have met criteria for emotional dysregulation. While numerous researchers addressing emotional dysregulation focus predominantly on symptoms related to temper, our experience suggests that lability and over-reactivity are more common in adult ADHD.

Fifth is comorbid anxiety related to attrition in clinical trials of medications to treat ADHD in adults?

Consequently, this paper will examine:

1. The extent of comorbidity of ADHD and anxiety in four dissimilar populations
2. The effect of anxiety on the presentation of ADHD patients overall and various ADHD subtypes
3. The influence of anxiety on response of ADHD subjects to ADHD treatment and changes in manifestations of anxiety during treatment of ADHD
4. The overlap between anxiety symptoms and factors/domains of ADHD
5. The association of retention in ADHD treatment or research protocols with anxiety

In attempting to answer these questions, we will make use of a number of clinical trials of ADHD treatment in which some ADHD subjects also had anxiety and also a number of clinical trials of anxiety treatment in which some subjects also had ADHD. We will also examine two populations from the first author's clinic: one a group of patients seeking treatment for specialized ADHD treatment and the other a group of forensic patients referred by legal authorities for assessment and treatment. We will examine all trials separately with regard to the relationship of anxiety and ADHD, but we will also combine results in order to take advantage of the confidence in findings afforded by basing statistical calculations and corresponding conclusions on a large number of subjects.

Methods

Subject Populations

Subjects for This Investigation Were Divided Into Four Separate Groups:

1. ADHD clinical trial subjects ($n = 1189$)—these data come from five unrelated ADHD clinical trials (bupropion, atomoxetine, atomoxetine for ADHD with comorbid alcohol abuse, extended release methylphenidate, and immediate release methylphenidate). They were chosen because each trial included an assessment of anxiety, either

the Hamilton Anxiety Scale (HAMA) or the Symptom Checklist-90 (SCL-90), collected at baseline and following double-blind treatment in four of the five studies.
2. Generalized anxiety disorder (GAD) clinical trials subjects (n = 78)—these data come from six different GAD clinical trials. Subjects were selected because ratings of ADHD symptoms were available. The Wender Utah Rating Scale [32] and the SR-WRAADDS [33] were utilized as part of our baseline evaluation of all potential subjects.
3. Clinic outpatients with ADHD (n = 105)—these patients with ADHD had not been involved in past clinical trials. Our normal intake procedures included assessment of both anxiety and ADHD symptom levels.
4. Forensic clinic outpatients (n = 89)—these data were drawn from our 177 forensic patients based on a diagnosis of either GAD and/or ADHD. We included measures of both ADHD and GAD in our intake assessment. Ninety-two percent of these 89 subjects had substance abuse or dependence. Eighty-eight were not included in the tabulation because they did not have a diagnosis of generalized anxiety disorder or ADHD diagnosis.

Descriptions of the Five ADHD Clinical Trials:

1. Bupropion for ADHD—this was a parallel, placebo-controlled trial of bupropion for adults with ADHD (n = 59). Admission was based on both DSM-IV criteria and the Utah criteria for ADHD. ADHD was evaluated using the Wender-Reimherr Adult Attention Deficit Disorder Scale and anxiety was evaluated using the HAMA. Comorbid depression was a primary exclusion criterion [34].
2. Atomoxetine for ADHD—this was a 10-week parallel, placebo-controlled trial of atomoxetine for adults with ADHD. Five hundred thirty-six subjects were enrolled based on DSM-IV criteria. ADHD was evaluated using the WRAADDS and Conners' Adult ADHD Rating Scale (CAARS) while anxiety was evaluated with the HAMA [2•].
3. Atomoxetine for ADHD with comorbid alcohol abuse—this was a 12-week parallel, placebo-controlled trial of atomoxetine. Adults with DSM-IV diagnoses of ADHD and alcohol abuse and/or dependence (n = 147) were abstinent from alcohol at least 4 days (maximum 30 days) before study randomization. This double-blind phase was followed by a maintenance phase in which the primary concern was alcohol relapse. ADHD was evaluated using the WRAADDS and the AISRS, and anxiety was evaluated using the HAMA [35].
4. Extended release methylphenidate—this was a 24-week parallel, placebo-controlled trial of MPH ER (Concerta) in adults with ADHD conducted in Europe. All 359 subjects met criteria for ADHD—combined type. ADHD was evaluated using the WRAADDS and CAARS while anxiety was evaluated with the SCL-90 Anxiety Scale [36].
5. Immediate release methylphenidate—this was a placebo-controlled crossover trial of MPH (N = 116) that used two 4-week treatment arms. Double-blind completers were eligible for a 24-month open-label treatment phase. While subjects were enrolled based on the Utah criteria most were subsequently judged as meeting DSM criteria. ADHD was evaluated using the WRAADDS while anxiety was evaluated with the SCL-90 Anxiety Scale [37].

ADHD Measures

Wender-Reimherr Adult Attention Deficit Disorder Scale Both interview and self-report versions were used to measure ADHD symptoms and to divide subjects into two proposed ADHD categories: ADHD Inattentive Presentation and ADHD Emotional Dysregulation Presentation [28•, 33, 38].

Wender Utah Rating Scale (WURS) This is a widely accepted scale used to measure childhood symptoms consistent with persistence of ADHD from childhood into adulthood [32].

Conners' Adult ADHD Rating Scale (CAARS) [39] and the Adult ADHD Investigator Symptom Rating Scale (AISRS) [40] These were used to assess the 18 DSM ADHD items at baseline and to divide subjects into the three DSM presentations: inattentive, hyperactive/impulsive, and combined type ADHD.

In the anxiety trials, ADHD was defined by an elevated WURS score and a childhood history consistent with ADHD.

In the clinical samples, an ADHD diagnosis was based on current symptoms and functioning combined with a positive childhood history of ADHD.

Anxiety Measures

In the five ADHD clinical trials, high levels of anxiety were defined as scores of 10 or higher on the Hamilton Anxiety Rating Scale (HAMA) [41] and t scores of 50 or higher (outpatient psychiatric norms) on the anxiety scale of the Symptom Checklist 90 (SCL-90) [42]. The t scores were based on psychiatric outpatient norms. Cutpoints for the two instruments were determined to select patients with similar levels of anxiety.

In the clinic samples, anxiety was determined based on a chart review indicating diagnosis of GAD and level of anxiety measured by the SCL-90 and HAMA.

Statistical Methods

Baseline differences between anxiety groups were assessed using *t* test or chi-square as applicable. Differences were also described using an effect size statistic, Cohen's d.

All treatment effects were measured at the end of the end of the drug versus placebo phase or last visit carried forward. In particular, interaction effects between treatment (placebo versus active medication) and anxiety (low- versus high-anxiety subjects) were analyzed using ANOVA to identify differences in the treatment response of the two groups.

Results

Comorbidity Between ADHD and Anxiety

Agreement on the extent of overlap between ADHD and anxiety among these four otherwise dissimilar patient groups is quite high. As displayed in Table 1, within the five ADHD clinical trials, 30% of subjects experienced high levels of comorbid anxiety. In the six GAD trials, 24% of subjects appeared to have a comorbid ADHD disorder. Of the 106 patients in the ADHD clinic, 24% gave evidence of a comorbid anxiety disorder. Finally, of the 89 patients from the forensic clinic, 24% had both ADHD and an anxiety disorder.

Impact of Anxiety on Subjects in ADHD Trials

Table 2 displays the differences associated with high levels of anxiety for the 1189 subjects in the five ADHD clinical trials who generated useful anxiety scores. There was little difference in age or gender between the two groups. Hamilton Depression Rating Scales scores were significantly higher for the high-anxiety subjects although not at levels typical of an actual DSM-IV diagnosis.

Both groups had average WURS scores above the published cut off point for childhood symptoms associated with an ADHD diagnosis in adulthood. Eighty-eight percent of the high-anxiety sample had WURS scores of 42 or higher compared to 68% of low-anxiety patients $p=.001$.

Table 2 also shows that DSM-IV combined type ADHD was relatively more common in the high-anxiety subjects than the low-anxiety subjects and that the high-anxiety subjects had higher scores on the scales of inattention and hyperactive/impulsive. While these differences were consistently significant ($p \leq .001$), the effect sizes were small as measured by Cohen's d. (Two trials did not contribute DSM diagnostic data.)

The WRAADDS also showed that high-anxiety patients had a higher ADHD symptom load. ADHD Emotional Dysregulation Presentation was more common in the high-anxiety group than the low-anxiety group. Further, the high-anxiety subjects had higher scores in all seven WRAADDS domains compared to the low-anxiety group. While the *p*-values were consistently significant ($p \leq .001$) the effect sizes were in the low to moderate range and varied from a high of $d = .6$ for hyperactivity/restlessness to a low of $d = .2$ for disorganization.

Impact of Anxiety on ADHD Treatment Response in Clinical Trials

We compared treatment effects of ADHD medications in ADHD subjects with high-anxiety levels versus those with low levels of anxiety using ANOVA and examining for an interaction effect. Each trial was analyzed separately, and change in total ADHD symptom level from baseline to double-blind endpoint was the dependent variable. In every trial, the interaction was non-significant ($p > .05$), indicating that low- and high-anxiety subject had similar responses to ADHD treatment.

Table 3 displays the improvement in ADHD symptoms as a function of treatment (placebo versus active medication) for both anxiety groups. Student's *t* test and Cohen's d were used to assess the magnitude of treatment effects separately for both anxiety groups within each clinical trial. While the table expresses change as a percent of improvement compared to baseline, both Cohen's d and the *p* value were calculated from actual change scores. Two of the five trials showed statistically significant improvement for high-anxiety subjects and two of

Table 1 Extent of ADHD and comorbidity within each patient group

	Number	ADHD alone (%)	ADHD and GAD (%)	GAD alone (%)	ADHD + other diagnosis (%)
ADHD studies	1189	70	30	None	Unknown
Anxiety studies	78	None	24	76	Unknown
ADHD clinic	106	43	24	None	33
Forensic clinic patients with ADHD and/or GAD	89*	18	24	22	36

ADHD attention deficit hyperactivity disorder, *GAD* generalized anxiety disorder

*As noted in the "Methods" section, only 89 out of 177 patients in the forensic clinic were included in this analysis

Table 2 Differences between ADHD subjects with and without comorbid anxiety

Baseline measures	Low-anxiety subjects	High-anxiety subjects	*p* value, Cohen's d
Male *n* = 765	66%	34%	X^2 = 4.8, df = 1
Female *n* = 424	72%	28%	*p* = .04, *d* = .1
Age	37.9 ± 10.9	38.3 ± 11.6	*p* = .53, *d* = 0.0
Hamilton Depression Rating Scale	4.2 ± 2.9	9.7 ± 3.8	*p* = .0001, *d* = 1.6
Wender Utah Rating Scale			
Percent of Subjects over cutoff	68%	88%	X^2 = 22.1, df = 1, *p* = .001
Average scores	48.8 ± 12.7	57.5 ± 13.8	*p* = .0001, *d* = 0.7
DSM-IV characteristics			
Combined type *n* = 561*	69%	31%	X^2 = 10.1,
Inattentive type *n* = 201*	78%	22%	df = 2,
Hyperactive/impulsive type *n* = 30*	81%	19%	*p* = .01
Total score	33.3 ± 10.7	36.4 ± 10.1	*p* = .001, *d* = .3
Inattention	18.4 ± 6.2	19.7 ± 5.6	*p* = .001, *d* = .2
Hyperactive/impulsive	15.2 ± 6.4	17.3 ± 6.3	*p* = .001, *d* = .2
Utah ADHD diagnosis			
Inattentive Presentation *n* = 637*	74%	26%	X^2 = 48.1, df = 1,
Emotional Dysregulation *n* = 445*	54%	46%	*p* = .0001 *d* = .4
WRAADDS total	17.3 ± 4.6	20.0 ± 3.9	*p* = .001, *d* = 0.6
WRAADDS factors			
Attention Factor	6.0 ± 1.3	6.6 ± 1.1	*p* = .001, *d* = 0.5
Emotional Dysregulation Factor	5.7 ± 2.2	6.9 ± 1.9	*p* = .001, *d* = 0.6
WRAADDS domains			
Attention difficulties	3.2 ± 0.8	3.5 ± 0.7	*p* = .001, *d* = 0.4
Hyperactivity/restlessness	2.6 ± 1.1	3.1 ± 0.8	*p* = .001, *d* = 0.6
Temper	1.9 ± 1.2	2.4 ± 1.2	*p* = .001, *d* = 0.4
Affective lability	2.0 ± 1.1	2.5 ± 1.0	*p* = .001, *d* = 0.5
Emotional over-reactive	2.0 ± 1.3	2.5 ± 1.2	*p* = .001, *d* = 0.4
Disorganization	3.1 ± 0.9	3.2 ± 0.8	*p* = .001, *d* = 0.2
Impulsive	2.6 ± 0.9	2.8 ± 0.9	*p* = .001, *d* = 0.3

WRAADDS Wender-Reimherr Adult Attention Deficit Disorder Scale

*Percent meeting diagnostic criteria

the five trials showed significant improvement for low-anxiety subjects.

Did Symptoms of Anxiety Change With ADHD Treatment?

We assessed each of the items of the HAMA and SCL-90 anxiety scale for changes between baseline and the final visit. We selected anxiety items on the HAMA from the three studies which utilized this instrument (bupropion, atomoxetine, atomoxetine for ADHD with comorbid alcohol abuse) for the assessment. The SCL-90 was collected in two trials (extended release methylphenidate and immediate release methylphenidate) during the baseline phase but was employed during the double-blind phase in only the extended release methylphenidate trial.

The items that were most highly endorsed at baseline also improved the most as measured by change scores. No anxiety items showed a statistically significant increase during the trials. Subjects with low anxiety scores at baseline had limited scope for improvement. The high-anxiety patients accounted for all improvement in these anxiety items. Consequently, to examine potential treatment effects with respect to anxiety symptoms, we examined only subjects with high-anxiety levels. Table 4 presents the items most elevated at baseline and their subsequent improvement during the treatment phase.

Table 3 Anxiety and ADHD treatment response

STUDY	Low-anxiety subjects			High-anxiety subjects		
	PBO (%)	MED (%)	Cohen, *p* value	PBO (%)	MED (%)	Cohen, *p* value
Bupropion						
WRAADDS						
Percent improvement	17	17	$d = .1, p = .66$	22	34	$d = .4, p = .22$
Atomoxetine						
CARRS						
Percent improvement	24	33	$d = .2, p = .149$	24	33	$d = .4, p = .018$
WRAADDS						
Percent improvement	15	25	$d = .1, p = .282$	16	31	$d = .4, p = .024$
Atomoxetine for ADHD with comorbid alcohol abuse						
AISRS						
Percent improvement	16	29	$d = .3, p = .198$	31	37	$d = .3, p = .26$
Extended release methylphenidate						
CARRS						
Percent improvement	33	35	$d = .1, p = .323$	35	31	$d = .1, p = .573$
WRAADDS total						
Percent improvement	33	42	$d = .3, p = .037$	32	41	$d = .1, p = .573$
Immediate release methylphenidate						
WRAADDS						
Percent improvement	7	56	$d = 1.3$, $p = .001$	12	55	$d = 1.1$, $p = .001$

WRAADDS Wender-Reimherr Adult Attention Deficit Disorder Scale, *CAARS* Conners' Adult ADHD Rating Scale, *AISRS* Adult ADHD Investigator Symptom Rating Scale

Every item improved substantially during this period, but as indicated in the final column, there was no drug-placebo difference except for the intellectual item on the HAMA that reflects problems with attention.

Table 4 Outcomes at the end of double-blind for anxiety items most endorsed at baseline by high-anxiety subjects. (Percent improvement over baseline)

Item	Placebo (%)	Medication (%)	Medication/placebo statistics
HAMA			
Anxious mood	30	32	$p = .47, d = .3$
Tension	35	39	$p = .83, d = .0$
Insomnia	48	39	$p = .42$, $d =$ minus 0.2*
Intellectual (cognitive)	16	44	$p = .04, d = .5$
Depressed mood	27	43	$p = .24, d = .3$
Somatic (muscular)	55	57	$p = .49$, $d =$ minus 0.2*
SCL-90			
Nervousness or shakiness inside	39	43	$p = .56, d = .1$
Feeling tense or keyed up	47	44	$p = .93, d = .0$
Feeling so restless you could not sit still	47	63	$p = .55, d = .2$

HAMA Hamilton Anxiety Scale, *SCL-90* Symptom Check List-90

*Negative values indicate that the item improved more in the placebo arm

Even though Table 4 describes the trials combined, the lack of a significant treatment effect was found for all of these items in each study analyzed individually.

Impact of Anxiety on Subject Retention in ADHD Clinical Trials

Across these trials, 32% of subjects were in the high-anxiety group at baseline. This group constituted 33% of the subjects who remained through the last visit of the double-blind phase. Consequently, high levels of anxiety had no effect on subjects completing the short term, double-blind portions of our clinic trials. This finding was true within all five trials.

Conclusions

The comorbidity between anxiety and ADHD is high, and the percentage of patients with elevated levels of anxiety in ADHD clinical trials is closely similar to the other three, very different, groups. Further, 25 to 30% falls comfortably into the range established by previous reports.

We were particularly interested in the relationship between Emotional Dysregulation and anxiety. Anxiety was most closely related to the WRAADDS domain: hyperactivity/restlessness. We view emotional dysregulation and anxiety as overlapping dimensions, but having important differences. Most importantly, in our prior paper on ADHD diagnosis and factors present in ADHD [28•], we reported that hyperactivity/restlessness is distributed across both our two proposed adult ADHD presentations and cannot be used to separate the two presentations.

Patients with high levels of anxiety were consistently more impaired on multiple ADHD measures. This was particularly true for measures derived from the WRAADDS. They were more likely to be diagnosed as ADHD Emotional Dysregulation Presentation and had higher scores on the WRAADDS factors and domains. The WURS, which asks about childhood symptoms, was also was more frequently elevated in this group. The WRAADDS seemed more sensitive to symptoms display by ADHD subjects with high anxiety compared to DSM-based measures. In addition, based on inspection of the numerical values of Cohen's d scores, the WRAADDS seemed more useful than DSM-based measures in detecting treatment effects.

There was no difference in ADHD patients with high versus low anxiety preferentially or selectively dropping out of ADHD trials. This finding contrasts with a 2009 report by Victor [43] that attrition (in a naturalistic study of MPH in the treatment of ADHD) was more likely if patients had social anxiety and also with the finding that high levels of personality disorder led to attrition in an ADHD pharmacotherapy trial [44]. If these results regarding attrition generalize to retention in therapy, it would indicate that ADHD patients with anxiety are just as likely to remain in treatment as those without significant anxiety.

Importantly, there was no difference in ADHD treatment response due to high anxiety. The high- and low-anxiety groups showed essentially similar improvement as measured by the WRAADDS and the CAARS. This is consistent with a report by Victor and associates [45] who found that in a naturalistic study level of anxiety did not influence medication response. On the other hand, the finding that medication response is unrelated to comorbidity contrasts with prior work showing ADHD adults with high levels of personality disorder are less responsive to treatment [46].

These findings also suggest that US Food and Drug Administration anxiety warning with regard to stimulants should be reconsidered and that there is scope to treat anxious ADHD patients with a psychostimulant. In this regard, it is important to note that some investigators have reported evidence that both adults with ADHD [19] and adults without psychiatric illness [47] can experience a reduction in anxiety with a psychostimulant. Our ADHD subjects with anxiety had symptoms of tension and restlessness as opposed to being fearful and phobic, and so caution is warranted in applying these findings to all ADHD patients with anxiety or to all combinations of anxiety symptoms. This suggests that in assessing anxiety as part of an initial evaluation, attention should be paid to the specific symptoms of anxiety.

While some recommendations for dealing with ADHD patients who have significant comorbidities call for treating the diagnosis with the most severe symptoms first, an alternative is to recognize the great efficacy of medications for ADHD relative to medications used to treat anxiety. Additionally, the relatively rapid onset of the effect of psychostimulants versus medications for a range of comorbidities must be considered in this regard.

Although it is not clear why symptoms of anxiety should have declined in the course of the clinical trials, several possibilities suggest themselves. It could be that with the decline in ADHD symptoms, patients are better able to function and anxiety is reduced as a consequence. It could be as well that patients do not always discriminate among symptoms in the way that professionals try to, and as a consequence, improvement in one area is perceived by the patient as improvement in all areas. It could also be that the ongoing contact with a mental health professional in the course of a clinical trial has a salubrious effect on patients' anxiety.

Finally, in all four studies with outcome data regarding anxiety, it was a secondary measure both in terms of patient selection and outcome. Perhaps in a study that preferentially recruited ADHD subjects with high-anxiety levels, the results would be different. Conversely, with regard to the pharmacotherapy of ADHD, our data do not support the need to conduct

a carefully controlled clinical trial in ADHD subjects with high anxiety.

Limitations

These data come from five very different clinical trials of adult ADHD. Several of the studies had a treatment effect smaller than is generally true of ADHD medication treatment studies. The five trials varied greatly in the number of subjects, with the atomoxetine trials contributing almost half of the total number. The very large trials make a greater contribution to the data in Table 2, and if they are in some way atypical, distortion is introduced. Double-blind change in anxiety was collected for three trials for the HAMA, and only one trial for the SCL-90 and the trial with the strongest ADHD treatment response (IR methylphenidate) did not assess anxiety during the double-blind phase. We have examined two medications, although a number of other agents, especially dextroamphetamine, have been used to treat ADHD in adults. We did not use meta-analytic techniques. We did not correct for multiple comparisons in reporting *p* values.

Clinical Strategies

This report supports treating ADHD adults exhibiting high levels of anxiety with typical medications used to treat ADHD before resorting to benzodiazepines or SSRIs. Despite the association of high levels of anxiety with generally higher symptom loads, such patients respond as well as ADHD patients with minimal anxiety to commonly used ADHD medications. It is possible that SNRIs, vortioxetine, or the forthcoming medication dasotraline might have a role with such patients. Further, these patients are equally likely to complete treatment regimens. Emotional dysregulation symptoms should be included in assessing the success of interventions and any need to adjust medications. In contrast, only when symptoms of anxiety do not remit during ADHD treatment, one should consider additional pharmacologic treatment addressing the anxiety symptoms.

Key Findings:

Comorbidity for ADHD and GAD was 25–30% in several different patient populations.

1. When GAD was present in subjects with a primary ADHD diagnosis, all ADHD factors and domains were elevated.
2. ADHD subjects with high anxiety were more frequently diagnosed with our proposed category (ADHD Emotional Dysregulation Presentation).
3. Subjects with high levels of anxiety responded to ADHD treatment similarly to subjects with low levels of anxiety.
4. The presence of anxiety did not affect attrition from clinical trials and thus may not be a risk factor for leaving treatment programs.
5. Anxiety symptoms improved during ADHD clinical trials, but not as a direct response to the medications used.

Acknowledgments This material is the result of work supported by GlaxoSmithKline; Eli Lilly & Company; Medice, Germany; NIMH, USA; Cephalon; Sandoz; Solvay; Astra-Zenica; Bristol Myers Squibb; and Ciba-Geigy. This reanalysis was funded independently.

Compliance with Ethical Standards

Conflict of Interest Frederick W. Reimherr reports research support from GlaxoSmithKline; Eli Lilly & Company; Medice, Germany; NIMH, USA; Cephalon; Sandoz; Solvay; Astra-Zenica; Bristol Myers Squibb; and Ciba-Geigy. Barrie K. Marchant, Thomas E. Gift, and Tammy A. Steans each declare no potential conflicts of interest.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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