Published in final edited form as:

J Clin Psychiatry. 2010 December ; 71(12): 1612–1616. doi:10.4088/JCP.09m05344pur.

How Representative are Participants in a Clinical Trial for ADHD? Comparison With Adults From a Large Observational Study

Craig B.H. Surman, M.D.^a, Michael C. Monuteaux, Sc.D.^a, Carter R. Petty, M.S.^a, Stephen V. Faraone, Ph.D.^b, Thomas J. Spencer, M.D.^a, Nicole F. Chu, B.A.^a, and Joseph Biederman, M.D.^a

^a Clinical and Research Program in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Yawkey Center for Outpatient Care, YAW-6A-6900, 32 Fruit Street, Boston, MA 02114-3139, USA

^b Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, 13210

Abstract

OBJECTIVE—Clinical trials have demonstrated that pharmacotherapies can safely treat ADHD in adulthood. Eligibility criteria in these trials may significantly limit their external validity by excluding a significant portion of adults with ADHD in the general population. In particular, exclusion criteria may frequently exclude individuals with comorbid mental health conditions, which are common in the adult ADHD population.

METHOD—The authors addressed the representativeness of clinical trials by comparing 146 adult Clinical Trial participants with DSM-IV ADHD, and a Community Sample comprised of 124 adults with DSM-IV ADHD and 123 non-ADHD controls. Subjects were compared on socioeconomic status, Hollingshead Occupational code, cognitive measures, lifetime psychopathology and global assessment of function (GAF) ratings.

RESULTS—Adults with ADHD in the Community Sample had higher rates of lifetime psychiatric comorbidity, lower GAF, and lower occupational codes than those in the Clinical Trial. The clinical trial eligibility criteria would have excluded 61% of Community Sample ADHD adults. This excluded portion of the Community sample had higher rates of lifetime psychiatric comorbidity and lower GAF than clinical trial participants.

CONCLUSIONS—Adults with ADHD participating in the Clinical Trial had less evidence of functional impairment and endorsed less psychiatric comorbidity than the majority of Community Sample subjects with ADHD. This suggests that findings from clinical trials may have limited external validity for adults with ADHD in the general population, particularly for those adults with ADHD with the greatest burden of comorbid psychopathology.

II. Introduction

In recent years, several clinical trials for adults with ADHD have contributed to the advancement of safe and effective treatment for this disorder. However, because clinical trials have inclusion and exclusion criteria, it is possible that subjects participating in these

Address correspondence and reprint requests to: Craig Surman MD, Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Suite 2000, 185 Alewife Brook Parkway, Cambridge, MA, 02138; csurman@partners.org.

clinical trials are not representative of the larger population of adults with ADHD in the community. Of particular concern is the routine exclusion of subjects with comorbid psychiatric disorders from clinical trials of treatments for ADHD in adults, which are common in adults with ADHD in the general population.

Whether adults with ADHD participating in clinical trials are representative of the greater population of individuals with the disorder has implications for the external validity of these studies. If subjects with ADHD participating in clinical trials differ from subjects with ADHD in the general population, evidence from clinical trials may not provide accurate guidance for practitioners treating adults with ADHD that would have been excluded from clinical trials.

The main aim of the present study was to investigate whether adults with ADHD participating in clinical trials are representative of adults with ADHD in the community. To this end, we systematically identified and compared clinical correlates of adults with ADHD participating in a clinical trial and subjects with ADHD identified in a large community observational study. We hypothesized that subjects ascertained from the community will manifest higher levels of psychosocial impairments and psychiatric comorbidity than those participating in a clinical trial.

III. Methods

The Clinical Trial participants consisted of 146 adults with ADHD between 19 and 60 years of age recruited for participation in a double-blind, randomized, placebo controlled, six week trial of methylphenidate ascertained from clinical referrals and advertisements in the greater Boston area¹. Subjects had to satisfy full diagnostic criteria for DSM-IV ADHD based on clinical assessment and confirmed by structured diagnostic interview². We excluded potential subjects if they had clinically significant chronic medical conditions, abnormal baseline laboratory values, Intelligence Quotient (IQ) less than 80, delirium, dementia, or amnesic disorders, current impairing psychiatric condition other than ADHD (i.e. current major depression, panic disorder, or generalized anxiety disorder), history of a clinically unstable psychiatric condition (i.e., history of bipolar disorder or psychosis, suicidality), drug or alcohol abuse or dependence within the six months preceding the study, or previous adequate trial of stimulant (> 0.5 mg/kg/day of methylphenidate or equivalent). Current use of psychotropics, other than stable treatment with selective serotonin reuptake inhibitors, was also exclusionary. We also excluded pregnant or nursing females from participation.

The Community sample consisted of 124 subjects ascertained as part of a naturalistic study of ADHD in adults between the ages of 18 and 553. These subjects were ascertained from referrals to the Massachusetts General Hospital and advertisements in the greater Boston area. All subjects met full DSM-IV criteria for ADHD on the structured diagnostic interview², with onset of symptoms by age 7. Subjects were excluded if they had major sensorimotor handicaps (i.e. deafness, blindness) or psychosis. Non-ADHD controls were recruited through advertisements in the greater Boston area.

Both studies excluded subjects with inadequate command of the English language, or IQ less than 80, as measured by an IQ estimate from the Block Design and Vocabulary subtests of the Wechsler Adult Intelligence Scales-Revised⁴. No ethnic or racial group was excluded in these studies. These studies were approved by the institutional review board and all subjects completed a written informed consent process before inclusion in the study.

ASSESSMENT MEASURES

Subjects in both studies were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)⁵ supplemented with modules from the Kiddie Schedule for Affective Disorder and Schizophrenia for School-Age Children- Epidemiologic Version (K-SADS-E) to assess ADHD and other childhood disorders⁶. We conducted direct interviews with subjects. We considered a disorder positive if DSM-IV diagnostic criteria were unequivocally met. Although standardized algorithms were used to determine each diagnosis, interviewers conducting the assessment needed a mechanism to determine the clinical relevance of symptoms when subjects were only able to provide unclear or imprecise information. Thus, a committee of board-certified child and adult psychiatrists, who were blind to the subject's ADHD status, referral source and all other data, resolved diagnostic uncertainties. Diagnoses presented for review were considered positive only when the committee determined that diagnostic criteria were met to a clinically meaningful degree. We estimated the reliability of the diagnostic review process by computing kappa coefficients of agreement for clinician reviewers. For these diagnoses, the median reliability between individual clinicians and the review committee assigned diagnoses was .87. Kappa coefficients for individual diagnoses included the following: ADHD (1.0), conduct disorder (1.0), major depression (1.0), bipolar (0.78), separation anxiety (0.89), agoraphobia (.80), panic (.77), substance use disorder (1.0), and tics/Tourette's (0.68).

The interviewers were blind to the subject's ascertainment group and all prior assessments. The interviewers had undergraduate degrees in psychology and were extensively trained. First, they underwent several weeks of classroom style training, learning interview mechanics, diagnostic criteria and coding algorithms. Then they observed interviews by experienced raters and clinicians. They subsequently conducted at least six practice (non-study) interviews and at least three study interviews while being observed by senior interviewers. Trainees were not permitted to conduct interviews independently until they executed at least three interviews that achieved perfect diagnostic agreement with an observing senior interviewer. Joseph Biederman, MD supervised the interviewers throughout the study. We computed kappa coefficients of agreement by having experienced, board certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audio taped interviews. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was .98. Kappa coefficients for individual diagnoses included: ADHD (0.88), conduct disorder (1.0), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (.95), substance use disorder (1.0), and tics/Tourette's (0.89).

Interviewers assessed the degree of impairment on daily functioning associated with each disorder that subjects endorsed on a three-level ordinal scale: minimal (i.e. little to no impairment), moderate (i.e. difficulties in daily life tasks), or severe (i.e. unable to perform essential daily tasks). We analyzed major depression only if the depressive episode was associated with severe impairment, in order to avoid false positive diagnoses. This is consistent with prior research methods^{7,8}.

Socioeconomic status (SES) was measured by the Hollingshead measures – where occupational and educational status are coded between 1 and 7, with higher numbers reflecting lower social status, and these items are weighted to produce a total SES score, with low values indicating high SES⁹. As a measure of overall functioning, we used current and past lowest Global Assessment of Functioning (GAF).

STATISTICAL ANALYSIS

Comparisons were made between subjects with ADHD from the clinical trial (Clinical Trial ADHD sample, N=146), subjects with ADHD from the naturalistic study (Community Sample ADHD, N=124), and non-ADHD controls from the naturalistic study (Community Sample non-ADHD, N=123). Age and gender were compared between the groups to allow significant differences to be controlled for in all subsequent analyses. Comparisons were also made between the Clinical Trial ADHD group, subjects with ADHD from the naturalistic study who would have met inclusion criteria for the clinical trial (Screened-In, N=48), and subjects with ADHD from the naturalistic study who would have been excluded from the clinical trial (Screened-Out, N=76). Linear regression was used to analyze continuous variables (e.g. full scale IQ), logistic regression was used for binary variables (e.g. individual diagnoses), negative binomial regression was used for count variables (e.g. number of comorbidities), and ordered logistic regression was used for ordinal variables (e.g. SES).

We also compared Clinical Trial subjects with Community Sample subjects who were likely to have met the inclusion and exclusion criteria for the clinical trial. We categorized individuals from the Community Sample as “Screened Out” who met criteria for current subthreshold or full psychosis, severely impairing major depression, generalized anxiety, panic disorder, agoraphobia, anorexia, bulimia, alcohol or drug abuse or dependence, or bipolar disorder. Individuals were also excluded who met criteria for any alcohol or drug abuse or dependence in the past two years.

IV. Results

SOCIODEMOGRAPHIC CHARACTERISTICS OF THE SAMPLE

Clinical Trial subjects and Community Sample ADHD subjects were both significantly more likely to be older than the Community Sample non-ADHD group (Tables 1 and 2). Thus, all subsequent analyses controlled for these variables.

COMPARISON OF NATURALISTIC STUDY PARTICIPANTS AND SUBJECTS FROM THE CLINICAL TRIAL

As shown in Table 2, with the exception of cigarette dependence, rates of all other lifetime psychiatric comorbid disorders assessed were higher in the Community Sample ADHD group than the Clinical Trial group. Individuals from the Community Sample also had a significantly higher mean number of comorbidities than individuals with ADHD from the Clinical Trial Sample.

In addition, relative to the Community Sample non-ADHD group, the Community Sample ADHD group had significantly higher rates of all studied comorbidities, whereas the Clinical Trial sample only had significantly higher rates of Bipolar Disorder, Alcohol Dependence, Smoking Dependence and Antisocial Personality Disorder.

Current and past GAF scores were significantly more impaired in individuals with ADHD from the Community Sample than in those from the Clinical Trial sample. Individuals from the Community Sample had significantly lower occupation (lower Hollingshead occupation code) and lower socioeconomic status (higher Total Hollingshead SES score) than Clinical Trial subjects. There were no significant differences identified between the Community Sample and Clinical Trial ADHD groups on IQ, WRAT arithmetic and WRAT reading scores.

ADHD subjects from both groups had significantly more impaired WRAT arithmetic, past GAF, and current GAF scores, as well as lower educational attainment (lower education code) than community sample non-ADHD individuals. Although occupational and socioeconomic status was lower for subjects with ADHD from the Community Sample than in the non-ADHD Community Sample (as reflected in higher Total SES score and lower occupation Hollingshead code) there was no significant difference in the Hollingshead socioeconomic or occupation codes between the Clinical Trial group and the non-ADHD Community Sample.

COMPARISON OF COMMUNITY PARTICIPANTS WITH ADHD WHO WOULD AND WOULD NOT HAVE BEEN ELIGIBLE FOR THE CLINICAL TRIAL

As shown in Table 3, 61% of the ADHD Community Sample subjects fell into the Screened-Out category because they were unlikely to have met inclusion and exclusion criteria for the clinical trial at their time of assessment. These Screened-Out subjects had significantly higher rates of all assessed lifetime psychopathologies than both the Screened-In subjects who would have been eligible for the clinical trial and Clinical Trial participants. Major depression was the only lifetime psychopathology that was significantly more common among Clinical Trial participants than subjects who Screened-In from the community. As detailed in Table 3, Screened-Out subjects from the Community Sample had significantly more impaired mean current and past GAF than the Screened-In subjects and Clinical Trial subjects. In contrast, there was no significant difference between the mean current and past GAF scores of the Community Sample Screened-In group and that of the Clinical Trial Sample. Hollingshead socioeconomic status was significantly higher in both the Clinical Trial and Screened-In samples than the Screened-Out sample (as reflected in lower Total SES Hollingshead scores). The Clinical Trial sample had lower average occupational attainment than in the Screened-Out Community Samples (as reflected in higher Hollingshead Occupation code).

V. Discussion

This study evaluated whether adults with ADHD participating in clinical trials are representative of other adults with ADHD in the community. Measures of psychopathology and psychosocial functioning revealed that adults with ADHD in a clinical trial differed significantly from adults with ADHD in a community sample. Furthermore, a majority of the adults from our community sample would not have been eligible for the clinical trial. These findings suggest that results from clinical trials for adults with ADHD may not generalize to subjects with ADHD in the community.

Our analysis revealed that adults with ADHD who were recruited for a clinical trial had a significantly lower burden of all studied lifetime psychiatric comorbidities, except nicotine dependence, compared to other adults with ADHD in the community. They also had significantly better current and lifetime global assessment of functioning scores, and significantly higher occupation level. Differences between the Clinical Trial and Community Sample ADHD subjects are further emphasized by our finding that Community ADHD subjects, but not Clinical Trial subjects, had higher rates of major depression, multiple anxiety disorder, substance dependence, and lower occupational level and socioeconomic status than non-ADHD Community Sample subjects.

Our analysis also showed that 61% of ADHD individuals in the Community Sample would not have been eligible to participate in the clinical trial. Compared to eligible subjects, ineligible individuals had a higher burden of all psychopathologies studied, more impaired current and past global functioning, and lower socioeconomic status. Clinical Trial subjects did not differ from the trial-eligible Community subjects on any of the clinical or functional

domains studied except on lifetime presence of major depression, which was lower in the Clinical Trial subjects. Relative to Community ADHD subjects ineligible for the trial, Clinical Trial subjects had significantly lower rates of all lifetime psychopathologies, had higher current and past global functioning mean scores, and higher occupational and socioeconomic status.

The pattern of psychopathological and functional impairments in adults with ADHD from our Community sample is representative of impairments demonstrated in both epidemiologic and clinical studies of adults with ADHD. For example, the National Comorbidity Survey Replication (NCS-R), an epidemiologic assessment of United States adults between the ages of 18 and 44, found that adults with ADHD are at higher risk than non-ADHD subjects to have experienced another mental health condition in the past year with odds ratios of 2.7–7.5 for mood disorders, 1.5–5.5 for anxiety disorders, and 1.5–7.9 for substance use disorders¹⁰. Studies of comorbidity in clinical samples of adults with ADHD have similarly found higher rates of psychopathology when compared to samples of adults without ADHD^{11, 12, 13}. Studies have also clearly demonstrated a significant impact of ADHD on occupational, educational, and relationship roles^{2, 10, 14, 15}. Taken together, this evidence supports our conclusion that clinical trials have limited representativeness of community subjects with ADHD and that the findings reported in clinical trials may not generalize to community samples. It is possible that different estimates of efficacy and tolerability would be found if all subjects with ADHD were to be included in clinical trials. Expansion of eligibility for clinical trials in adult ADHD may extend evidence-based interventions for this population and may provide more externally valid information on how to best treat this disorder in the community.

Our findings need to be viewed in light of some methodological limitations. We did not screen our community sample for clinically significant medical comorbidity, which excluded participants from the clinical trial. Our assessment of representativeness was limited to the dimension of mental health. More comprehensive assessment of representativeness of clinical trial participants relative to community subjects would have identified medical conditions and treatments that are often exclusionary for trial participation. This would typically include conditions for which sympathomimetics are contraindicated, such as hypertension and hyperthyroidism, and medications that impair cognitive function such as sedatives. Our report also does not assess the extent to which the clinical trial would have excluded clinically significant presentations that do not meet criteria as Axis I conditions, such as suicidality or severe personality disorders. In addition, since the vast majority of participants in our studies were Caucasian, our findings may not generalize to other racial groups. Despite these considerations, we have demonstrated that a typical clinical trial in ADHD adults is limited in its validity for the larger community of adults with ADHD.

Our investigation suggests that typical eligibility criteria in clinical trials for adults with ADHD actually exclude the large subpopulation of adults with ADHD that carries the greatest comorbidity burden. The higher rate of psychopathology in these excluded individuals also implies that clinical trials for adults with ADHD are not including adults with ADHD who have the greatest need for treatment. Intervention trials with less restrictive inclusion criteria could provide more externally valid information, and could extend the ability of practitioners to effectively manage ADHD in the general population. This could be accomplished through clinical trials that included individuals with the most common psychiatric and medical comorbidities complicating ADHD, such as mood and substance use disorders, and common stabilized conditions that may be exacerbated by sympathomimetic ADHD agents, such as hypertension.

Acknowledgments

Data analyzed in this work comes from studies supported by grants from the National Institute of Health to Stephen Faraone (R01MH57934) and to Thomas Spencer (R29MH57511). Novartis Pharmaceuticals Corporation supported a portion of the cost of active medication in the latter study. There were no other sponsors of this study.

Author Disclosures

Dr. Surman has or is receiving research support from Abbott, Alza, Cephalon, Eli Lilly, the Hilda and Preston Davis Foundation, McNeil Pharmaceuticals, Merck, New River, National Institutes of Health, Organon, Pfizer, Shire Laboratories, Inc, and Takeda. He is currently or has been a speaker for Janssen-Ortho, McNeil Pharmaceuticals, Novartis Pharmaceuticals, and Shire Laboratories, Inc. He is currently or has been a consultant/advisor for McNeil Pharmaceuticals, Shire Laboratories, Inc, and Takeda.

Nicole Chu, Michael Monuteaux, and Carter Petty report no conflicting interests.

Dr. Thomas Spencer receives research support from the following sources: Shire Laboratories Inc, Cephalon, Eli Lilly & Company, Glaxo-Smith Kline, Janssen, McNeil Pharmaceuticals, Novartis Pharmaceuticals, Pfizer, and NIMH. He is a speaker for the following speaker's bureaus: Shire Laboratories, Inc, Eli Lilly & Company, Glaxo-Smith Kline, Janssen, McNeil Pharmaceuticals, Novartis Pharmaceuticals. He is on the advisory board for the following pharmaceutical companies: Shire Laboratories Inc, Cephalon, Eli Lilly & Company, Glaxo-Smith Kline, Janssen, McNeil Pharmaceuticals, Novartis Pharmaceuticals, and Pfizer.

Dr. Stephen Faraone has received research support and consults to Shire Pharmaceutical Development. He receives grant support from Eli Lilly & Company, and the National Institutes of Health.

Dr. Joseph Biederman is currently receiving research support from the following sources: Alza, AstraZeneca, Bristol Myers Squibb, Eli Lilly & Company, Janssen, McNeil Pharmaceuticals, Merck, Organon, Otsuka, Shire, NIMH, and NICHD. In previous years, he has received research support, consultation fees, or speaker's fees for/ from the following additional sources: Abbott, AstraZeneca, Celltech, Cephalon, Eli Lilly & Company, Esai, Forest, Glaxo, Gliatech, Janssen, McNeil Pharmaceuticals, NARSAD, NIDA, New River, Novartis, Noven, Neurosearch, Pfizer, Pharmacia, The Prechter Foundation, Shire, The Stanley Foundation, UCB Pharma, Inc., and Wyeth.

References

1. Spencer T, Biederman J, Wilens T, et al. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005; 57(5):456–63. [PubMed: 15737659]
2. Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry*. 1993; 150(12):1792–1798. [PubMed: 8238632]
3. Faraone SV, Biederman J, Spencer T, et al. Diagnosing adult attention deficit hyperactivity disorder: are late onset and subthreshold diagnoses valid? *Am J Psychiatry*. 2006; 163:1720–1729. [PubMed: 17012682]
4. Wechsler, D. The Psychological Corporation. San Antonio, TX: 1981. Manual for the Wechsler Adult Intelligence Scale—Revised. Wechsler Adult Intelligence Scale III..
5. First, M.; Spitzer, R.; Gibbon, M., et al. Structured Clinical Interview for DSM-IV Axis I Disorders. American Psychiatric Press; Washington, DC: 1997.
6. Orvaschel, H. Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic Version. Nova Southeastern University, Center for Psychological Studies; Ft Lauderdale, FL: 1994.
7. Gershon ES, Hamovit J, Guroff JJ, et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry*. 1982; 39(10):1157–1167. [PubMed: 7125846]
8. Leckman JF, Sholomskas D, Thompson D, et al. Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch Gen Psychiatry*. 1982; 39:879–883. [PubMed: 7103676]
9. Hollingshead, AB. Four Factor Index of Social Status. Yale University Press; New Haven, CT: 1975.

10. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006; 163:716–723. [PubMed: 16585449]
11. Biederman J, Faraone SV, Spencer T, et al. Gender differences in a sample of adults with attention deficit hyperactivity disorder. *Psychiatry Res*. 1994; 53:13–29. [PubMed: 7991729]
12. Biederman J, Faraone SV, Monuteaux MC, et al. Gender effects on attention-deficit/hyperactivity disorder in adults, revisited. *Biol Psychiatry*. 2004; 55:692–700. [PubMed: 15038997]
13. McGough JJ, Smalley SL, McCracken JT, et al. Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. *Am J Psychiatry*. 2005; 162(9):1621–1627. [PubMed: 16135620]
14. Manuzza S, Klein RG, Bessler A, et al. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. *Arch Gen Psychiatry*. 1993; 50(7):565–576. [PubMed: 8317950]
15. Murphy K, Barkley RA. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. *Compr Psychiatry*. 1996; 37(6):393–401. [PubMed: 8932963]

Table 1

Age and gender of adults with and without ADHD from a naturalistic observational community study versus a randomized, double blind clinical trial.

	Community non-ADHD N=123	Clinical Trial ADHD N=146	Community ADHD N=124	Test Statistic	p-value
Age	29.9±9.0 ^{ab}	37.1±10.2	36.1±10.8	F _(2,388) =19.9	<0.001
Gender (Male)	56 (46)	88 (60)	64 (52)	$\chi^2_{(2)}=8.4$	0.051

^a p<0.05 versus Clinical Trial ADHD

^b p <0.05 versus Community ADHD

Table 2

Comparison of adults with and without ADHD from a naturalistic observational community study versus a randomized, double blind clinical trial sample.

	Community non-ADHD N=123	Clinical Trial ADHD N=146	Community ADHD N=124	Test Statistic	p-value
ADHD Symptoms	---	13.8±3.1	14.2±2.8	$z=0.68$	0.50
<u>Lifetime Comorbidity</u>					
Bipolar Disorder	0 (0) ^{ab}	6 (4) ^b	23 (19)	Fisher's Exact	<0.001
Major Depression ¹	7 (6) ^b	9 (6) ^b	39 (31)	$\chi^2_{(2)}=35.34$	<0.001
Multiple Anxiety Disorders ²	13 (11) ^b	18 (12) ^b	43 (35)	$\chi^2_{(2)}=26.72$	<0.001
Alcohol Dependence	7 (6) ^{ab}	24 (17) ^b	35 (28)	$\chi^2_{(2)}=17.02$	<0.001
Substance Dependence	7 (6) ^b	12 (8) ^b	27 (22)	$\chi^2_{(2)}=15.79$	<0.001
Smoking Dependence	19 (15) ^{ab}	51 (35)	54 (44)	$\chi^2_{(2)}=15.30$	<0.001
Antisocial Personality	3 (2) ^{ab}	17 (12) ^b	28 (23)	$\chi^2_{(2)}=17.26$	<0.001
Number of Comorbidities	0.5±0.8 ^{ab}	1.0±1.2 ^b	2.0±1.7	$\chi^2_{(2)}=78.2$	<0.001
<u>Cognitive Function</u>					
Full Scale IQ	116.2±12.6	113.7±14.2	114.2±14.1	$F_{(2,373)}=0.10$	0.91
WRAT Arithmetic	106.8±12.5 ^{ab}	98.5±11.7	98.4±14.3	$F_{(2,378)}=11.34$	<0.001
WRAT Reading	108.4±8.7	105.2±8.6	106.2±10.4	$F_{(2,377)}=2.22$	0.11
<u>Other Functional Measures</u>					
Past GAF Score	60.0±8.1 ^{ab}	52.3±6.2 ^b	46.7±7.3	$F_{(2,386)}=94.20$	<0.001
Current GAF Score	68.2±4.7 ^{ab}	60.0±4.9 ^b	56.4±7.4	$F_{(2,386)}=127.26$	<0.001
Hollingshead Total SES	1.7±0.7 ^b	1.9±0.9 ^b	2.2±1.0	$\chi^2_{(2)}=21.35$	<0.001
Hollingshead Education	6.2±0.7 ^{ab}	5.5±1.0	5.6±1.0	$\chi^2_{(2)}=37.43$	<0.001
Hollingshead Occupation	6.6±1.6 ^b	6.5±1.8 ^b	5.5±2.2	$\chi^2_{(2)}=21.98$	<0.001

Defined by 2 or more of the following: avoidant disorder, separation anxiety disorder, specific phobia, generalized anxiety disorder, social phobia, agoraphobia, panic disorder, posttraumatic stress disorder, and obsessive-compulsive disorder

¹ All analyses adjusted for age and sex

² Major Depression with severe impairment

^a p<0.05 versus Clinical Trial ADHD

^b p<0.05 versus Community ADHD

Table 3

Naturalistic community sample adults stratified by clinical trial screening criteria

	Clinical Trial ADHD N=146	Community Screened-in N=48	Community Screened-out N=76	Test Statistic	p-value
ADHD Symptoms	13.8±3.1	14.0±2.9	14.2±2.8	$\chi^2(2)=0.56$	0.75
<u>Lifetime Comorbidity</u>					
Bipolar Disorder	6 (4) ^b	3 (6) ^b	20 (26)	$\chi^2(2)=20.83$	<0.001
Major Depression¹	9 (6) ^{ab}	8 (17) ^b	31 (41)	$\chi^2(2)=33.86$	<0.001
Multiple Anxiety Disorders²	18 (12) ^b	8 (17) ^b	35 (46)	$\chi^2(2)=27.28$	<0.001
Alcohol Dependence	24 (17) ^b	9 (19) ^b	26 (34)	$\chi^2(2)=11.76$	0.003
Substance Dependence	12 (8) ^b	5 (10) ^b	22 (29)	$\chi^2(2)=16.55$	<0.001
Smoking Dependence	51 (35) ^b	12 (31) ^b	39 (51)	$\chi^2(2)=7.92$	0.02
Antisocial Personality	17 (12) ^b	6 (12) ^b	22 (29)	$\chi^2(2)=12.64$	0.002
Number of Comorbidities	1.0±1.2 ^b	1.1±1.4 ^b	2.6±1.7	$\chi^2(2)=66.86$	<0.001
<u>Cognitive Function</u>					
Full Scale IQ	113.7±14.2	115.1±15.0	113.6±13.7	$F_{(2,250)}=0.38$	0.69
WRAT Arithmetic	98.5±11.7	97.8±15.3	98.8±13.7	$F_{(2,255)}=0.05$	0.95
WRAT Reading	105.2±8.6	105.3±11.7	106.9±9.5	$F_{(2,254)}=0.79$	0.46
<u>Other Functional Measures</u>					
Past GAF Score	52.3±6.2 ^b	50.6±6.9 ^b	44.2±6.4	$F_{(2,263)}=41.36$	<0.001
Current GAF Score	60.0±4.9 ^b	61.5±4.5 ^b	53.2±7.0	$F_{(2,263)}=44.70$	<0.001
Hollingshead Total SES	1.9±0.9 ^b	2.0±0.7 ^b	2.4±1.0	$\chi^2(2)=14.82$	<0.001
Hollingshead Education	5.5±1.0	5.8±1.0	5.5±1.0	$\chi^2(2)=2.85$	0.24
Hollingshead Occupation	6.5±1.8 ^b	6.1±1.8	5.2±2.4	$\chi^2(2)=15.81$	<0.001

Defined by 2 or more of the following: avoidant disorder, separation anxiety disorder, specific phobia, generalized anxiety disorder, social phobia, agoraphobia, panic disorder, posttraumatic stress disorder, and obsessive-compulsive disorder

¹ All analyses adjusted for age and sex

² Major depression with severe impairment

^a p<0.05 versus Screened-in Community

^b p<0.05 versus Screened-out Community