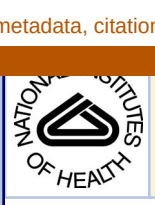



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# Three-Year Latent Class Trajectories of Attention-Deficit/ Hyperactivity Disorder (ADHD) Symptoms in a Clinical Sample Not Selected for ADHD

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## Abstract

**Objective—**This study aims to examine trajectories of attention-deficit/hyperactivity disorder (ADHD) symptoms in the Longitudinal Assessment of Manic Symptoms (LAMS) sample.

**Method—**The LAMS study assessed 684 children aged 6-12 with Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) and rating scales semi-annually for 3 years. Though selected for elevated manic symptoms, 526 had baseline ADHD diagnoses. With growth mixture modeling (GMM), we separately analyzed inattentive and hyperactive/impulsive symptoms, covarying baseline age. Multiple standard methods determined optimal fit. Chi-square and Kruskal-Wallis analysis of variance (ANOVA) compared resulting latent classes/trajectories on clinical characteristics and medication.

**Results—**Three latent class trajectories best described inattentive symptoms; 4 classes best described hyperactive/impulsive symptoms. Inattentive trajectories maintained their relative position over time. Hyperactive/impulsive symptoms had 2 consistent trajectories (least and most severe). Another (4.5%) started mild, then escalated; and a fourth (14%) started severe but improved dramatically. The improving trajectory had the highest rate of ADHD and lowest rate of bipolar diagnoses. Three-fourths of the mildest inattention class were also in the mildest hyperactive/impulsive class; 72% of the severest inattentive class were in the severest hyperactive/impulsive class; but the severest inattention class also included 62% of the improving hyperactive-impulsive class.

**Conclusion—**An ADHD rather than bipolar diagnosis prognosticates a better course of hyperactive/impulsive, but not inattentive, symptoms. High overlap of relative severity between inattention and hyperactivity/impulsivity confirms the link between these symptom clusters. Hyperactive/impulsive symptoms wane more over time. Group means are insufficient to understand individual ADHD prognosis. A small subgroup deteriorates over time in hyperactivity/impulsivity and needs better treatments than currently provided.

### Keywords

ADHD; GMM; longitudinal symptoms; inattention; hyperactivity/impulsivity

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder manifested in symptoms of inattentiveness, disorganization, distractibility, overactivity, and impulsiveness. The *DSM*, both VI and 5,[1-2] lists 9 inattentive and 9 hyperactive/impulsive symptoms. Most follow-up studies of participants diagnosed with ADHD as children show persistence of inattentive symptoms (Inattn) and considerable waning of hyperactive-

impulsive symptoms (HA/Imp), with more persistence of impairment than of symptoms and worse outcomes than comparison participants without ADHD.[3-6] In a twin study, hyperactivity/impulsivity (HA/Imp) in middle childhood predicted inattentiveness (Innattn) in adolescence, but Inattn in childhood did not predict HA/Imp in adolescence.[5]

Although most follow-up studies simply reported the mean symptom levels or diagnostic proportions for the sample at various follow-up times, some tracked latent classes of symptom trajectories over time with growth mixture modeling (GMM). A literature search found 6 reports showing ADHD latent class symptom trajectories over time (Table 1), using various measures of symptom severity, varied foci (inattention, hyperactivity, all ADHD symptoms, or a proxy for *DSM* symptoms) and various follow-up times, from 12 hours in a laboratory school to 12 years. The most common number of latent classes found was 3.

The largest GMM sample tracked 12,486 twins and 1,346 single births from age 6 to 12, focusing on inattentive symptoms separately by sex.[7] It identified 3 trajectories in both boys and girls (stable low, low-increasing, and high-decreasing, the latter two crossing). The only apparent difference by sex was that trajectories started and ended lower for girls, with similar slopes. Trajectories were also similar for twins and singletons.

The second-largest sample was a community sample of 754 children (half high-risk) recruited in kindergarten.[8] It examined the relationship of ADHD symptoms to early illicit drug use. It also revealed a 3-class model for 6-year ADHD symptom trajectories. Two started high: one with symptom decrease in third grade, then increase in 6$^{th}$ grade, and one with increase, then decrease. A third class showed no or minimal symptoms throughout. Class 1 (decrease, then increase) demonstrated significantly earlier onset of illicit drug use than Class 3; Class 2 (increase, then decrease) was not significantly different from either of the other classes in drug use. The results held when conduct problems were covaried.

The largest diagnosed ADHD sample (N=486, age 7-10 at baseline, all with combined type ADHD) was from the National Institute of Mental Health (NIMH) Multimodal Treatment Study of Children with ADHD (MTA), done on the mean of all 18 *DSM-IV* symptoms.[9] It also resulted in 3 latent classes over a 3-year period, all starting prior to treatment at an item mean of about 2.0 (range 1.9-2.1) on a 0-3 severity scale and influenced by the 14 months of treatment provided to three quarters of the MTA children. Class 1, 34% of the sample, improved by only about -0.4 point (item mean) with 14 months of treatment, but maintained that gain at 24 months and improved further by 36 months, suggesting a good eventual prognosis. Class 2, 52% of the sample, was slightly milder at baseline than the other two classes (1.9 vs. 2.1), showed a sharp symptom decline to about 0.8 with 14 months of treatment, and consistently maintained that improvement to 36 months. Class 3, 14% of the sample, showed as much improvement as Class 2 with 14 months of treatment but then regressed steadily and by 36 months had almost returned to baseline.

Jester et al. tracked hyperactivity/inattention and aggressive behavior in 335 children of alcoholic and nonalcoholic fathers for 12 years from aged 3-5 to aged 16 at 3-year intervals in a high-risk prospective study of substance use and comorbid problems.[10] Aggressive behavior decreased throughout childhood and adolescence, but HA/Inattn behaviors

remained constant. GMM found 2 trajectories for HA/Inattn and 2 for aggression. The worse HA/Inattn trajectory was predicted by lower emotional support and intellectual stimulation by parents. The worse aggression trajectory was predicted by family conflict and lack of cohesiveness. When 4 classes were developed from a 2X2 combination of the 2 hyperactivity/inattention and 2 aggression trajectories (healthy=low on both trajectories; HA/Inattn =high onHA/Inattn , low on aggression; aggressive=high on aggression, low onHA/Inattn ; and comorbid, high on both), the aggressive and comorbid classes had the highest risk of alcohol problems, and the healthy class, the lowest.[11]

Sonuga-Barke et al. found 3 trajectories of ADHD symptoms over a 12-hour day (low and stable, high and increasing, and intermediate and increasing) in 184 children with diagnosed ADHD while taking placebo in a laboratory school study.[12] This demonstrated variability in diurnal course. The 3 classes responded differentially to the two methylphenidate preparations being compared.

Although not using GMM, Lubke et al. derived latent class attention-problem profiles separately at 7, 10, and 12 years of age in several thousand children.[13] Three classes were found at each age. The most severe class contained all the children who had diagnosed combined-type ADHD and the mild class had no diagnosed ADHD. Inspection of the graphs for the 3 ages suggests waning of HA/Imp problems, but not concentration problems.

The Longitudinal Assessment of Manic Symptoms (LAMS) study provides another longitudinal sample large enough (N=684) for a GMM analysis.[14-15] Although not selected for ADHD, 538 of the 707 children with baseline assessments in this sample had an initial ADHD diagnosis (307 combined type, 108 inattentive type; 49 hyperactive-impulsive type, 74 not otherwise specified, or NOS). See “Method” for further details. This sample differs in four ways from most of the others: 1) Unlike the Robbers, Malone, Jester, and Lubke samples,[7-8,10-11,13] it has rigorous standardized clinical diagnoses of ADHD. 2) However, unlike the Swanson and Sonuga-Barke samples,[9,12] it was not selected for a diagnosis of ADHD, but for related (manic) symptoms and therefore includes some children without an ADHD diagnosis but with some ADHD symptoms. This could provide some insight into what happens with subdiagnostic ADHD symptoms.[16-17] 3) The age range (6-12 at entry) is broader than all except Sonuga-Barke’s.[12] 4) Assessment points --every 6 months-- are more frequent than all except Sonuga-Barke’s.[12] Thus the LAMS sample allows us to expand on previous reports in several ways, including examination of Inattn and HA/Imp separately, across a broad range of age, diagnoses, and initial severity, with more intensive repetition of follow-up assessment. We tested the following hypotheses:

1. Without the influence of a consistent and specified study treatment, there will be less visibly dramatic differences in the shapes of latent class trajectories in this sample than in the MTA; in particular, the 14-month inflection seen in the MTA trajectories will not be seen.
2. Children with the most severe initial symptoms will remain the most severe at the end of three years; i.e., initial relative severity will be the strongest determinant of relative end severity.[18]

3. HA/Imp symptoms will decrease more over time than Inattn symptoms, consistent with developmental trends for improvements in inhibitory mechanisms,[19] as well as trends identified in prior ADHD research.

4. ADHD diagnoses will be significantly less prevalent in the lowest ADHD symptom severity class.

## Method

### Study Sites and Participant Ascertainment

The data analyzed here are from the first three years of the NIMH-supported LAMS study, approved by the Institutional Review Boards at each of the four university-affiliated LAMS sites. Written informed consent and assent were obtained before any study procedures.

The LAMS study is a 4-site epidemiological study designed to track a cohort of children aged 6-12 selected mainly for having elevated symptoms of mania (ESM+), to determine characteristics of pediatric bipolar disorder and predictors of eventual development of bipolar disorder (BD).[14] Annual assessments included a comprehensive diagnostic and functional battery, with abbreviated, more focused assessments at the 6-month intervals.

Participants were recruited from 9 child outpatient mental health clinics (2 in Northeast Ohio, 1 in Pittsburgh, 5 in Columbus, and 1 in Cincinnati). Patients aged 6 to 12 years attending new evaluations at the respective clinics were eligible for screening. Their parents/guardians were asked to complete the Parent General Behavior Inventory – 10 Item Mania Scale (PGBI-10M) to screen for ESM+,[20-21] defined as a score of 12 or more out of a possible 30. PGBI-10M items were scored 0-3 (none to most severe), describing hypomanic, manic, and biphasic symptomatology. They discriminate BD from other diagnoses.[20-21] All patients whose parent/guardian rated them at or above 12 (ESM+) were invited to participate. In addition, a demographically matched comparison group of patients with scores 11 or lower (ESM-) were selected. Of the 707 who had baseline assessment, 685 were eligible to continue longitudinally (those with intellectual or developmental disability were excluded after baseline assessment).

### Assessments

All participants were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Episode (KSADS-PL),[22] with additional mood onset and offset items derived from the Washington University in St. Louis KSADS.[23-24] Diagnoses of bipolar spectrum disorders (BPSD), depression, anxiety, ADHD, and disruptive behavior disorder were derived from the KSADS; and proxy diagnoses of disruptive mood dysregulation disorder (DMDD) were taken from analyses by Axelson et al.[25]

The LAMS study used the following criteria for bipolar disorder-not otherwise specified (BP-NOS): (a) elated mood plus two associated manic symptoms (e.g., grandiosity, decreased need for sleep, pressured speech, racing thoughts, increased goal-directed activity, etc.), or irritable mood plus three associated symptoms; (b) change in the participant's level

of functioning (i.e., increase or decrease of episodes); (c) symptoms present for at least 4 hours within a 24-hour period; and (d) at least 4 episodes of 4 hour duration or a total of 4 days in the child's lifetime. These criteria were also used in the Course and Outcome of Bipolar Youth (COBY) study.[26] A licensed child psychiatrist or psychologist reviewed and confirmed all diagnoses. In addition, interrater reliability of interviewers was checked by rating taped administrations of the K-SADS-PL-W, Children's Depression Rating Scale-Revised (CDRS-R),[27-28] and the Young Mania Rating Scale (YMRS).[29] The kappa for K-SADS-PL-W psychiatric diagnoses was 0.82 and more specifically, the kappa for bipolar diagnoses was 0.93. Demographic information was obtained from parents/guardians. A more detailed description of the baseline assessment and a description of the 707 children and adolescents with baseline assessments are outlined in Findling et al.[15]

## Psychometric Scales

Manic symptoms were assessed by parent report with the Parent General Behavior Inventory –10 Item Mania Scale (PGBI-10M; alpha=.89 in the present sample),[20-21] and by interview of the child and parent with the Young Mania Ratings Scale (YMRS; alpha=.76).[29-33] PGBI-10M items were scored 0-3 (none to most severe), describing hypomanic, manic, and biphasic symptomatology. Examples are: "Has your child experienced periods of several days or more when, although he/she was feeling unusually happy and intensely energetic (clearly more than your child's usual self), he/she was also physically restless, unable to sit still, and had to keep moving or jumping from one activity to another?" or "Have there been periods of several days or more when your child's friends or other family members told you that your child seemed unusually happy or high – clearly different from his/her usual self or from a typical good mood?". This scale discriminates BD from other diagnoses.[20-21] Total scores range from 0 to 30, and a cut score of 12 identified ESM+ children. Functional assessment was measured by the Children's Global Assessment Scale (CGAS).[34] The presence and severity of depressive symptoms were assessed using the Child Depression Rating Scale-Revised (CDRS-R; alpha=.81).[27-28,33] Parent-reported dimensional scores of *DSM-IV* inattentive and hyperactive-impulsive symptoms of ADHD (alpha=.94), symptoms of oppositional defiant disorder (ODD; alpha=.92), and symptoms of conduct disorder (CD; alpha=.81) were examined with the Child and Adolescent Symptom Inventory-4-Parent Version (CASI-4R).[35-36] CASI-4R symptoms are rated 0-3, 3 being the most severe; the item mean for each symptom cluster is usually analyzed. Medication use and other treatments were recorded on the Services Assessment for Children and Adolescents (SACA).[37] The Parent Stress Survey (PSS), a 25-item parent self-report scale designed to assess parental stress due to raising a psychiatrically impaired child,[38] was also used. Each item has a yes-no response, followed by a Likert scale from 0 (not at all stressful) to 4 (very stressful). The total score ranges from 0 (no stress) to 100 (highest stress). Coefficient alpha is 0.87.[38]

## Sample Characteristics

Of the 707 children with baseline LAMS assessment, 621 were EMS+ and 86 were ESM.[15] A majority (n=538) had ADHD while a minority (n=162) had a bipolar spectrum disorder (BPSD), most of them (n=117) with comorbid ADHD. Thus this sample, not selected for ADHD, was dominated by the second-largest group of children with diagnosed ADHD ever

followed longitudinally with serial in-person assessments (the MTA started with 579 ADHD participants).[39] Of the 707 with baseline assessment, 685 are eligible for longitudinal study, and of these, 684 have usable ADHD symptom data, 526 with diagnosed ADHD: 107 inattentive type, 47 HA/Imp type, 302 combined type, and 70 NOS. Of the 684, 178 had a proxy diagnosis of DMDD by Axelson et al.[25]

### Statistical Analyses

Using M-Plus 7, we analyzed GMMs separately on the 9 Inattn symptoms and the 9 HA/Imp symptoms. Both models included baseline age as a covariate. One of the 685 longitudinal participants, a girl with combined type ADHD, had missing ADHD dimensional data for all assessment points and was excluded from analyses. Optimal fit was determined by a combination of Bayes Information Criteria (BIC, raw and adjusted), Aike Information Criteria (AIC), the adjusted Lo-Mendell-Rubin (LMR) likelihood ratio (LR) test, the bootstrap LR test, entropy (Table 1) , and consideration of how clinically interesting the resulting trajectories were. Three latent classes best described Inattn assessments while four latent classes best described HA/Imp assessments. Chi-squared and ANOVA analyses--according to level of measurement-- compared classes on baseline characteristics and medication use at each of the 7 assessment points. Due to non-normality of the continuous outcome variables, the nonparametric Kruskal-Wallis ANOVA was employed for comparison among classes. Cross-tabulation evaluated overlapping membership between Inattn classes and HA/Imp classes. Exploratory analyses comparing class characteristics used alpha = 0.05 for the omnibus test of each domain and set-wise Bonferroni correction for multiple comparisons.

## Results

Based on a priori criteria, the model with optimal fit for Inattn was three classes/trajectories, and for HA/Imp was four classes/trajectories (Table 1). Inattn trajectories (Figure 1, panel A) mainly differed in severity, although there was some modest fluctuation over time in the most severe and least severe trajectories. These at first appeared to regress toward the middle trajectory, which showed no change, but then, with a significant quadratic term for time, trended back toward their own baselines. In contrast, three of the four HA/Imp trajectories (Figure 1, panel B) showed the expected symptom decrease over time and with different slopes; further, three trajectory slopes crossed. Class 2, the only exception to decreasing over time (actually increasing significantly), was <5% of the sample. Of special interest is Class 4, which started relatively severe (item mean ~2.2), then declined steeply. Unfortunately, this favorable slope was only 14% of the sample. Thus for both symptom clusters, Class 1 is the most favorable trajectory (consistently mildest across time) and Class 3, the least favorable (consistently most severe across time). For Inattn, Class 2 is intermediate in severity and consistent over time. For HA/Imp, Class 2 had the least favorable slope (0.12, $p$=0.049; worsening over time) and Class 4 the most favorable slope (-0.59, $p$=0.005; improving notably over time).

Tables 3A and 3B present demographic and clinical comparisons of the different trajectories within each symptom domain, and Table 4 presents medication use by time point. Neither

Inattn nor HA/Imp classes differed significantly in sex, race, ethnicity, depressive disorder, nor anxiety disorder.

Inattn classes differed from each other in 12 ways: 1) the proportion with baseline ADHD diagnosis ($p<0.001$): Class 3 had the most while Class 1 had the fewest, consistent with Hypothesis 4; 2) the proportion with baseline disruptive behavior disorder (ODD or CD) ($p<0.001$); Class 1 had the lowest proportion; 3) the proportion with baseline BPSD diagnosis ($p<0.001$); Class 3 had the highest while Class 2 had the lowest; 4) the proportion that were ESM+ ($p=0.012$); Class 3 had the highest while Class 1 had the lowest proportion; 5) the proportion with proxy DMDD ($p=0.006$): Class 3 had the highest and Class 1 the lowest proportion; 6) manic symptoms as measured on the YMRS and PGBI-10M ($p<0.001$); Class 3 had the highest scores; 7) depressive symptoms on the CDRS-R ($p<0.001$); Class 3 had the highest scores; 8) global functioning, as noted on the baseline C-GAS ($p<0.001$); Class 3 had the lowest functioning; 9) parent stress scores ($p<0.001$: Class 3 was the highest; 10) baseline age ($p=0.028$), with Class 3 being the oldest (9.6 years) and Class 2 the youngest (9.2 years); 11) the proportion receiving stimulants ($p<0.001$), with Class 1 having the lowest proportion at all times (18-29%, compared to 42-57% in Class 3); 12) the proportion receiving any medication ($p=0.045$ to $<0.001$), again with Class 1 having the lowest proportion at all times (42-61%, compared to 67-79% in Class 3).

In summary, Inattn Class 1, with the lowest severity throughout, had the lowest proportion of baseline ADHD and disruptive behavior disorder diagnoses, lowest proportion of ESM+, lowest proportion of DMDD, lowest rating of manic symptoms, lowest proportion of parent stress scores and highest global functioning. Conversely, Class 3, with the most severe Inattn ratings over time and oldest age at entry, had the highest proportion of ADHD, disruptive behavior disorder, DMDD, and BPSD diagnoses, highest proportion of ESM+, worst manic and depressive symptom severity scores, and lowest global functioning.

The four HA/Imp classes differed significantly in nine ways: 1) the proportion with baseline ADHD diagnosis ($p=<0.001$), with Class 4 having the highest rate and Class 1, the lowest; 2) the proportion with disruptive behavior disorder ($p<0.001$), with Class 1 having the lowest proportion; 3) the proportion with a BPSD diagnosis ($p=0.021$), with Class 3 having the highest and Class 1 the lowest; 4) the proportion of ESM+ ($p<0.001$), with Classes 3 and 4 higher than Classes 1 and 2; 5) the proportion with DMDD, with Class 3, the highest and Class 1, the lowest; 6) the proportion with manic symptoms as measured on the YMRS and PGBI-10M ($p<0.001$), with Class 1 having the lowest and Class 3 the highest severity; 7) global functioning as measured by the baseline C-GAS ($p<0.001$), with Class 1 the highest functioning; 8) parent stress severity ($p=0.003$), with Class 3 the most severe; and 9) the proportion receiving stimulants $p<0.001$), with Class 3 (46-61%) and Class 4 (46-52%) having the highest proportions. The proportion taking any medication was significant only at baseline, when Class 1 had the lowest rate (53%).

In sum, Class 1, with the most consistently favorable HA/Imp trajectory, had the lowest proportion of ADHD, disruptive behavior disorder, BPSD, and DMDD diagnoses as well as second-lowest proportion of ESM+, lowest manic symptom scores, lowest parent stress, and highest global functioning. Class 4, which had the steepest decline of HA/Imp symptoms,

had the highest proportion of ADHD diagnoses, second-highest proportion of DMDD, and the second-lowest proportion of BPSD diagnoses, even though it had the highest initial proportion of ESM+.

Cross tabulation of the two latent class groups (Table 5) shows that 77% of the consistently mildest Inattn class (Class 1) falls in the consistently mildest HA/Imp class; and 72% of Inattn Class 3, with consistently severe symptoms, fell into HA/Imp Class 3, which also had consistently severe symptoms. Of note, consistently severe Inattn Class 3 also included 62% of the HA/Imp Class 4, which had dramatically improving symptoms.

## Discussion

The new GMM latent classes presented here complement and contrast with previous GMM analyses. This was the first study to separately track both Inattn and HA/Imp *DSM* symptoms; others tracked either only Inattn symptoms or a composite of Inattn and HA/Imp (Table 1). This study had more frequent assessments than any other longitudinal study. In contrast to the previous reports, which never exceeded 3 latent trajectories, this study found 4 HA/Imp trajectories, possibly because it was the only one to separately track the *DSM* HA/Imp symptoms. This demonstrated different courses of the two symptom clusters over time.

Inspection of graphs shows that hypothesis 1 is supported: there is no sharp decrement at one year as in the MTA. Hypothesis 2, relative initial severity predicting relative end severity, is supported for Inattn, but not HA/Imp. Hypothesis 3, HA/Imp symptoms declining more than Inattn, is partially supported by a nonsignificant trend; the exception, Class 2, was <5% of the sample. Hypothesis 4, ADHD diagnoses rarer in the lowest severity classes, was supported.

For the same initial severity of HA/Imp symptoms, an ADHD rather than bipolar diagnosis predicts a better trajectory of ADHD symptoms. Inattn symptoms tend to remain at a more consistent severity over time than HA/Imp symptoms. Decreasing HA/Imp symptoms were associated with a high rate of stimulant medication, possibly confounded with the high rate of ADHD diagnosis in the class showing the sharp decrease.

As predicted, LAMS symptom trajectories do not show the sharp improvement at 1 year found in the MTA trajectories, resulting from standardized, systematic MTA treatments. In the LAMS sample, although medication use differed significantly across classes at all assessment points, the change within class did not differ appreciably, except for a moderate increase between baseline and 6-month assessment for all classes, with a subsequent leveling off. This initial medication increase could have played a role in the classes that showed a decline, but would not fit with the classes showing an increase of symptoms. Importantly, none of the classes showed an inflection at 6 months that could be attributed to the initial medication increase. This difference between MTA and LAMS trajectories might be taken as indirect confirmation that improvement noted in the beginning of the MTA trajectories resulted from the specific treatment protocols rather than being a common course of the disorder. However, this conclusion must be tempered by realization that the

LAMS sample was not selected for ADHD with the same initial ADHD symptom threshold requirement that could have predisposed the MTA sample to regress to the mean.[40]

Also as hypothesized, relative initial severity of Inattn predicted relative 3-year severity, but the same did not hold true for HA/Imp symptoms over time. Not only did three quarters of the HA/Imp trajectories show the expected waning of symptoms over time, but there was a slope crossing between Class 2 and Classes 3 and 4, with Class 2 starting lower and ending significantly higher ($p$=0.0001) than Class 4 and higher than Class 3. Thus Class 2 was an exception to HA/Imp waning, but it was only 4.5% of the sample. In contrast, the 3 Inattn trajectories maintained their relative severity over time without appreciable waning of severity. HA/Imp Class 4, with the most favorable slope, had the highest proportion of ADHD diagnoses and lowest proportion of BPSD diagnoses, suggesting that HA/Imp symptoms resulting from ADHD rather than from BPSD tend to improve over time (at least if treated). Class 2, with the least favorable slope and only 31 children, had the second-highest proportion BPSD, second-lowest proportion ADHD, lowest proportion ESM+, second-lowest proportion DMDD, second-lowest parent stress score, lowest proportion male, lowest proportion non-Hispanic white, and youngest age, all nonsignificant. It is not clear why HA/Imp symptoms increased so dramatically in this small class, but possibilities include that the younger age and/or higher proportion of girls and/or minorities allowed more maturation-linked development of overlapping symptoms from other disorders.

The overlaps of Inattn classes and HA/Imp classes in Table 5 are for the most part not surprising: the most consistently favorable trajectory of one symptom cluster tends to match the most consistently favorable of the other, and similarly with the consistently severe trajectories. This confirms the link between the two symptom clusters over time. However, a noteworthy exception is that three fifths of HA/Imp Class 4, showing the best change over time (statistically and clinically significant decrease in HA/Imp symptoms), falls into Inattn Class 3, the worst over time. This appears to be a dramatic illustration of the greater waning over time of HA/Imp symptoms compared to Inattn symptoms, which tend to be more persistent. The mildest HA/Imp class outnumbers the mildest Inattn class (both Class 1) 257 to 103. This probably reflects the presence of inattentive type ADHD in the sample; the 107 with inattentive type could have severe Inattn without HA/Imp.

Self-reported parent stress was examined as a measure of family dysfunction. Both ADHD symptom clusters showed a significant difference in parent stress by class. As might be expected, the children with highest symptom severity had the most stressed parents, and those with relatively lower severity had less stressed parents. This is compatible with Jester et al.'s report of less parental support in the worse HA/Inattn trajectory.[10] A causal link cannot be determined from the available data, but a likely speculation is that more severe child symptoms disrupt family function more severely, which stresses parents more. An alternative speculation could involve a genetic link between a vulnerable, highly symptomatic child and a fragile, easily stressed parent.

Because this sample was recruited for having elevated symptoms of mania, it is possible that severe mood dysregulation as described by Leibenluft,[41] and incorporated into the *DSM-5* diagnosis of DMDD, somehow influenced the trajectories. Actually, 26% of this sample met

a proxy diagnosis for DMDD at entry.[25] Though ADHD was more common in the group who met DMDD criteria vs. the rest of the sample (79% vs. 61%), this was not significantly different in multivariate analyses. As might be expected, this diagnosis was more common ($p$=0.004-0.001) in class 3, the consistently worst trajectory, than in class 1, the consistently least severe trajectory, for both Inattn and HA/Imp.

Limitations of this study are in some ways the reverse of the strengths that make it interesting: the sample was not selected for ADHD, limiting the findings' applicability to ADHD as such, but the fact that 526/684 had an ADHD diagnosis suggests this limitation is not severe. Further, not selecting for ADHD with a severity criterion may have minimized regression to the mean. The presence of BPSD in a large proportion introduces a confounder in view of the overlap between ADHD and bipolar symptoms. However, in a previous publication, we showed that the parent raters were able to distinguish chronic symptoms of inattention and hyperactivity from episodic increases in the same symptoms.[42] The uncontrolled nature of concomitant treatment at local clinics undoubtedly introduced some noise into the trajectories, although we were able partially to tease this out by the analyses presented. Also, latent class analysis did not necessarily identify the "true" models, but rather those that fit optimally according to currently recommended criteria for evaluating model fit. Use of a different sample, measures, or schedule of assessment frequency all could lead to preference for a different model. However, this concern is tempered by the use of multiple criteria and the fact that the 3-class model of Inattn was consistent with prior GMMs that used only inattentive symptoms or a combination of Inattn and HA/Imp.

One of the main clinical lessons from both this set of GMM analyses and the prior GMMs is that we need to look beyond group mean findings to understand individual patients, their prognosis, and their treatment needs. For example, HA/Imp Class 3 and Class 4 start at approximately the same severity but diverge dramatically. Both classes had a high proportion of ADHD diagnoses (87.3 and 90%), so what made the difference? It is unlikely to be treatment with medication, because Class 3 had at least as high a rate of medication (stimulant and other) as Class 4. One possibility could be the difference in BPSD diagnoses (28.5% for Class 3 and 18% for Class 4) and baseline manic symptom scores on the YMRS (19.4 vs. 17.5); thus, bipolar comorbidity considerably worsens the prognosis for HA/Imp symptoms. However, one cannot depend on a rating scale screen to make that distinction, because paradoxically, Class 4 had the nominally highest proportion (94%) of ESM+, indicating that they passed the screening threshold on a scale proven sensitive to manic symptoms, yet this class had a low proportion of BPSD diagnoses. The explanation, of course, is the great overlap between ADHD symptoms and some manic symptoms, a diagnostic pitfall. It is sometimes necessary to track a patient over time to clarify the diagnostic issues. Episodicity of bipolar symptoms in contrast to chronicity of ADHD symptoms is one of the key distinctions. In regard to treatment response, both the Inattn Class 3 and the MTA Class 3 detect a subgroup that initially seems to respond to treatment with diminishing symptoms but then regresses towards baseline severity. We need to devise new treatments to meet the needs of that subgroup, for whom the current evidence-based treatments, proven on group means, are not adequate.

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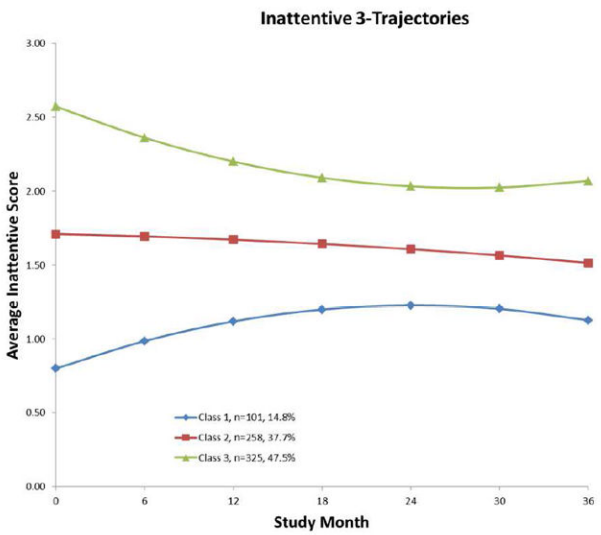
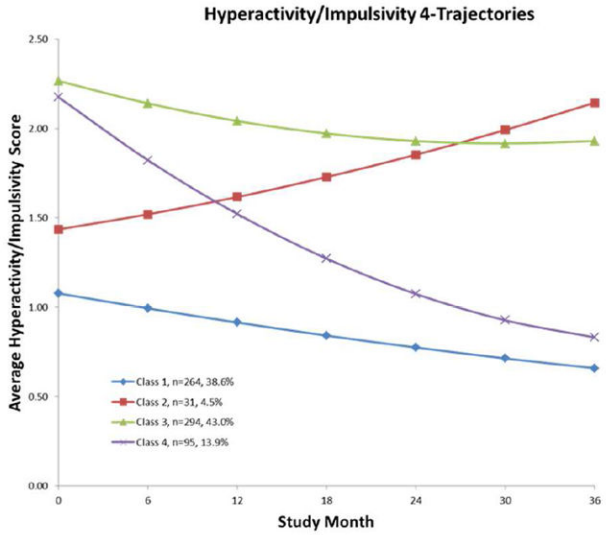
### Clinical Guidance

- All ADHD symptoms show some improvement with time (and maturation) and treatment, although this does not necessarily improve function/impairment.
- Hyperactive/impulsive symptoms generally improve more over time than inattentive symptoms.
- We need to look beyond group mean findings to understand individual patients and their prognosis; subgroups of patients vary from the mean in their course.
- Although treatment is associated with overall improvement on average, analyses identified a subgroup with significant worsening over time despite treatment. New treatments, or at least creative clinical treatment planning, are needed for this subgroup.
- BPSD appears to interfere with the improvement of ADHD symptoms over time, particularly the HA/Imp symptoms. This is probably only partially a result of the overlap in symptoms.
- Inattentive symptoms, being more resistant to improvement from the combined effects of maturation and treatment, deserve additional clinical attention. As the patient matures, addition of cognitive-behavioral treatment, organizational or skills training, supportive habit training, coaching/mentoring, and/or computer-based attention training may be considered.




Inattentive 3-Trajectories
Autoregressive Parameter Estimates

- Class 1 (Blue) Slope = 0.26, $p = 0.004$ Curvature = -0.0051, $p = 004$
- Class 2 (Red) Slope = -0.04, $p$ = NS Curvature = -0.0004, $p$ = NS
- Class 3 (Green) Slope = -0.38, $p < 0.001$ Curvature = 0.0069, $p < 0.001$

Class 1 has significant increasing slope and significant negative curvature.
Class 2 has neither significant slope nor significant curvature. It is essentially constant.
Class 3 has significant decreasing slope and significant positive curvature.

Hyperactivity/Impulsivity 4-Trajectories
Autoregressive Parameter Estimates

- Class 1 (Blue) Slope = -0.14, $p = 0.089$ Curvature = 0.0013, $p$ = NS
- Class 2 (Red) Slope = 0.12, $p = 0.049$ Curvature = 0.0015, $p$ = NS
- Class 3 (Green) Slope = -0.22, $p = 0.013$ Curvature = 0.0037, $p = 0.044$
- Class 4 (Purple) Slope = -0.59, $p = 0.005$ Curvature = 0.0069, $p = 0.033$

Class 1 has a trending significant $p$-value (< .10) for slope (decreasing) with no significant curvature.
Class 2 has significant slope with no significant curvature.
Classes 3 & 4 have both significant decreasing slopes and positive curvature.

**Figure 1.**

Growth mixture model latent classes of attention-deficit/hyperactivity disorder (ADHD) symptom trajectories in the Longitudinal Assessment of Manic Symptoms (LAMS) sample, not selected for ADHD, but with 526/684 having ADHD. Panel A = inattention; panel B = hyperactivity/impulsivity. NS = not significant.

Panel A. Inattention latent class trajectories over 3 years. Inattention Class 1 (blue, 14.8% of sample) and Class 3 (green, 47.5%) have significant linear (slope, $p = 0.004$ and 0.001) and quadratic (curvature, $p = 0.004$ and 0.001) terms for time. Class 2 (red, 37.7%) has neither significant slope nor curvature.

Panel B. Hyperactive/impulsive latent class symptom trajectories over 3 years. Class 1 (blue) = 38.5%; Class 2 (red) = 4.5%; Class 3 (green) = 43%; Class 4 (purple) = 13.9%. Classes 3 and 4 have both significant decreasing linear (slope, [$p = 0.013$ and 0.005]) and quadratic (curvature, $p = 0.044$ and 0.033) terms. Class 2 shows a significant increasing linear slope (0.12, $p = 0.049$) without significant curvature. Class 1 has no significant time terms.

**Table 1**

Relevant studies using growth mixture modeling of latent class trajectories of Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms

| Reference | N, sample selection | Design | Measures | # of classes | Description of classes |
|---|---|---|---|---|---|
| Jester 2005[10] | 335 children of alcoholic fathers and comparison children of non-alcoholic fathers (71% boys)<br><br>Not selected for ADHD | Prospective study of alcohol and drug use in high risk and control families.<br><br>5 assessments from age 3-5 every 3 years for 12 years. Parallel latent class analysis of two trajectories (attention problems and aggression) | Attention Problems and Aggression sub-scales of the Child Behavior Checklist (CBCL, parents) and Teacher Report Form (teachers) | 2 for inattention-hyperactivity, 2 for aggression overlapping same subjects<br><br>4 classes derived in 2×2 combination of high and low attention problems with high and low aggression | Inattention/hyperactivity classes: one high and persisting (severe), one low severity<br><br>Aggression classes: one high and decreasing (severe), one low severity<br><br>Class 1 (comorbid, n=82, 24.5%): high inattention/hyperactivity and high aggression<br><br>Class 2 (aggressive, n=12, 3.6%): low inattention/hyperactivity and high aggression<br><br>Class 3 (inattentive/hyperactive, n=110, 32.8%): high inattention/ hyperactivity and low aggression<br><br>Class 4 (healthy, n=131, 39.1%): low inattention/hyperactivity and low aggression |
| Swanson 2007[9] | 383 boys, 102 girls, Total N=485.<br><br>All combined type ADHD by structured interview, clinical interview, and cutpoint on parent and teacher rating. | 36-month follow-up of 14-month MTA randomized clinical trial. 4 assessments at baseline, 14, 24, and 36 months. Age 7-10 at baseline, 10-13 at end. | Swanson, Nolan & Pelham scale (SNAP; all 18 *DSM-IV* ADHD symptoms rated 0-3) by parents and teachers. Item mean (average symptom severity across both ADHD domains) | 3 | Class 1 (34%): small 14-month improvement followed by gradual further improvement with increasing benefit from medication over time<br><br>Class 2 (52%): large 14-month improvement maintained for 3 years<br><br>Class 3 (14%): initial large 14-month improvement followed by deterioration |
| Jester 2008[11] | 335 children of alcoholic fathers and comparison children of non-alcoholic fathers (71% boys) (same sample as Jester, 2005).<br><br>Not selected for ADHD | Prospective study of alcohol and drug use in high risk and control families. Assessments (every 3 years from age 7 to age 16)<br><br>Parallel latent class analysis of two trajectories (attention problems and aggression) | Aggressive Behavior and Attention Problems subscales of CBCL and Teacher Report Form | 2 for inattention-hyperactivity, 2 for aggression, making 4 total when crossed 2×2, high and low of each | Class 1 (comorbid, 24%): high inattention/hyperactivity and high aggression<br><br>Class 2 (aggressive, 4%): low inattention/hyperactivity and high aggression<br><br>Class 3 (inattentive/hyperactive, 33%): high inattention/hyperactivity and low aggression<br><br>Class 4 (healthy, 39%): low inattention/hyperactivity and low aggression |

| Reference | N, sample selection | Design | Measures | # of classes | Description of classes |
|---|---|---|---|---|---|
| Sonuga-Barke 2008[12] | 136 boys, 48 girls All diagnosed with ADHD (COMACS study)<br>Age 6-12 years<br>All diagnosed with ADHD | Comparison of 2 Methylphenidate preparations in the Analog Classroom Setting<br>12-hr day, assessments every 1 1/2 hours | Swanson, Kotkin, Atkins, M-Flynn, Pelham (SKAMP), includes 6 deportment items and 7 attention items. Parents also completed the SNAP. | 3 | High and increasing (n=23, 12.4%)<br>Intermediate and increasing (n=75, 40.5%)<br>Low and stable (n=71, 38.4%) |
| Malone 2010[8] | N=754 from 21 schools; 367 with high disruptive behavior scores<br>387 controls<br>Not selected for ADHD | Fast Track Project; Annual measurements for 12 years starting in kindergarten /(ADHD symptoms in years 3, 6, and 9) | NIMH Diagnostic Interview Schedule for Children (DISC; *DSM III-R* criteria); used sympiom counts for Inattention and Hyperactivity. Beginning in year 8, youths completed the Tobacco, Alcohol, and Drugs Measure, indicating age at first use of for each drug. | 3 | Class 1 (24%): High with initial decrease then slight increase in ADHD symptoms (concave)<br>Class 2 (18%): High with initial increase then decrease in ADHD symptoms (convex)<br>Class 3 (58%): No or minimal symptoms through childhood and adolescence.<br>Concave trajectory showed earlier onset of illicit drug use than the minimal-problem class |
| Robbers 2011[7] | Twins selected from the Netherlands Twin Register: 6,161 boys, 6,325 girls. Singletons selected from Zuid-Holland study (longitudinal study representing the general population) (n=2,600) Not selected for ADHD | Ages 7, 10, and 12; assessments by parents and teachers as part of ongoing studies not specifically focused on ADHD | Attention Problems sub-scale of CBCL (parents) and Teacher Report Form (teachers) | 3 | Stable-low (62-71%)<br>Low-increasing (15-18%)<br>High-decreasing (14-21%) |

Note: MTA = Multimodal Treatment Study of Children with ADHD; NIMH = National Institute of Mental Health.

**Table 2**

Growth Mixture Model Analysis of Inattentive and Hyperactive-Impulsive Symptoms Followed Over 3 Years

| Comparison of Different GMM Models | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Inattentive** | | | | | | | |
| **Classes** | **AIC** | **BIC** | **adjBIC** | **LMR LR *p*-value** | **adjLMR LR *p*-value** | **bootLRT *p*-value** | **Entropy** |
| 1 | 21400.039 | 21486.070 | 21425.742 | n/a | n/a | n/a | n/a |
| 2 | 21351.990 | 21456.133 | 21383.105 | 0.0000 | 0.0000 | 0.0000 | 0.662 |
| 3 | 21324.630 | 21446.884 | 21361.156 | 0.0026 | 0.0033 | 0.0000 | 0.748 |
| 4 | 21318.981 | 21459.347 | 21360.918 | 0.0465 | 0.0529 | 0.2000 | 0.781 |
| **Hyperactive/Impulsive** | | | | | | | |
| Classes | AIC | BIC | adjBIC | LMRLR *p*-value | adjLMR LR *p*-value | bootL RT *p*-value | Entropy |
| 1 | 21296.349 | 21382.380 | 21322.053 | n/a | n/a | n/a | n/a |
| 2 | 21258.279 | 21362.422 | 21289.394 | 0.0037 | 0.0044 | 0.0000 | 0.571 |
| 3 | 21245.000 | 21367.255 | 21281.526 | 0.2283 | 0.2283 | 0.0000 | 0.557 |
| 4 | 21227.400 | 21367.766 | 21269.337 | 0.2179 | 0.2179 | 0.0000 | 0.623 |

Note: The best fit for inattentive symptoms is 3 classes/trajectories (shown in figure 1A) and for hyperactive/impulsive symptoms 4 classes/trajectories (shown in figure 1B). adjBIC = adjusted Bayes Information Criteria; adjLMR LR = adjusted Lo-Mendell-Rubin Likelihood Ratio test; AIC = Aike Information Criteria; BIC = Bayes Information Criteria; bootLRT = Bootstrap Likelihood Ratio test; GMM = growth mixture modeling; LMR LR = Lo-Mendell-Rubin Likelihood Ratio test.

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## Table 3

A. Demographic and clinical Characteristics of the latent Classes for Inattentive Symptoms over 3 Years

| | Inattentive Symptoms | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Class 1** | **Class 2** | **Class 3** | **Overall p** | **1 vs. 2 p** | **1 vs. 3 p** | **2 vs. 3 p** |
| **Demographics**: | **n = 101** | **n = 258** | **n = 325** | | | | |
| Race (% White) | 63.37 | 62.79 | 66.46 | 0.628 | 1.000 | 0.651 | 0.404 |
| Gender (% Male) | 62.38 | 70.16 | 66.15 | 0.326 | 0.196 | 0.564 | 0.348 |
| Ethnicity (% Hispanic) | 4.95 | 5.43 | 3.38 | 0.468 | 1.000 | 0.672 | 0.316 |
| Baseline Age (Years (SD)) | 9.3 (1.9) | 9.2 (2.0) | 9.6 (1.9) | 0.028 | 0.795 | 0.109 | 0.011 |
| **Baseline Diagnoses (%):** | **n = 101** | **n = 258** | **n = 325** | | | | |
| Bipolar | 20.79 | 13.95 | 30.46 | <.001 | 0.152 | 0.078 | <.001 |
| Depressive Disorder | 12.87 | 15.50 | 20.31 | 0.135 | 0.641 | 0.125 | 0.166 |
| Anxiety | 32.67 | 29.84 | 32.00 | 0.812 | 0.693 | 0.996 | 0.639 |
| DBD | 34.65 | 51.55 | 56.31 | <.001 | 0.006 | <.001 | 0.289 |
| ADHD | 37.62 | 77.91 | 88.62 | <.001 | <.001 | <.001 | <.001 |
| ESM+[b] | 81.19 | 86.05 | 91.38 | 0.012 | 0.324 | 0.007 | 0.056 |
| DMDD | 15.84 | 24.03 | 31.08 | 0.006 | 0.121 | 0.004 | 0.073 |
| **Dimensional Measures** | | | | **Kruskal-Wallis p** | **1 vs. 2 p** | **1 vs. 3 p** | **2 vs. 3 p** |
| Baseline YMRS | **n = 101** | **n = 258** | **n = 325** | | | | |
| Mean (SD) | 14.7 (9.9) | 14.8 (8.3) | 19.1 (9.1) | <.001 | 0.760 | <.001 | <.001 |
| Baseline CGAS | **n = 100** | **n = 256** | **n = 323** | | | | |
| Mean (SD) | 57.9 (10.5) | 56.2 (9.6) | 52.9 (9.7) | <.001 | 0.312 | <.001 | <.001 |
| Baseline CDRS | **n = 101** | **n = 258** | **n = 325** | | | | |
| Mean (SD) | 33.0 (10.6) | 32.1 (9.3) | 37.4 (11.2) | <.001 | 0.763 | <.001 | <.001 |
| Baseline GBI | **n = 100** | **n = 249** | **n = 322** | | | | |
| Mean (SD) | 9.0 (6.4) | 10.5 (6.2) | 15.7 (6.9) | <.001 | 0.051 | <.001 | <.001 |
| Parent Stress Scores | **n = 101** | **n = 258** | **n = 325** | | | | |
| Mean (SD) | 7.3 (4.4) | 8.4 (4.3) | 9.5 (4.2) | <.001 | 0.043[a] | <.001 | <.001 |

B. Demographic and Clinical Characteristics of the Latent Class Trajectories for Hyperactive-Impulsive Symptoms over 3 Years

| | Hyperactive/Impulsive Symptoms | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Class 1** | **Class 2** | **Class 3** | **Class 4** | **Overall p** | **1 vs. 2 p** | **1 vs. 3 p** | **1 vs. 4 p** | **2 vs. 3 p** | **2 vs. 4 p** | **3 vs. 4 p** |

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| **Demographics:** | **n = 264** | **n = 31** | **n = 294** | **n = 95** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Race (% White) | 67.42 | 48.39 | 65.31 | 60.00 | 0.143 | 0.056 | 0.661 | 0.238 | 0.096 | 0.355 | 0.416 |
| Gender (% Male) | 66.29 | 58.06 | 67.01 | 72.63 | 0.468 | 0.477 | 0.928 | 0.313 | 0.423 | 0.194 | 0.369 |
| Ethnicity (% Hispanic) | 4.55 | 6.45 | 4.42 | 3.16 | 0.879 | 0.980 | 1.000 | 0.779 | 0.950 | 0.775 | 0.809 |
| Baseline Age (Years (SD)) | 9.5 (1.9) | 9.2 (1.8) | 9.3 (1.9) | 9.4 (2.0) | 0.649 | 0.354 | 0.281 | 0.613 | 0.655 | 0.577 | 0.794 |
| **Baseline Diagnoses (%):** | **n = 264** | **n = 31** | **n = 294** | **n = 95** | | | | | | | |
| Bipolar | 18.18 | 19.35 | 28.57 | 18.95 | 0.021 | 0.986 | 0.005 | 0.991 | 0.379 | 1.000 | 0.085[a] |
| Depressive Disorder | 19.70 | 16.13 | 15.99 | 15.79 | 0.663 | 0.814 | 0.301 | 0.494 | 1.000 | 1.000 | 1.000 |
| Anxiety | 32.20 | 32.26 | 32.31 | 25.26 | 0.601 | 1.000 | 1.000 | 0.258 | 1.000 | 0.596 | 0.243 |
| DBD | 40.91 | 58.06 | 58.84 | 54.74 | <.001 | 0.102 | <.001 | 0.027[a] | 1.000 | 0.908 | 0.558 |
| ADHD | 60.61 | 64.52 | 88.78 | 90.53 | <.001 | 0.820 | <.001 | <.001 | <.001 | 0.002 | 0.773 |
| ESM+[b] | 80.68 | 80.65 | 93.20 | 93.68 | <.001 | 1.000 | <.001 | 0.005 | 0.036[a] | 0.073 | 1.000 |
| DMDD | 17.42 | 25.81 | 33.33 | 28.42 | <.001 | 0.37 | <.001 | 0.033 | 0.517 | 0.959 | 0.444 |
| **Dimensional Measures** | | | | | **Kruskal-Wallis p** | **1 vs. 2 p** | **1 vs. 3 p** | **1 vs. 4 p** | **2 vs. 3 p** | **2 vs. 4 p** | **3 vs. 4 p** |
| Baseline YMRS | **n = 264** | **n = 31** | **n = 294** | **n = 95** | | | | | | | |
| Mean (SD) | 13.8 (8.3) | 15.1 (10.2) | 19.5 (9.1) | 17.4 (9.1) | <.001 | 0.471 | <.001 | <.001 | 0.005 | 0.180 | 0.030[a] |
| Baseline CGAS | **n = 262** | **n = 31** | **n = 292** | **n = 94** | | | | | | | |
| Mean (SD) | 57.3 (10.2) | 54.6 (7.4) | 52.8 (9.7) | 54.8 (9.2) | <.001 | 0.148 | <.001 | 0.044[a] | 0.425 | 0.876 | 0.123 |
| Baseline CDRS | **n = 264** | **n = 31** | **n = 294** | **n = 95** | | | | | | | |
| Mean (SD) | 33.9 (10.6) | 33.9 (8.8) | 35.7 (10.8 | 34.7 (11.1) | 0.229 | 0.703 | 0.039[a] | 0.532 | 0.585 | 0.991 | 0.393 |
| Baseline GBI | **n = 257** | **n = 30** | **n = 289** | **n = 95** | | | | | | | |
| Mean (SD) | 9.4 (6.1) | 10.8 (7.0) | 15.4 (6.7) | 14.5 (7.4) | <.001 | 0.211 | <.001 | <.001 | <.001 | 0.014[a] | 0.162 |
| Parent Stress Scores | **n = 264** | **n = 31** | **n = 294** | **n = 95** | | | | | | | |
| Mean (SD) | 8.1 (4.2) | 8.4 (5.3) | 9.4 (4.3) | 8.7 (4.2) | 0.003 | 0.874 | <.001 | 0.255 | 0.146 | 0.616 | 0.138 |

Note: ADHD = attention-deficit/hyperactivity disorder; CDRS = Child Depression Rating Scale; CGAS = Child Global Assessment Scale; DBD = disruptive behavior disorders; DMDD = disruptive mood dysregulation disorder; ESM = elevated symptoms of mania; GBI = General Behavior Inventory 10-Item Mania subscale; YMRS = Young Mania Rating Scale.

[a] Not significant after Bonferroni correction for multiple comparisons.

[b] ESM+ = baseline score ≥12 on the GBI -10M.

**Table 4**

Differential medication use over the 3 year period by the different latent classes

| ***Inattentive*** | **Class 1** | **Class 2** | **Class 3** | ***p*-values** | | | |
|---|---|---|---|---|---|---|---|
| | **n = 101** | **n = 258** | **n = 325** | **Overall** | **1vs. 2** | **1vs. 3** | **2 vs. 3** |
| **Baseline Medications** | **(%)** | **(%)** | **(%)** | | | | |
| Stimulants | 18.81 | 42.64 | 42.15 | <.001 | <.001 | <.001 | 0.974 |
| Any Prescribed Medication | 41.58 | 65.50 | 66.77 | <.001 | <.001 | <.001 | 0.816 |
| | **n = 85** | **n = 199** | **n = 259** | | | | |
| **6 Month Medications** | **(%)** | **(%)** | **(%)** | | | | |
| Stimulants | 29.41 | 45.23 | 53.67 | <.001 | 0.019 | <.001 | 0.090 |
| Any Prescribed Medication | 61.18 | 73.87 | 77.61 | 0.012 | 0.046[a] | 0.005 | 0.414 |
| | **n = 86** | **n = 193** | **n = 246** | | | | |
| **12 Month Medications** | **(%)** | **(%)** | **(%)** | | | | |
| Stimulants | 23.26 | 49.22 | 52.44 | <.001 | <.001 | <.001 | 0.567 |
| Any Prescribed Medication | 60.47 | 73.06 | 76.83 | 0.013 | 0.050[a] | 0.005 | 0.426 |
| | **n = 76** | **n = 187** | **n = 219** | | | | |
| **18 Month Medications** | **(%)** | **(%)** | **(%)** | | | | |
| Stimulants | 25.00 | 48.66 | 56.16 | <.001 | <.001 | <.001 | 0.159 |
| Any Prescribed Medication | 57.89 | 72.73 | 79.00 | 0.002 | 0.028[a] | <.001 | 0.174 |
| | **n = 81** | **n = 175** | **n = 211** | | | | |
| **24 Month Medications** | **(%)** | **(%)** | **(%)** | | | | |
| Stimulants | 28.40 | 47.43 | 56.87 | <.001 | 0.01 | <.001 | 0.081 |
| Any Prescribed Medication | 61.73 | 72.00 | 76.30 | 0.045 | 0.133 | 0.019 | 0.397 |

| ***Hyperactive/Impulsive*** | **Class 1** | **Class 2** | **Class 3** | **Class 4** | ***p*-values** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **n = 264** | **n = 31** | **n = 294** | **n = 95** | **Overall** | **1vs. 2** | **1vs. 3** | **1vs. 4** | **2 vs. 3** | **2 vs. 4** | **3 vs. 4** |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline Medications** | **(%)** | **(%)** | **(%)** | **(%)** | | | | | | | |
| Stimulants | 28.79 | 25.81 | 45.58 | 50.53 | <.001 | 0.891 | <.001 | <.001 | 0.055 | 0.028[a] | 0.470 |
| Any Prescribed Medicine | 53.41 | 61.29 | 69.39 | 67.37 | 0.001 | 0.520 | <.001 | 0.025[a] | 0.471 | 0.688 | 0.809 |
| Medication | | | | | | | | | | | |
| | **n = 216** | **n = 30** | **n = 206** | **n = 91** | | | | | | | |
| **6 Month Medications** | **(%)** | **(%)** | **(%)** | **(%)** | | | | | | | |
| Stimulants | 36.57 | 40.00 | 55.83 | 52.75 | <.001 | 0.871 | <.001 | 0.012# | 0.153 | 0.317 | 0.715 |
| Any Prescribed | | | | | | | | | | | |
| Medication | 67.59 | 73.33 | 78.16 | 78.02 | 0.068 | 0.672 | 0.020[a] | 0.090 | 0.721 | 0.781 | 1.000 |
| | **n = 213** | **n = 28** | **n = 197** | **n = 87** | | | | | | | |
| **12 Month Medications** | **(%)** | **(%)** | **(%)** | **(%)** | | | | | | | |
| Stimulants | 36.62 | 35.71 | 58.88 | 45.98 | <.001 | 1.000 | <.001 | 0.169 | 0.035[a] | 0.463 | 0.059 |
| Any Prescribed | | | | | | | | | | | |
| Medication | 67.14 | 71.43 | 79.19 | 72.41 | 0.057 | 0.809 | 0.008 | 0.449 | 0.493 | 1.000 | 0.272 |
| | **n = 197** | **n = 27** | **n = 175** | **n** = 83 | | | | | | | |
| **18 Month Medications** | **(%)** | **(%)** | **(%)** | **(%)** | | | | | | | |
| Stimulants | 39.09 | 29.63 | 61.14 | 49.40 | <.001 | 0.460 | <.001 | 0.143 | 0.004 | 0.116 | 0.100 |
| Any Prescribed | | | | | | | | | | | |
| Medication | 69.04 | 70.37 | 80.00 | 69.88 | 0.092 | 1.000 | 0.022 | 1.000 | 0.376 | 1.000 | 0.101 |
| | **n = 190** | **n = 28** | **n = 171** | **n = 78** | | | | | | | |
| **24 Month Medications** | **(%)** | **(%)** | **(%)** | **(%)** | | | | | | | |
| Stimulants | 38.42 | 35.71 | 60.82 | 50.00 | <.001 | 0.947 | <.001 | 0.108 | 0.022 | 0.280 | 0.143 |
| Any Prescribed | | | | | | | | | | | |
| Medication | 68.42 | 75.00 | 77.19 | 69.23 | 0.270 | 0.628 | 0.081 | 1.000 | 0.989 | 0.739 | 0.237 |

Note: Stimulant use differed across classes by *p<0.001* at all time points. All medication use differed across classes at all time points for intention but only at baseline for hyperactivity/impulsivity.

[a]Not significant after Bonferroni correction for multiple comparisons

**Table 5**

Overlap of the 3 Inattentive Classes with the 4 Hyperactive-Impulsive Classes

| Hyperactive/Impulsive Class | Inattentive Class | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | Total |
| 1 | 75 | 125 | 64 | 264 |
| 2 | 12 | 9 | 10 | 31 |
| 3 | 10 | 92 | 192 | 294 |
| 4 | 4 | 32 | 59 | 95 |
| Total | 97 | 226 | 266 | 684 |

Note: overlap of consistently mild Class 1 of each symptom cluster and similar overlap of consistently severe Class 3 of each symptom cluster.