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Original Research

# Is Stimulant Treatment in Children and Adolescents with Mood Dysregulation Associated with Adverse Outcomes?

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**Abstract**

The aim of this paper is to examine effects of stimulant treatment in children and adolescents with high levels of emotional dysregulation in a psychiatric outpatient clinic. Subjects were referred children and adolescents 6-17 years of age who presented to a child psychiatric outpatient clinic between September 2016-November 2021 and received a prescription for a stimulant medication. Children were stratified into those with low and high levels of emotional dysregulation as defined by an aggregate T-score of <180 or ≥210 on the combined Attention Problems, Aggressive Behavior, and Anxious/Depressed subscales of the Child Behavior Checklist (CBCL; CBCL-AAA). We analyzed patient prescription, diagnosis, and hospital visit data extracted from the electronic medical record from any time prior to referral through three months after referral. Patients with higher CBCL-AAA scores at clinic intake had

a significantly different medication and diagnosis profile and were more likely to have a higher dosage of stimulants than patients with lower scores. These patients also were more likely to receive an additional medication class during follow-up, which was driven by second-generation antipsychotics (SGAs). Emergency room visits and inpatient psychiatric admissions were rare but present only in the group with higher CBCL-AAA scores. These results suggest that stimulant treatment affects youth with high versus low levels of emotional dysregulation adversely with a need for higher stimulant doses and treatment augmentation with SGAs. The CBCL may be a useful tool for identifying poor outcomes with stimulant treatment.

**Keywords**
Adverse events; stimulants; pediatric; adolescent; mood dysregulation

## 1. Introduction

Stimulants are a prescription drug class that increase dopamine and norepinephrine in the brain and are most commonly used in the treatment of attention-deficit/hyperactivity disorder (ADHD) [1]. Prescription stimulants are comprised of drugs such as amphetamines (AMPH) and methylphenidate (MPH) [1].

Stimulants have been shown to be safe, well-tolerated, and effective in the treatment of the core symptoms of pediatric ADHD, but the small number of studies which address stimulant effects in populations with emotional dysregulation focus on bipolar disorder (BPD) and report mixed outcomes [2-5]. Some studies find stimulants to be safe and effective in children with bipolar disorder. MPH was effective in alleviating symptoms of ADHD in a sample of youth with stabilized BPD, with no significant change in scores on the Children's Depression Rating Scale (CDRS-R) or Young Mania Rating Scale (YMRS) [3]. Similarly, MPH had a positive impact on symptoms of depression in a sample of children and adolescents (8-17 years old) with comorbid ADHD and BPD [4]. Additionally, in children participating in the Multimodal Treatment Study of Children with ADHD who also had manic symptoms, treatment with MPH did not increase the risk of adverse events or poor response [6]. In children with bipolar disorder and symptoms of ADHD, amphetamines were shown to decrease scores on the YMRS without any significant side effects or worsening of symptoms of mania [7]. In adults, similar positive outcomes have been reported. A meta-analysis of adults with bipolar depression found that treatment with dopaminergic agents (including stimulants) was not associated with adverse events, poor tolerability, or an increased risk of switch to mania [8].

However, there is an equally robust literature warning against the use of stimulants in children with bipolar disorder. Based on extensive analysis, the FDA placed a warning label on stimulants alerting prescribers of the possibility that they can cause or worsen mania [9]. In a retrospective analysis of the clinic records of 82 youth with BPD, stimulants were associated with treatment-emergent mania within several weeks of exposure [10]. A study of hospitalized children with BPD reported that those treated with stimulants had a significantly more severe course of illness during hospitalizations compared to those without [11]. A study of children with ADHD with polygenic risk scores for BPD who initiated stimulant treatment were more likely to discontinue that treatment

[12]. Similar findings have been reported in adults. In a study of a large sample of adults with BPD (N = 2307), Viktorin et al. found that treatment with MPH without a concurrent mood stabilizer significantly increased the relative risk for mania [13].

The contradictory evidence for and against the use of stimulants in children with bipolar disorder highlights the need for more information regarding the effects of stimulant treatment on the clinical course of children with varying levels of emotional dysregulation. Finding a marker which identifies children at the highest risk of poor outcomes with stimulant treatment would be of great clinical utility. The Child Behavior Checklist (CBCL), a parent-completed scale, could provide a simple clinical indicator of this risk [14]. Our group has reported extensively on the use of the CBCL as a screener for emotional dysregulation in ADHD youth [14-17] and as a predictor of risk for a pediatric BPD diagnosis [18-20]. Combined T-scores on the Attention Problems, Aggressive Behavior, and Anxious/Depressed CBCL subscales make up a useful profile (CBCL-AAA) reflecting intense emotions [20-22]. A combined CBCL-AAA T-score of ≥210 signals severe emotional dysregulation. This profile has been identified in a substantial minority (19%) of children with ADHD [14] and has been associated with a pediatric BPD diagnosis.

To this end, we conducted an investigation of the effects of stimulant treatment on clinically-referred children in an outpatient service. Based on the literature which reports mixed outcomes for simulant use in children with BPD, we used the CBCL-AAA score ≥210 as an indicator of severe emotional dysregulation and as a proxy of a BPD diagnosis. We stratified children by high and low levels of emotional dysregulation as defined by the combined CBCL-AAA subscale scores in order to examine the effect of stimulant prescription in the context of severe emotional dysregulation associated with pediatric BPD. Based on the literature surrounding stimulants and mood disorders, we hypothesized that children with elevated levels of emotional dysregulation as defined by the CBCL-AAA would be at greater risk for poor outcomes with stimulant treatment.

## 2. Methods

### *2.1 Sample*

Our sample was derived from a pool of 991 newly referred children and adolescents of both sexes, 6-17 years of age, who presented to a child psychiatric outpatient clinic at a major medical center between September 2016 and November 2021 and whose parent completed the CBCL as part of the intake process. There was no selection bias based on social class, ethnic background, or insurance restrictions. We received institutional review board approval to review, analyze, and report anonymously on these patients as part of a retrospective chart review. For this study, patients were included in the analysis if they had an aggregate T-score on the CBCL-AAA scales <180 or ≥210 (see *Defining Emotional Dysregulation* below) and were prescribed stimulants as their first psychiatric medication class after completing the CBCL (Figure 1). Patients were excluded if they had CBCL-AAA T-scores 180-209 (n = 429), did not receive any psychiatric prescriptions after completing the CBCL (n = 228), or did not receive stimulants as their first psychiatric medication class after completing the CBCL (n = 153). Thus, our final sample for analysis included 181 patients.

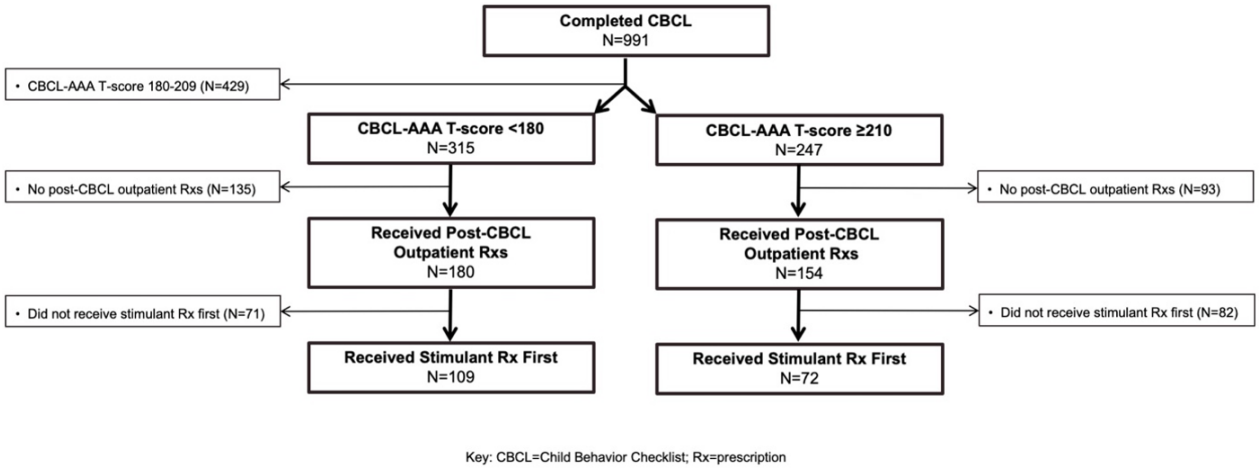


**Figure 1** Patient Flow Chart for Analysis.

### *2.2 Assessment Procedures*

Before their child's initial evaluation, the parent or guardian completed the CBCL as part of an intake battery of assessments. The CBCL is an empirically-derived 113-item parent-rated assessment of a child's behavior problems and social competence [23]. Raw scores are calculated and used to generate T-scores for eight clinical scales, two composite clinical scales, one total clinical scale, and four competence scales.

### *2.3 Defining Emotional Dysregulation*

Patients were stratified into three groups based on their aggregate CBCL-AAA T-scores. We considered patients with CBCL-AAA T-scores ≥ 210 to have high levels of severe emotional dysregulation [24]; patients with CBCL-AAA T-scores 180-209 to have emotional impulsivity or deficient emotional self-regulation [21]; and patients with CBCL-AAA T-scores < 180 to have minimal or no emotional dysregulation (i.e., non-clinical range). For the purpose of this study, we only included patients with CBCL-AAA T-scores <180 or ≥210. We chose to focus only on the patients with severe levels of emotional dysregulation at ≥210 in comparison to those without clinical levels of emotional dysregulation at <180 and excluded children with scores between 180 and 209.

### *2.4 Medical Record Data*

Prescription, diagnosis, and hospital visit data were extracted from the electronic medical record for each patient for any time prior to referral through three months (i.e., 90 days) after referral as part of the retrospective chart review. We restricted the post-referral time frame to three months to capture adverse reactions to stimulant medications that happen relatively quickly after prescribing. Prescriptions of interest included stimulants (amphetamine/dextroamphetamine, dextroamphetamine, lisdexamfetamine, dexmethylphenidate, methylphenidate), second generation antipsychotics (aripiprazone, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, cariprazine, lumateperone), antidepressants (fluoxetine, sertraline, escitalopram, citalopram, paroxetine, bupropion, mirtazapine, vortioxetine, venlafaxine, duloxetine, vilazodone, fluvoxamine), antianxiety medications (buspirone, lorazepam, clonazepam, diazepam, alprazolam), and other psychiatric medications (gabapentin, topiramate,

oxcarbazepine, lithium, valproic acid/valproate, lamotrigine, carbamazepine) that do not fit into the other four medication classes. Diagnoses of interest included ADHD, bipolar disorder, depressive disorders, persistent mood disorders, unspecified mood disorders, anxiety disorders, psychosis, and suicidal ideations or attempts. Hospital visits of interest were emergency room visits or hospitalization associated with a primary diagnosis from the list above.

### *2.5 Terminology and Variable Derivation*

The index stimulant prescription was the first outpatient stimulant prescription in the electronic medical record after completion of the CBCL.

The percent of follow-up time with stimulant prescriptions was calculated by splitting each child's 90-day follow-up period into three 30-day bins, starting at the date of the index stimulant prescription, counting the number of bins with a stimulant prescription issued, and dividing each child's total number of months exposed to stimulants by three (i.e., the number of 30-day bins comprising the follow-up period). The percent of follow-up time with any psychiatric prescription was calculated in a similar way, but instead of counting the number of bins with stimulant prescriptions, we counted the number of bins with other psychiatric medication prescriptions.

Total daily doses of stimulants are reported in MPH dose equivalents. AMPH and dexmethylphenidate (d-MPH) doses were converted to MPH dose equivalents by multiplying the AMPH and d-MPH doses by two to allow us to combine doses for different stimulant families. Lisdexamfetamine (LDX) doses were first converted to AMPH dose equivalents using the following conversions: LDX 20 mg = AMPH 5 mg, LDX 30 mg = AMPH 10 mg, LDX 40 mg = AMPH 15 mg, LDX 50 mg = AMPH 20 mg, LDX 60 mg = 25 mg, and LDX 70 mg = 30 mg. Once LDX doses were converted to AMPH dose equivalents, they were then converted to MPH dose equivalents by multiplying by two.

### *2.6 Statistical Approach*

Comparator groups for this analysis were patients with CBCL-AAA T-scores ≥ 210 versus patients with CBCL-AAA T-scores < 180. Demographic differences were analyzed using t-tests, chi-square tests, and Fisher's exact tests. Depending on the type of outcome, prescription characteristics and diagnoses were examined using linear, logistic, exact logistic, firth logistic, Poisson, or truncated Poisson regression models. Analyses of prescription characteristics and diagnoses controlled for age at index stimulant prescription. All tests were two-tailed and performed at the 0.05 alpha level using Stata 17.0 [25].

## 3. Results

### *3.1 Demographic Characteristics*

Of the 181 patients included in the analysis, 72 (40%) had CBCL-AAA T-scores ≥ 210 and 109 (60%) had T-scores < 180. Patients with CBCL-AAA T-scores ≥ 210 were significantly younger at referral and at the time of their index outpatient stimulant prescription compared to patients with CBCL-AAA T-scores < 180 (Table 1). There were no significant differences between the two groups in sex, race, or ethnicity.

**Table 1** Demographic and clinical characteristics of patients with CBCL-AAA T-scores < 180 and patients with CBCL-AAA T-scores ≥ 210.

| | Patients with CBCL-AAA T-score <180 N = 109 | Patients with CBCL-AAA T-score ≥210 N = 72 | P-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Age at referral (years) | 12.1 ± 3.5 | 10.6 ± 3.2 | 0.003 |
| Age at index outpatient stimulant prescription (years) ‡ | 12.2 ± 3.5 | 10.7 ± 3.2 | 0.004 |
| | N (%) | N (%) | |
| Male | 74 (68) | 50 (69) | 0.83 |
| Race | | | 0.51† |
| Asian | 3 (3) | 2 (3) | |
| Black | 5 (5) | 3 (4) | |
| White | 89 (82) | 54 (75) | |
| More than one | 4 (4) | 7 (10) | |
| Unknown | 8 (7) | 6 (8) | |
| Ethnicity | | | 0.96 |
| Hispanic | 2 (2) | 1 (1) | |
| Non-Hispanic | 90 (83) | 59 (82) | |
| Unknown | 17 (16) | 12 (17) | |

‡Index outpatient stimulant prescription defined as first stimulant prescription after completing the CBCL upon referral. †Analysis compares three groups: Caucasian vs. not Caucasian vs. Unknown.

### *3.2 Pre-referral Characteristics*

As shown in Figure 2A, stimulants were the most commonly prescribed psychotropic medication class prior to patients being referred to the child psychiatric outpatient clinic, but there was no significant difference in the rate between the two groups. There were, however, significantly greater percentages of patients with CBCL-AAA T-scores ≥ 210 prescribed second-generation antipsychotics (SGAs) and antidepressants prior to referral compared to those with CBCL-AAA T-scores < 180.

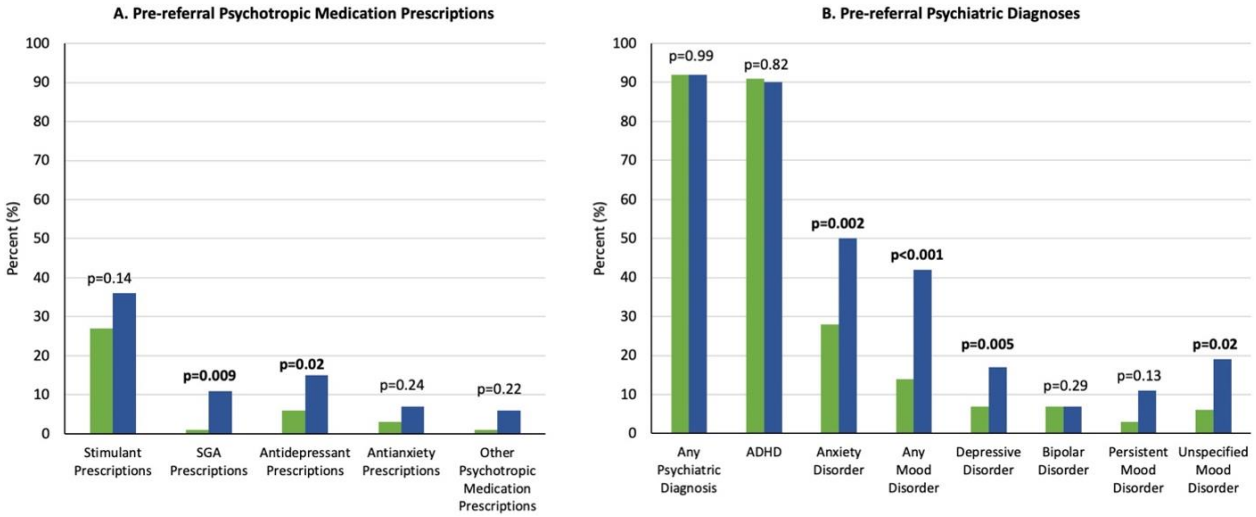


**Figure 2** Pre-referral Psychotropic Medication Prescriptions and Psychiatric Diagnoses.

There was no difference between the two groups in the percentage of patients with psychiatric diagnoses prior to referral (Figure 2B), but there was a significant difference in the total number of pre-referral diagnoses. On average, patients with CBCL-AAA T-scores ≥ 210 had more pre-referral psychiatric diagnoses compared to patients with CBCL-AAA T-scores < 180 (<180: 1.4 ± 0.9 vs. ≥210: 2.0 ± 1.2; p = 0.002). Examining the specific psychiatric diagnoses, patients with CBCL-AAA T-scores ≥ 210 had significantly higher rates of pre-referral anxiety disorder and mood disorder diagnoses, with the mood disorder diagnoses driven by depressive and unspecified mood disorders (Figure 2B).

### *3.3 Prescription Characteristics*

On average, patients with CBCL-AAA T-scores ≥ 210 had a higher total daily dose of their index stimulant prescription compared to patients with CBCL-AAA T-scores < 180 (Table 2). There were no significant differences between the two groups in the percentage of patients who changed their total daily dose of stimulant, patients whose index stimulant was an MPH formulation versus AMPH formulation, or patients who changed their stimulant formulation, or patients who received immediate- or extended-release stimulants (Table 2). Additionally, there was no significant difference in stimulant adherence, with both groups having stimulant prescriptions for an average of 72-75% of the three-month follow-up period.

**Table 2** Psychotropic medication prescription characteristics over the course of 3 months in patients with CBCL-AAA T-scores < 180 and patients with CBCL-AAA T-scores ≥ 210.

| | Patients with CBCL-AAA T-score <180 N = 109 | Patients with CBCL-AAA T-score ≥210 N = 72 | P-value[1] |
|---|---|---|---|
| **Stimulant Characteristics** | | | |
| Total daily dose of first stimulant (mg)[*] | 28.1 ± 18.4 | 32.6 ± 25.0 | **0.02** |
| Change in stimulant total daily dose | 67 (61) | 39 (54) | 0.33 |
| Days to change in stimulant total daily dose | | | 0.09 |
| Mean ± SD | 31.0 ± 17.2 | 31.8 ± 20.1 | |
| Median (IQR) | 28 (21) | 28 (27) | |
| First stimulant: MPH formulation | 81 (74) | 52 (72) | 0.46 |
| Change in stimulant formulation | 8 (7) | 5 (7) | 0.93 |
| Days to change in stimulant formulation | | | 0.78 |
| Mean ± SD | 70.8 ± 16.3 | 72.6 ± 10.9 | |
| Median (IQR) | 75.5 (14.5) | 69 (11) | |
| Type of first stimulant | | | 0.63 |
| Immediate-release (IR) | 31 (28) | 19 (26) | |
| Extended-release (ER) | 48 (44) | 36 (50) | |
| Multiple stimulant prescriptions with combination of IR and ER | 30 (28) | 17 (24) | |
| Percent of follow-up with stimulant prescriptions | 0.72 ± 0.26 | 0.75 ± 0.27 | 0.57 |
| Days to last stimulant prescription | | | 0.87 |
| Mean ± SD | 53.2 ± 31.0 | 54.8 ± 31.3 | |
| Median (IQR) | 64 (42) | 64 (30.5) | |

| | | | |
|---|---|---|---|
| **Combined Psychotropic Medication Class Characteristics** | | | |
| Percent of follow-up with any prescription | 0.73 ± 0.26 | 0.79 ± 0.26 | 0.27 |
| Total # of medication classes during follow-up | 1.2 ± 0.5 | 1.6 ± 0.7 | **0.02** |
| Total # of prescriptions written in 3 months (all classes) | 4.7 ± 2.8 | 6.3 ± 3.4 | **<0.001** |

[1]Analyses control for age at index stimulant prescription. [*]Total daily dose reported in the MPH dose equivalents as defined in the Methods.

Examining all psychotropic medication classes, patients with CBCL-AAA T-scores ≥ 210 were prescribed significantly more medication classes and had a significantly higher total number of prescriptions written in the three-month follow-up time compared to patients with CBCL-AAA T-scores < 180 (Table 2). However, there was no significant difference between the two groups in the percentage of follow-up with any psychotropic medication prescription.

As shown in Figure 3A, a significantly greater percentage of patients with CBCL-AAA T-scores ≥ 210 were prescribed stimulants and another psychotropic medication class, when looking at index and follow-up combined, compared to patients with CBCL-AAA T-scores < 180. This is reflected both at the index prescription and throughout follow-up when examined individually. A significantly greater percentage of patients with CBCL-AAA T-scores ≥ 210 had an additional psychotropic medication class prescribed along with their stimulant prescription at index, which was driven by SGA and antidepressant prescriptions (Figure 3B). One patient with CBCL-AAA T-scores < 180 had an SGA prescription at index and was prescribed a total daily dose of 25 mg, while nine patients with CBCL-AAA T-scores ≥ 210 had SGA prescriptions at index and were prescribed an average total daily dose of 7.1 ± 9.1 mg. This sample was too small to compare statistically. Similar to the pattern seen at index, a greater percentage of patients with CBCL-AAA T-scores ≥ 210 added another medication class during the three-month follow-up, and this was primarily driven by the addition of SGAs (Figure 3C). One patient with CBCL-AAA T-scores < 180 added an SGA and was prescribed a total daily dose of 4 mg, while seven patients with CBCL-AAA T-scores ≥ 210 added an SGA and were prescribed an average total daily dose of 15.3 ± 15.2 mg. Again, this sample was too small to compare statistically. Among the patients who added another medication class during follow-up, there was a statistically significant difference in the length of time for an additional medication to be added, but this difference was only two weeks: 42.9 days in those with CBCL-AAA T-scores ≥ 210 vs. 28.1 days in those with CBCL-AAA T-scores < 180 (Figure 3D). There was no significant difference between the two groups in the percentage of patients who added multiple medication classes (<180: 3% vs. ≥210: 4%; p = 0.63).

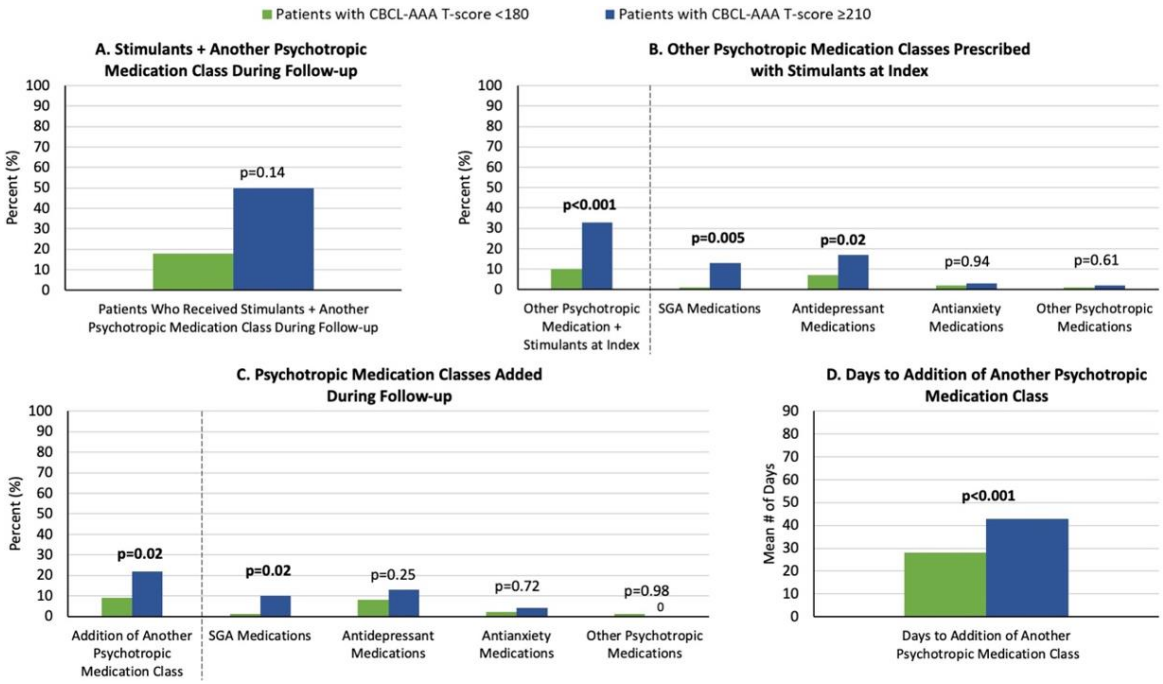


**Figure 3** Psychotropic Medication Prescriptions at Index and During Follow-up.

### *3.4 New Psychiatric Diagnoses and Emergency Room/Inpatient Visits*

As shown in Table 3, there were no significant differences between the two groups in the rates of newly developed mood disorder, psychosis, or suicidal ideation or attempt diagnoses during the three-month follow-up. Emergency room/inpatient visits were rare. There was no significant difference in the rates of these visits between the two groups (<180: 0% vs. ≥210: 3%; p = 0.18), although those with CBCL-AAA T-scores scores < 180 group had no ER visits or psychiatry inpatient admissions while the rate in those with CBCL-AAA T-scores ≥ 210 was 3%.

**Table 3** New mood, psychosis, and suicidal ideation/attempt diagnoses after index stimulant prescription.

| | Patients with CBCL-AAA T-score <180 N=109 | Patients with CBCL-AAA T-score ≥210 N=72 | P-value[1] |
|---|---|---|---|
| | N (%) | N (%) | |
| Any Mood Disorder | 5 (5) | 2 (3) | 0.84 |
| Depressive Disorders | 0 (0) | 2 (3) | 0.16 |
| Persistent Mood Disorders | 2 (2) | 0 (0) | 0.4 |
| Unspecified Mood Disorders | 3 (3) | 1 (1) | 0.57 |
| Bipolar Disorder | 0 (0) | 0 (0) | n/a |
| Psychosis | 0 (0) | 0 (0) | n/a |
| Suicidal Ideation or Attempt | 0 (0) | 1 (1) | 0.41 |

[1]Analyses control for age at index stimulant prescription.

## 4. Discussion

We found that among pediatric patients prescribed stimulants, those with a high level of emotional dysregulation as defined by their CBCL-AAA score received higher doses of stimulants and were more likely to receive treatment augmentation with SGA medication during the follow-up period than patients with a low level of emotional dysregulation. Although rare and not statistically significant, ER visits and inpatient psychiatric admissions occurred only in the stimulant-treated group with high levels of emotional dysregulation (3%), and not at all in the group with low emotional dysregulation. While suggestive of the negative impact of stimulant treatment, it is important to note that these visits/admissions may be due to the general severity of illness of patients with high emotional dysregulation or the higher dose of medication received, rather than as an outcome of treatment with stimulants.

Further, patients with an elevated CBCL-AAA profile had a significantly different diagnosis profile at referral than patients with lower scores, with higher scoring patients more likely to have pre-referral diagnoses of anxiety and mood disorders and more likely to already be taking medications to treat mood disorders (SGAs and anti-depressants). Of note, despite that CBCL-AAA T-scores ≥ 210 are highly associated with a diagnosis of bipolar disorder, only 7% of the high scoring patients had a pre-referral diagnosis of bipolar disorder [23]. Additionally, only 42% of the high scoring patients had a pre-referral mood disorder diagnosis, with unspecified mood disorder being the most common of those diagnoses at a rate of 19%.

High scoring patients also had a higher total daily dose of their index stimulant prescription. During the follow-up period, patients with high scores were more likely than those with low scores to add another psychotropic medication class to their treatment in addition to their original stimulant treatment (22% versus 9%). This difference was primarily driven by the addition of newly prescribed SGAs; patients with high levels of emotional dysregulation were more likely to receive a newly prescribed SGA along with their stimulant prescription during the follow-up period.

Prior literature has reported mixed outcomes for stimulant use in children with ADHD and BPD. Some studies found that stimulants are generally safe across all age groups with comorbid ADHD and BPD [3, 4]. These studies showed MPH to be well-tolerated with TEM, psychosis, or worsening of mood and without an increase in adverse events due to treatment [3, 4]. One study of stimulant-naïve children even found that those with high levels of anxiety/depression at baseline had decreased levels of irritability after MPH treatment [26].

However, our results are consistent with studies that report severe adverse events associated with stimulant treatment in bipolar populations. Some studies have reported hallucinations and other psychotic symptoms in children with ADHD due to stimulant treatment [9, 27]. Additionally, treatment-emergent mania and increased mood-cycling, including increased irritability, has been shown to occur after stimulant treatment in children with bipolar disorder [28, 29]. A study of hospitalized adolescents with BPD reported that history of stimulant treatment was associated with a more severe overall course of illness during hospitalization as measured by length of hospital stay, number of 'as needed' (PRN) medications, and need for seclusion/restraint to control patients' agitation [12]. While the authors indicated the more severe course could be due to variables other than stimulant treatment, this outcome was not accounted for by ADHD diagnosis, manic or mixed state, or anti-depressant treatment. Taken together, these findings raise the concern that clinicians who add SGAs or other mood stabilizers to stimulant treatment in patients with bipolar disorder and ADHD may be treating agitation, which is the result of stimulant use in this population. Given emerging evidence of poor outcomes with stimulants in patients with BPD, our study supports the notion that clinicians should be cautious when prescribing stimulants to children with high levels of emotional dysregulation.

In our study, we used the CBCL-AAA subscale T-scores as a proxy for high and low levels of emotional dysregulation. An emerging literature suggests that the CBCL may be useful in identifying children at risk for depression, anxiety, and bipolar disorder [20, 30-32]. This study, stratifying by high and low levels of emotional dysregulation, raises the possibility of using the CBCL as a simple, external, predictor of risk when prescribing stimulant medications. This is especially important for pediatricians, who may not have access to expert psychiatric diagnosis of pediatric BPD.

The pharmacologic mechanism underlying the effects of stimulants on emotional regulation, positive or negative, is unclear as is the neurobiology of emotional dysregulation. When stimulants do have a positive impact on emotional regulation, it may be due to improvement of executive functioning (improving ability to suppress emotional response) and/or impact on brain regions associated with emotional processing in the amygdala, prefrontal cortex, and inferior frontal gyrus (attenuating emotional reactivity) [33, 34]. Future research connecting the neurobiology of emotional dysregulation to the neuropharmacology of stimulants is needed to help guide clinicians in weighing the risks and the benefits of stimulant use in the setting of emotional dysregulation and to identify patients at risk for poor outcome.

The findings presented in this study are subject to methodological limitations. This sample only captures participants within one outpatient clinic over a defined time period, and the sample size is small relative to the total number of patients treated with stimulants. The sample of patients who received SGAs either at index or during follow-up was small and did not allow for more in depth analyses of prescription characteristics. Future studies would benefit from examining whether medication type or dosage varies by gender, age, or body weight and if combination treatment effects are different than stimulant treatment alone. Additionally, this study only follows patients for a limited time period. Follow-up CBCL-AAA scores were not available, which would have strengthened our investigation of the effects of stimulant treatment on emotional dysregulation over time. Information recorded in identifiable fields in our electronic health record limited the outcomes we were able to investigate. While it would have been informative to compare the adverse effect profile between the two groups, we did not have access to that information. This data does not address the outcome of patients who transferred care elsewhere or who did not follow-up within the clinics surveyed. It also does not address other important factors that can affect levels of emotional dysregulation such as environmental stressors or parenting styles. Finally, our sample was primarily causcasian and limited to patients within our academic-medical care center, so results may not be generalizable to other patient populations.

Despite these limitations, this study contributes to a literature suggesting caution in the use of stimulant medications in children with emotional dysregulation and supports the role of the CBCL in identifying children at risk for poor stimulant outcomes. Further research is needed to guide the safe prescription of stimulants across the spectrum of children with emotional dysregulation.

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**Author Contributions**

Hannah O'Connor was involved in designing the study and analyzing results, as well as writing the manuscript. Dr. Joseph Biederman conceived the idea, designed the study, and supervised the project. Maura DiSalvo collected data and analyzed the results. Dr. Gagan Joshi and Dr. Stephen V. Faraone supervised the project. Dr. Janet Wozniak was involved in designing the study and writing the manuscript.

**Competing Interests**

Hannah O'Connor has no conflicts of interest relevant to this article to disclose.

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commercialize a digital health intervention to improve adherence in ADHD. Through MGH corporate licensing, Dr. Biederman held a US Patent (#14/027,676) for a non-stimulant treatment for ADHD, a US Patent (#10,245,271 B2) on a treatment of impaired cognitive flexibility, and a patent pending (#61/233,686) on a method to prevent stimulant abuse. In 2022: Dr. Biederman received honoraria from UC Davis for Grand Rounds and the MGH Psychiatry Academy for tuition-funded CME courses. In 2021: Dr. Biederman received an honorarium for a scientific presentation from Multi-Health Systems, and a one-time consultation for Cowen Healthcare Investments. He received honoraria from AACAP, the American Psychiatric Nurses Association, BIAL - Portela & Cª. S.A. (Portugal), Medscape Education, and MGH Psychiatry Academy for tuition-funded CME courses. In 2020: Dr. Biederman received an honorarium for a scientific presentation from Tris and from the Institute of Integrated Sciences - INI (Brazil), and research support from the Food & Drug Administration. He received honoraria from Medlearning Inc, NYU, and MGH Psychiatry Academy for tuition-funded CME courses.

Maura DiSalvo has no conflicts of interest relevant to this article to disclose.

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2008, Bantam Books. Her spouse receives royalties from UpToDate; consultation fees from Indorsia, Cozen O'Connor, Noctrix, FoxRothschild, Sterne Kessler Goldstein & Fox, Teladoc Health, Inc., and The International Law Firm of Winston & Strawn LLP; and research support from Merck, NeuroMetrix, American Regent, NIH, NIMH, the RLS Foundation, and the Baszucki Brain Research Fund. In the past, he has received honoraria, royalties, research support, consultation fees or speaker's fees from: Emalex, Disc Medicine, Avadel, HALEO, OrbiMed, CVS, Otsuka, Cambridge University Press, Advance Medical, Arbor Pharmaceuticals, Axon Labs, Boehringer-Ingelheim, Cantor Colburn, Covance, Cephalon, Eli Lilly, FlexPharma, GlaxoSmithKline, Impax, Jazz Pharmaceuticals, King, Luitpold, Novartis, Neurogen, Novadel Pharma, Pfizer, Sanofi- Aventis, Sepracor, Sunovion, Takeda, UCB (Schwarz) Pharma, Wyeth, Xenoport, Zeo.

This work is published in honor of Joseph Biederman, MD, who passed away January 5, 2023. Dr. Biederman was a pioneer of child psychiatry and the founder of the field of pediatric psychopharmacology. He dedicated his career to examining the cause, diagnosis, and treatment of ADHD and related disorders across the lifespan, and was a fierce advocate for his patients and their families. Dr. Biederman mentored hundreds of people, both professionally and personally, and treated thousands of patients throughout his more than 40-years career at Massachusetts General Hospital. In addition to his exceptional competence as a psychopharmacologist, he was considered an empathetic physician beloved by all who knew him.

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