ORIGINAL RESEARCH

Key Words: bipolar, stimulant, attention deficit, augmentation, depression

Frequency of Stimulant Treatment and of Stimulant-Associated Mania/Hypomania in Bipolar Disorder Patients

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ABSTRACT ~ ***Objective:*** *Stimulants have been used to treat ADHD or augment bipolar depression treatment in patients with bipolar disorder (BD). However, the effects of stimulant treatment in BD patients have been insufficiently studied. To date, this is the largest study on amphetamine/methylphenidate treatment and associated mania/hypomania in BD patients.* ***Method****: Charts of patients evaluated at the Emory Bipolar Disorder Specialty Clinic from 7/05 to 10/07 and diagnosed with BD were randomly reviewed. Past diagnostic and treatment information were obtained from patient reports and collateral information. Bipolar diagnosis and past stimulant-associated mania were assessed by a board-certified psychiatrist using Structured Clinical Diagnostic Interview. Methylphenidate, amphetamine, and modafinil were considered stimulants. Multivariate regression models were used to identify predictors of receiving stimulant treatment and of experiencing stimulant-associated mania.* ***Results:*** *Of the 137 adult BD patients (72% BDI; 28% BDII/ NOS), 25% had prior stimulant treatment for ADHD or bipolar depression. Among those with prior stimulant treatment (21 with methylphenidate, 17 with amphetamine, and 6 with modafinil), 43% were treated with a concurrent mood stabilizer, and some with different types of stimulants sequentially. The rate of stimulant-associated mania/hypomania was 40%. Having axis-I comorbidity, absence of past substance addiction, and currently being unemployed were three factors significantly associated with prior stimulant treatment. After adjusting for important clinical variables, absence of axis-I comorbidity was associated with stimulant-associated mania.* ***Conclusions:*** *BD patients commonly receive stimulant treatment and often experience stimulant-associated mania/hypomania. More studies are needed to examine the safety and efficacy of stimulant treatment in BD patients.* Psychopharmacology Bulletin. *2008;41(4):37–47.*

INTRODUCTION

Despite recent therapeutic advances, bipolar depression remains a significant challenge for clinicians and a major source of suffering for patients (1–4). Additionally, patients with bipolar disorder (BD) often complain of cognitive or attentional problems (5), and many have comorbid ADHD. The latest

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National Comorbidity Survey Replication reported that 21% of BD patients also carry a diagnosis of ADHD (6). As a result, clinicians have resorted to using stimulants to treat refractory bipolar depression or comorbid ADHD in BD patients (7–10). Whether stimulants exert adverse effects on the course of BD is an important question with many clinical implications. However, to date, studies on the effects of stimulant treatment on BD patients have been very limited. Since mood-elevating agents such as antidepressants have been known to induce mania and rapid cycling in BD (11–13), it is possible that stimulants may produce similar adverse effects in BD patients. Two studies in adolescent BD patients suggested that prior stimulant treatment was associated with an earlier age at onset of BD (14) and a more severe hospital course (15). Other studies on the subject include 2 small studies on methylphenidate/amphetamine treatment in adult BD patients (7,9), one retrospective study on stimulant-associated treatment-emergent mania in pediatric BD patients (16), and one prospective study of amphetamine treatment in pediatric BD patients with comorbid ADHD (8), with mixed results. The only randomized clinical trial in adult BD patients has been with modafinil, given concurrently with a mood stabilizer for bipolar depression, with a manic switch rate of 15% (versus 11% with placebo) (10).

To date, this is the largest study of amphetamine/methylphenidate treatment and associated mania/hypomania in adult BD patients. Predictors of prior stimulant treatment and of stimulant-associated mania/hypomania in BD patients were also explored.

METHOD

137 consecutive alphabetically organized charts of adult patients evaluated at the Emory Bipolar Disorder Specialty Clinic from 7/05 to 10/07 and diagnosed with BD (type I, II, NOS) were reviewed. Demographic (age, ethnicity, education, employment) and clinical characteristics (sex, bipolar subtype, lifetime axis-I comorbid illnesses, age at onset of mood symptoms, age at first diagnosis of BD, duration of illness, number of affective episodes, family history, history of psychosis, number of suicide attempts, number of hospitalizations), as well as history of prior stimulant treatment, duration and reason for stimulant treatment, effect of stimulant treatment on mood, and stimulant-associated mania/hypomania were collected. Past diagnostic and treatment information were obtained by patient reports, collateral information where possible, and systematic psychiatric history at the initial evaluation by a board-certified psychiatrist (SNG). Bipolar diagnosis and *prior* stimulant-associated mania/hypomania were assessed by

a board-certified psychiatrist (SNG) using the Structured Clinical Interview for DSM-IV Axis I Disorders (17), the mood modules, at the initial evaluation. Specifically, the association of stimulants with past mania/hypomania was operationalized as time-related mania/hypomania following initiation of stimulant use (within 2 months or less of beginning stimulants), with no detectable relation to other medication changes. Background use of antidepressants or changes in other concomitant medications was also assessed, and where uncertain, possible association between stimulant use and manic/hypomanic episodes was not made. All stimulant treatment had occurred in the past, and thus assessment of stimulant-associated manic symptoms was retrospective. Substance addiction here refers to either substance abuse or addiction, based on DSM-IV criteria.

Agents considered stimulants for this study were methylphenidate (Ritalin, Concerta, Metadate, Focalin), amphetamine (Adderall, Dexedrine), pemoline (Cylert) and modafinil (Provigil). Mood stabilizers included lithium, divalproex sodium, carbamazepine, or lamotrigine.

Demographic and clinical characteristics of groups *with* versus *without* prior stimulant treatment, and of groups *with* versus *without* stimulant-associated mania were reported descriptively and further analyzed in regression models. Predictors of two outcomes, prior stimulant treatment and stimulant-associated mania/hypomania, were explored using backward conditional stepwise logistic regression models. In predicting prior stimulant treatment, variables included in the model were BD subtype, axis-I comorbidity, past substance addiction, current substance addiction, age at onset of mania, sex, age at first diagnosis of BD, education, and employment. In predicting stimulant-associated mania, variables included in the model were duration of stimulant treatment, concurrent mood stabilizer treatment, and axis-I comorbidity. We assessed multiple regression models with different variables, but no more than one variable per ten subjects per model, as is the standard recommendation (18).

RESULTS

Table 1 presents selective demographic and clinical characteristics of the total patient sample. Of the 137 BD patients, 25% had prior stimulant treatment, either for childhood or adult ADHD or augmentation of bipolar depression treatment (low energy or poor concentration). Table 2 compares demographic and clinical characteristics of two groups based on prior stimulant treatment. No or modest differences were noted, except for lifetime axis-I comorbidity and history of ADHD. Over half of patients treated with stimulants had a reported history of childhood or adult ADHD.

TABLE 1

SELECTIVE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE TOTAL PATIENT SAMPLE (N = 137)

CHARACTERISTICS	
Age, mean ± SD (years)	38.8 ± 12.6
Sex, % (N)	
Male	51.1 (70)
Female	48.9 (67)
Ethnicity, % (N)	
White	94.9 (130)
Others	5.1 (7)
BD subtype, % (N)	
BDI	72.3 (99)
BDII or NOS	27.7 (38)
Any axis I comorbidity, % (N)	
Yes	63.5 (87)
No	36.5 (50)
Axis-I comorbid conditions, %[a]	
GAD	19.5
Panic disorder	14.9
PTSD	8.0
Eating disorder	5.7
OCD	11.5
Substance addiction (past or current)	64.4
Childhood or adult ADHD	21.8
Prior stimulant treatment, % (N)	
Yes	24.8 (34)
No	75.2 (103)
Stimulants, % (N)[b]	
Methylphenidate	56.8 (21)
Amphetamine	45.9 (17)
Modafinil	16.2 (6)
Pemoline	2.7 (1)
Duration of stimulant treatment, mean ± SD (weeks)	144 ± 207
Range	2 – 728
Median	30

[a]Percentage >100 due to some patients having more than one axis-I comorbid conditions.
[b]Percentage >100 due to some patients taking more than one stimulant sequentially.
Abbreviations: SD, standard deviation; GAD, Generalized Anxiety Disorder; PTSD, Post-traumatic Stress Disorder; OCD, Obsessive Compulsive Disorder; ADHD, Attention/Deficit Hyperactivity Disorder.

Of those with prior stimulant treatment, 43% took stimulants concurrently *with* a mood stabilizer (lithium, valproate, carbamazepine, or lamotrigine) and/or antipsychotic (olanzapine or aripiprazole), and 57% took stimulants *without* a concurrent mood stabilizer or antipsychotics. Stimulants were used to treat ADHD in 54% of the cases and for

TABLE 2

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF 137 BD SUBJECTS WITH VERSUS WITHOUT PRIOR STIMULANT TREATMENT

CHARACTERISTICS	NO STIMULANT TREATMENT (N = 103)[a]	PRIOR STIMULANT TREATMENT (N = 34)[a]	MEAN DIFFERENCE[#] (95% CI) OR OR*(95% CI)
Age, mean ± SD (years)	39.3 ± 12.6	37.4 ± 12.8	1.94 (−3.0, 6.9)[#]
Education, % (N)			
HS	21.0 (21)	26.5 (9)	0.75 (0.30, 1.84)*
College and above	79.0 (79)	73.5 (25)	
Current employment, % (N)			
No	40.0 (40)	55.9 (19)	0.53 (0.24, 1.16)*
Yes	60.0 (60)	44.1 (15)	
Ethnicity, % (N)			
White/Caucasian	94.3 (99)	97.1 (34)	0.49 (0.057, 4.22)*
Other	5.7 (6)	2.9 (1)	
Sex, % (N)			
Male	49.5 (51)	55.9 (19)	0.77 (0.36, 1.69)*
Female	50.5 (52)	44.1 (15)	
Bipolar subtype, % (N)			
I	75.7 (78)	61.8 (21)	0.52 (0.23, 1.18)*
II, NOS	24.3 (25)	38.2 (13)	
Age at onset of mood symptoms, mean ± SD (years)	18.8 ± 9.2	16.4 ± 8.2	2.4 (−1.1, 5.9)[#]
Age at first diagnosis of BD, mean ± SD (years)	32.4 ± 11.4	33.2 ± 13.1	0.81 (−5.6, 4.0)[#]
Duration of illness, mean ± SD (years)	20.0 ± 12.9	21.0 ± 12.7	0.96 (−6.0, 4.1)*
Number of total affective episodes,%(N)			
=5 episodes	20.2 (17)	13.3 (4)	1.41 (0.42, 4.72)[#]
>5 episodes	79.8 (67)	86.7 (26)	
Number of manic episodes, %(N)			
=5	41.3 (33)	26.9 (6)	2.27 (0.82, 6.31)[#]
>5	58.7 (46)	73.1 (19)	
Number of depressive episodes, % (N)			
=5	40.2 (31)	21.4 (6)	2.47 (0.90, 6.79)[#]
>5	59.8 (46)	78.6 (22)	
Family history, % (N)			
BD	48.5 (48)	54.5 (18)	
Other[b]	42.4 (42)	36.4 (12)	—
None	9.1 (9)	9.1 (3)	
Number of suicide attempts, mean ± SD	0.7 ± 1.5	0.9 ± 1.9	0.19 (−0.8, 0.4)*
Number of hospitalization, mean ± SD	1.8 ± 2.2	1.9 ± 3.1	0.04 (−1.0, 0.9)*
History of psychosis, % (N)	42.6 (43)	35.3 (12)	0.74 (0.33, 1.65)[#]
Past substance addiction,% (N)	44.7 (46)	32.3 (11)	0.59 (0.26, 1.34)[#]

(*continued*)

TABLE 2 (*CONTINUED*)

CHARACTERISTICS	NO STIMULANT TREATMENT (N = 103)[a]	PRIOR STIMULANT TREATMENT (N = 34)[a]	MEAN DIFFERENCE[#] (95% CI) OR OR*(95% CI)
Current substance addiction, % (N)	11.6 (12)	20.6 (7)	1.97 (0.70, 5.49)[#]
Having axis I comorbid conditions, % (N)	57.3 (59)	82.3 (28)	3.48 (1.33, 9.13)[#]
History of childhood or adult ADHD, % (N)	0.97 (1)	52.9 (18)	114.8 (14.3, 919.9)[#]

[a]Variability in column numbers reflects missing data for variable being examined.
[b]Other: ADHD, suicidality, unipolar depression, GAD, OCD, substance addiction, schizophrenia.
*refers to odds ratio.
[#]refers to mean difference.

augmentation of bipolar depression treatment in 46%. The overall rate of stimulant-associated mania/hypomania was 40.5% in BD patients with prior stimulant treatment. In particular, 50% of patients taking stimulants *without* a concurrent mood stabilizer or antipsychotics experienced stimulant-associated mania/hypomania versus 31.2% of patients taking stimulants concurrently *with* a mood stabilizer and/or an antipsychotic (RR = 1.60, 95% CI: 0.68, 3.74). Of the patients not experiencing stimulant-associated mania, 33% reported some clinical benefit with stimulants for mood symptoms.

Tables 2 and 3 provide univariate comparisons of those who received stimulants versus not, and those who experienced stimulant-induced mania versus not. Small to medium effect size differences were seen between groups in many variables. Relevant variables were included in multivariate regression models. In the first regression model, three factors emerged as being significantly associated with prior stimulant treatment: axis-I comorbidity (OR = 9.85, 95% CI: 2.6, 37.1, p=0.001), *no* past substance addiction (OR = 5.67, 95% CI: 1.77, 18.21, p=0.004), and currently being unemployed (OR = 3.19, 95% CI: 1.15, 8.85, p=0.026). In the second regression model (after controlling for duration of stimulant treatment and concurrent mood stabilizer use), the only significant predictor of stimulant-associated mania/hypomania was absence of axis-I comorbidity (OR = 10.6; 95% CI: 1.1, 106.6, p=0.045).

DISCUSSION

In a clinical sample of patients with BD, stimulant treatment was frequent (25%) and stimulant-associated mania was common (40%). Furthermore, multivariate regression suggested predictors of prior stimulant treatment to be lifetime axis-I comorbidity, no past substance

TABLE 3

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF 37[a] BD PATIENTS WITH PRIOR STIMULANT TREATMENT

CLINICAL CHARACTERISTICS	STIMULANT-ASSOCIATED MANIA/ HYPOMANIA (N = 15)[b]	NO MANIC SWITCH (N = 22)[b]	MEAN DIFFERENCE[#] (95% CI) OR OR*(95% CI)
Sex, % (N)			
Male	46.7 (7)	63.6 (14)	2.0 (0.53, 7.60)*
Female	53.3 (8)	36.4 (8)	
Diagnosis, % (N)			
BD I	60.0 (9)	63.6 (14)	0.86 (0.22, 3.31)*
BD II, NOS	40.0 (6)	36.4 (8)	
Age at onset of a major mood episode, mean ± SD (years)	16.7 ± 6.4	16.8 ± 9.3	0.11 (−5.7, 5.5)[#]
Duration of illness, mean ± SD (years)	21.9 ± 13.7	20.1 ± 11.6	1.7 (−6.7, 10.2)[#]
Age at first diagnosis of BD mean ± SD (years)	33.4 ± 13.9	33.8 ± 12.6	0.42 (−9.5, 8.7)[#]
Number of total affective episodes			
=5 episodes	16.7 (2)	10.0 (2)	0.56 (0.068, 4.57)*
>5 episodes	83.3 (10)	90.0 (18)	
Number of manic episodes			
=5	25.0 (3)	21.4 (3)	0.90 (0.14, 5.65)*
>5	75.0 (9)	78.6 (11)	
Number of depressive episodes			
=5	33.3 (4)	11.1 (2)	0.25 (0.037, 1.67)*
>5	66.7 (8)	88.9 (16)	
Family history, % (N)			
BPD	50.0 (6)	58.8 (10)	
Other	33.3 (4)	29.4 (5)	—
No	16.7 (2)	11.8 (2)	
Number of suicide attempts, mean ± SD	1.1 ± 2.7	0.6 ± 0.91	0.54 (−0.7,1.8)[#]
Number of hospitalization, mean ± SD	1.6 ± 2.1	1.9 ± 3.5	0.26 (−2.3, 1.8)[#]
History of psychosis, % (N)	40.0 (6)	27.3 (6)	1.78 (0.44, 7.18)*
History of substance addiction			
Past	33.3 (5)	27.3 (6)	1.33 (0.32, 5.55)*
Current	20.0 (3)	22.7 (5)	0.85 (0.17, 4.26)*
Having lifetime axis-I comorbidity[c]	66.7 (10)	90.9 (20)	0.20 (0.033, 1.22)*
History of comorbid conditions, % (N)			
Zero or one	46.7 (7)	45.5 (10)	0.95 (0.26, 3.55)*
Two or more	53.3 (8)	54.5 (12)	

(*continued*)

TABLE 3 (*CONTINUED*)

CLINICAL CHARACTERISTICS	STIMULANT-ASSOCIATED MANIA/HYPOMANIA (N=15)[b]	NO MANIC SWITCH (N=22)[b]	MEAN DIFFERENCE[#] (95% CI) OR OR*(95% CI)
History of ADHD (childhood or adult), % (N)	53.3 (8)	54.5 (12)	0.95 (0.26, 3.55)*
Stimulant taken concurrently with MS or antipsychotic[d], % (N)	33.3 (5)	52.4 (11)	0.46 (0.12, 1.79)*
Duration of stimulant treatment, mean ± SD (weeks)	137.1 ± 234	150.0 ± 191.8	12.9 (−143.5, 69.4)[#]
Stimulant effect on mood symptoms, % (N)			
Slightly better		33.3 (7)	—
Unchanged	—[##]	47.6 (10)	
Worse	19.0 (4)		
Employment, % (N)			
Yes	33.3 (5)	50.0 (11)	0.50 (0.13, 1.95)*
No	66.7 (10)	50.0 (11)	
Education, % (N)			
HS	33.3 (5)	18.2 (4)	0.44 (0.10, 2.04)*
College and above	66.7 (10)	81.8 (18)	

[a]Three patients reported history of taking a stimulant with and without a concurrent mood stabilizer; therefore, 3 additional stimulant trials were added.
[b]Variability in column numbers reflects missing data for variable being examined.
[c]Axis-I comorbidity consisted of substance addiction, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive compulsive disorder, eating disorder, or ADHD.
[d]MS, mood stabilizer (lithium, divalproex, carbamazepine, lamotrigine); antipsychotics observed in this study consisted of olanzapine or aripiprazole.
*Refers to odds ratio.
#Refers to mean difference.
##By definition, these patients worsened on stimulants due to having mania.

addiction, and being currently unemployed. Moreover, after other clinical factors were controlled for, absence of axis-I comorbidity significantly correlated with stimulant-associated mania/hypomania. It is important to note that causality cannot be established based on such observational data. However, our data demonstrate that there is a non-zero rate of association of mania with stimulant use observationally, and that the possibility of a causal relationship cannot be presumed to be nonexistent.

There have been 6 studies (7–10, 16, 19) on stimulant treatment in pediatric and adult BD patients (2 with modafinil as an augmentation for adult bipolar depression, 4 with methylphenidate or amphetamine with or without a concurrent mood stabilizer for ADHD or bipolar depression in adults or children). Of studies with methylphenidate or amphetamine, the largest sample was 30, followed for up to 16 weeks, while our study followed 36 subjects (excluding one patient treated only with modafinil), for an average of 144 weeks (median = 30 weeks). The

higher rate of stimulant-associated mania/hypomania in our study may be related to larger sample size, longer duration of follow up, and real-world treatment setting (i.e., use of stimulants with and without concurrent mood stabilizer).

The findings of our regression models are unique and not previously addressed in other studies. Why BD patients receive stimulant treatment is an important question. Our exploratory results suggest that not having past substance addiction and having axis-I comorbidity were factors that led to more stimulant treatment. Interestingly, currently unemployed BD patients were more likely to have prior stimulant treatment, which may imply that stimulant use may not enhance longevity of employment status. About one-third of the patients who did not experience stimulant-associated mania or hypomania seemed to have some mood benefits with stimulants. However, again causality cannot be established and thus we do not know whether such benefit can be attributed to stimulant use or not. A conservative judgment might be that while some patients may benefit from stimulant use for mood symptoms without developing mania/hypomania, in our sample, such benefit was outweighed by a larger group that experienced associated mania/hypomania. Somewhat surprisingly, the only predictor of stimulant-induced mania/hypomania we identified was absence of axis-I comorbidity. This result was exploratory, although adjusted for some important clinical confounding factors (like duration of stimulant treatment and concurrent mood stabilizer). Since this finding contradicts studies of antidepressant-induced mania, which suggested that substance abuse, for example, is such a predictor (20), future studies are needed to reassess this observation.

Among the methodological limitations of this study are its observational nature and retrospective design. Potential confounding factors include mania/hypomania as the natural course of the bipolar illness or associated with concurrent antidepressant use. In the course of the clinical interview, the investigator attempted to isolate the effect of stimulants specifically, in time-relation to acute mania/hypomania, as opposed to background use of antidepressant or other medications. However, the possibility of recall bias exists with a retrospective study. Lack of systematic assessment of past ADHD using diagnostic rating scales is another limitation of the study. It was unknown how reported prior ADHD diagnosis was assessed by patients' previous clinicians. Misdiagnosis thus could go in either direction (more ADHD than diagnosed or less ADHD than diagnosed) and no specific direction of bias can be assumed.

In summary, BD patients received stimulant treatment rather frequently (1:4), and stimulant-associated mania/hypomania was significant (40%).

Additionally, currently being unemployed, no past substance addiction, and having axis-I comorbidity were significantly associated with prior stimulant treatment. An exploratory finding suggested that absence of axis-I comorbidity may be related to increased risk of stimulant-associated mania. More studies are needed to examine the safety and efficacy of stimulant treatment in BD patients.✤

DISCLOSURES

Dr. Ghaemi currently receives research grants from GlaxoSmith Kline and Pfizer. He currently serves on the speakers' bureaus of GlaxoSmithKline, Astra Zeneca, Pfizer, Janssen and Abbott Laboratories, and has served on the advisory boards of GSK, Janssen, Pfizer, Shire, and Abbott Laboratories. Neither he nor his family hold equity positions in pharmaceutical corporations.

Dr. Wingo has no disclosures of potential conflicts of interest.

FUNDING SOURCE

None.

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