

# Bupropion as an Add-on Therapy in Depressed Bipolar Disorder Type I Patients With Comorbid Cocaine Dependence

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**Objectives:** The treatment of bipolar disorder type I (BD-I) with a comorbid cocaine dependence disorder (CDD) is a challenge in current psychiatric practice. Drugs with proven efficacy in manic/mixed episodes, such as atypical antipsychotics and mood stabilizers, sometimes do not prevent depressive relapses; on the other hand, the use of antidepressants during acute depressive episodes may increase the risk of a manic switch. The aim of the present study was to investigate the short-term efficacy of bupropion augmentation in acutely depressed BD-I patients with co-occurring CDD.

**Methods:** Twelve depressed BD-I patients, with a comorbid CDD, treated with valproate 1000 to 1500 mg/d and aripiprazole 10 mg/d, were randomly assigned to receive bupropion 150 mg/d as an open-label add-on therapy (n = 5) or to continue their previous treatment (n = 7).

**Results:** After 4 weeks of observation, patients receiving add-on therapy with bupropion have improved in terms of Hamilton Depression Rating Scale scores and Drug Abuse Screening Test scores, with respect to those of the comparison group, whereas no significant increase of Young Mania Rating Scale scores over time was observed.

**Conclusions:** Our preliminary findings suggest that combining bupropion with mood stabilizers and atypical antipsychotics may be a good therapeutic option in short-term treatment of depressed BD-I patients with comorbid CDD.

**Key Words:** bipolar disorder, cocaine dependence disorder, bupropion, add-on strategies

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A wide percentage of bipolar disorder type I (BD-I) patients are affected by comorbid substance use disorders (SUDs),<sup>1</sup> with alcohol, *Cannabis*, and cocaine as most involved substances.<sup>2</sup> In large epidemiological studies on BD-I patients, lifetime prevalence rates of alcohol or other SUDs were of 60% and 40%, respectively.<sup>3,4</sup> The relations between BD and SUD are complex, and patients may be divided into different subgroups: 1) those using alcohol or drugs as a self-medication for depressive and manic symptoms; 2) those in whom substance use may

precipitate a latent mood disorder; and 3) those in whom the co-occurrence of the 2 conditions may be the result of common risk factors.<sup>5</sup>

The natural history of BD-I is characterized by recurrent manic/mixed and depressive episodes. The treatment of each type of acute episode is associated with the risk of a mood switch—from mania to depression and vice versa. Treatment-emergent mania has been especially associated with antidepressants (ADs), although recent data suggest that this risk has been probably overestimated.<sup>6,7</sup> On the other hand, efficacious treatments for manic/mixed episodes, such as second-generation antipsychotics (SGAs) and mood stabilizers (MSs), sometimes do not succeed in preventing depressive relapses,<sup>8,9</sup> and first-generation antipsychotics are reported to even accelerate depressive switches.<sup>10</sup> In BD without comorbid SUD, quetiapine monotherapy and olanzapine/fluoxetine combination are the only 2 FDA-approved therapeutic strategies.<sup>11,12</sup> Other recommended treatment options are MSs, olanzapine monotherapy,<sup>13</sup> and combined SGA/MS treatments.<sup>14</sup> In a recent guideline, Yatham et al<sup>15</sup> state that bupropion or selective serotonin reuptake inhibitors, in conjunction with an MS, could be safely used as first-line options for the short-term treatment of acute BD. In patients experiencing a depressive relapse during maintenance treatment with an atypical antipsychotic, a reduction in doses is also suggested to achieve a clinical improvement.<sup>16</sup>

The treatment of BD with concomitant cocaine dependence disorder (CDD) is even more complex. Bipolar disorder type I patients with SUD often report an early illness onset and a worse prognosis.<sup>17</sup> They also show a higher occurrence of acute mood episodes, violent conducts, and suicidal behaviors with respect to BD-I patients without substance-related disorders.<sup>18</sup> Nevertheless, only a small number of studies focus on this important subpopulation of patients.<sup>19–22</sup> The reasons for this paucity of data might be the following: a current SUD is usually an exclusion criteria in most of the pharmacological studies on BD-I, so the available data on efficacy and safety of pharmacological treatments are few.<sup>23</sup> Moreover, patients with SUD often show poor compliance to treatment and have a high rate of dropouts, thus resulting in a reduced study completion. Nevertheless, the large percentage of BD-I complicated by SUD highlights the need to provide more information about these patients, particularly at risk for suicide, aggression, and impulsivity and with frequent legal issues.<sup>24</sup>

In an open-label study by Brady et al,<sup>25</sup> valproate was reported to significantly improve depressive and manic symptoms and to reduce the amount of substances used in 9 bipolar patients with comorbid alcohol, cocaine, or polysubstance abuse. Same results were reported by Salloom et al<sup>26</sup> in a sample of 7 bipolar patients with comorbid CDD. Valproate, combined with lithium or other agents, is therefore recommended for the management of cocaine dependence in BD.<sup>27</sup>

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TABLE 1. Demographic and Clinical Variables

Subject Details	Add-on		No Add-on		F	ANOVA	
	(n = 5)		(n = 7)			df	P
Variable	Mean	SD	Mean	SD			
Age, y	38.6	4.4	38.3	8.4	0.01	1,10	0.94
Education, y	12.8	1.8	10.9	2.7	1.98	1,10	0.19
Age of BD onset, y	24.0	5.8	24.7	5.6	0.05	1,10	0.83
Duration of BD illness, y	14.6	5.9	13.6	5.5	0.09	1,10	0.76
Acute episodes of BD illness	3.8	1.8	5.9	3.0	1.88	1,10	0.20
Depressive episodes	2.2	1.3	3.3	1.4	1.89	1,10	0.19
Manic/mixed episodes	1.6	0.5	2.6	1.7	1.45	1,10	0.25
Hospitalizations caused by BD	1.6	0.5	2.4	1.5	1.34	1,10	0.27
Age of SUD onset, y	28.6	8.6	31.3	9.1	0.27	1,10	0.61
Duration of SUD illness, y	10.0	6.1	7.0	2.7	1.37	1,10	0.27
Hospitalizations caused by SUD	0.4	0.5	0.4	0.8	0.01	1,10	0.94
	n	%	n	%		$\chi^2$	P
Sex						1.03	0.31
Female	2	40.0	1	14.3			
Male	3	60.0	6	85.7			
Married	0	0.0	1	14.3		0.78	0.37
Employed	3	60.0	5	71.4		0.17	0.68
Familiarity for mood disorders	3	60.0	5	71.4		0.17	0.68
Familiarity for SUDs	1	20.0	1	14.3		0.07	0.79
Psychotic features during the acute phases of the illness	3	60.0	2	28.6		1.19	0.27
Rapid-cycling BD	0	0.0	1	14.3		0.78	0.37
BD onset preceding SUD onset	4	80.0	6	85.7		0.07	0.79
Substance currently used							
Cocaine	5	100.0	7	100.0		0.01	0.99
Alcohol	1	20.0	2	28.6		0.04	0.83
Cannabinoids	3	60.0	5	71.4		0.17	0.68
Opiates	1	20.0	1	14.3		0.07	0.79

df indicates degrees of freedom (effect, error).

Aripiprazole, for its particular mechanism of action as a partial dopamine-2 receptor agonist, has also been suggested to have some efficacy on BD with comorbid SUD.<sup>28,29</sup> A study conducted on bipolar and schizoaffective patients with current SUD evidenced a significant improvement in mood symptoms and substance craving after shifting from other antipsychotics to aripiprazole in 9 patients with cocaine-related disorders.<sup>30</sup>

The role of bupropion in the treatment of CDD has been reviewed by Castells and colleagues,<sup>31</sup> and it was proposed as a promising therapeutic strategy, especially in dual opioid-cocaine-dependent patients,<sup>32</sup> but currently, there are no available data on BD patients with comorbid CDD. The aim of the present study was to investigate the efficacy of bupropion as a short-term add-on therapy to combined MS/SGA treatment in a sample of acutely depressed BD-I patients with comorbid CDD.

## METHODS

### Subjects and Procedures

Patients aged 18 to 60 years, consecutively admitted to Psychiatric Rehabilitation Clinic "Villa Jolanda" (Jesi, Italy) from January 2012 to December 2012 with a *DSM-IV-TR* (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,

*Text Revision*) (American Psychiatry Association, 2000) diagnosis of major depressive episode in BD-I and comorbid CDD were considered eligible for the study. Inclusion criteria were Hamilton Depression Rating Scale (HAM-D)<sup>33</sup> score of 17 or higher at baseline, urinary samples positive for cocaine consumption, current maintenance treatment with MSs and/or antipsychotics, and good compliance. Exclusion criteria were the presence of a medical condition that could either interfere with the assessment of drug treatment or be unsafe for the patient (ie, cirrhosis, renal impairment, unstable hypertension, hypotension, diabetes mellitus, convulsions), pregnancy and breastfeeding, or noneffective contraception. The study was approved by the local ethics committee and conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki (1964). All participants provided written informed consent before enrollment. Patients' medical and family history was collected and then recorded in a specific Case Report Form. Fifteen depressed BD-I inpatients were evaluated; 14 gave their written informed consent and were enrolled in the study (T0). Twelve patients were in treatment with valproate 1000 to 1500 mg/d (mean dosage,  $1458 \pm 144$  mg/d; mean blood level,  $73.1 \pm 16.2$  mg/L) plus aripiprazole 20 mg (n = 12), 1 patient was treated with valproate 1500 mg/d plus olanzapine 20 mg, and 1 patient was treated with lithium 900 mg

**TABLE 2.** HAM-D, DAST, and YMRS Scores: Overtime Changes and Response Rate

	Add-on (n = 5)		No Add-on (n = 7)		ANOVA		F	df	P	Duncan Post Hoc Test
	Mean	SD	Mean	SD	Effect	Significant Effects				
HAM-D										
T0	20.8	1.5	20.9	2.0	Group	4.96	1,10	0.050	Add-on<No add-on	
T1	20.0	1.9	19.9	1.8	Time	50.54	2	< 0.001	T2<T0; T2<T1	
T2	13.0	2.1	19.1	1.7	Group × time	25.25	2,20	< 0.001	Add-on T2<No add-on T2	
DAST										
T0	16.4	1.1	17.6	1.5	Group	8.10	1,10	0.017	Add-on<No add-on	
T1	15.8	1.6	16.7	1.3	Time	25.65	2	< 0.001	T2<T0; T2<T1	
T2	11.0	1.9	15.9	2.5	Group × time	8.84	2,20	0.018	Add-on T2<No add-on T2	
YMRS										
T0	4.8	3.5	3.1	1.1	Group	1.01	1,10	0.320	/	
T1	4.0	2.8	3.0	1.2	Time	4.76	2	0.020	T2<T0	
T2	3.4	2.9	2.4	0.5	Group × time	0.64	2,20	0.538	/	
						Expected vs Observed $\chi^2$				
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>		$\chi^2$	<b>df</b>	<b>P</b>		
Response rate at T2						12.01	5	0.034		
Full response (HAM-D reduction ≥50%)	1	20	0	0						
Partial response (HAM-D reduction >25% and <50%)	4	80	0	0						
No response (HAM-D reduction <25%)	0	0	7	100						
df indicates degrees of freedom (effect, error).										

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(blood level, 0.7 mmol/L) plus aripiprazole 20 mg. Treatments with valproate or lithium were continued at the same dosage, whereas SGA dosage was halved (aripiprazole 10 mg/d, olanzapine 10 mg/d). After 2 weeks (T1), 2 patients retired their consent to the study and dropped out. The other 12 patients, all treated with valproate 1000 to 1500 mg/d (mean dosage,  $1458 \pm 144$  mg/d; mean blood levels,  $73.5 \pm 10.1$ ) plus aripiprazole 10 mg/d were randomly assigned to one of the following 2 groups: the first group (patients,  $n = 7$ ) continued the previous treatment; in the second group (patients,  $n = 5$ ), bupropion 150 mg/d was prescribed as an open-label add-on therapy. Patients were told that bupropion was added as an AD agent, whereas no mention was made of its possible efficacy on cocaine craving. After 4 weeks of treatment, participants were reassessed (T2).

### Effectiveness Assessments

The primary end point was to assess the improvement on depressive symptoms in terms of mean HAM-D scores and frequencies of full responders (HAM-D score reduction  $\geq 50\%$ ), partial responders (HAM-D score reduction  $> 25\%$  and  $< 50\%$ ), and no responders (HAM-D score reduction  $< 25\%$ ).

The secondary end point was to evaluate the improvement on symptoms of drug abuse, as measured by the Drug Abuse Screening Test (DAST).<sup>34</sup> Symptoms of manic/hypomanic switches were also measured by means of the Young Mania Rating Scale (YMRS).<sup>35</sup> Treatment outcomes were assessed at week 0 (T0), week 2 (T1), and week 6 (T2).

### Statistical Analysis

Statistical analysis was performed using Statistica 6.1 software (Statsoft Italia Srl., Vigonza, Padova, Italy). Chi-square

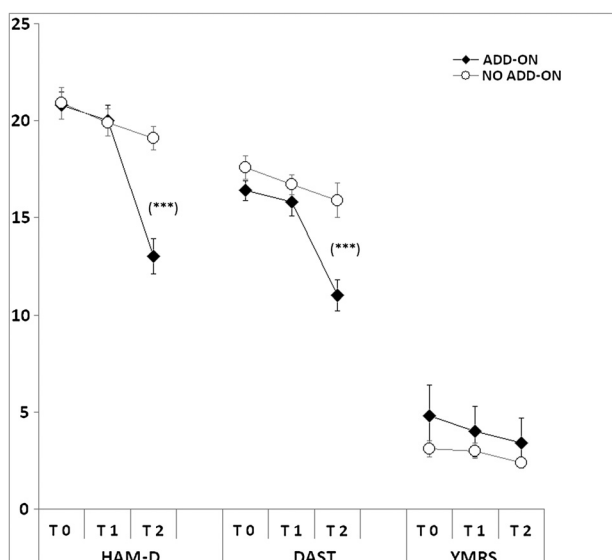
tests were used to compare categorical sociodemographic and clinical data. One-way analysis of variance (ANOVA) was used to analyze the continuous demographic and clinical data.

A 2-group ("ADD-ON" vs "NO ADD-ON")  $\times$  3-time (T0, T1, T2) mixed ANOVA was performed to assess the between-group significant changes over time in terms of HAM-D, DAST, and YMRS scores. Homogeneity of variance was assessed by means of Brown-Forsythe test. Significant effects ( $P < 0.05$ ) were dissected using Duncan post hoc test.

### RESULTS

The 2 groups ("ADD-ON," "NO ADD-ON") were comparable in terms of age, sex, education, marital and employment status, years of BD and CDD, number of acute mood episodes, number of hospitalizations, and current use of substances other than cocaine (Table 1). The onset of BD preceded the CDD in the majority of cases (4 of 5 patients in the "ADD-ON" group and 6 of 7 patients in the "NO ADD-ON" group).

All the patients assessed at T1 completed the study, and none dropped out. At the end of the study period (T2), 4 (80%) patients in the "ADD-ON" group could be classified as "partial responders" and 1 (20%) as "full responder," whereas all the patients in the "NO ADD-ON" group ( $n = 7$ , 100%) could be classified as "no responders," and the difference was statistically significant (observed vs expected frequencies,  $\chi^2_3 = 12.001$ ,  $P = 0.035$ ). The 2-group  $\times$  3-time ANOVA showed that, at T2, the HAM-D and DAST scores were significantly lower in the "ADD-ON" group with respect to the "NO ADD-ON" group, whereas no differences were observed in terms of YMRS score (Table 2; Fig. 1). The following side effects were reported: (a) in the "ADD-ON" group: headache ( $n = 2$ , 40%), insomnia ( $n = 1$ , 20%), nausea ( $n = 2$ , 40%); (b) in the "NO ADD-ON"



**FIGURE 1.** HAM-D and DAST scores significantly decreased at T2 in the bupropion ADD-ON group with respect to the NO ADD-ON group. \*\*\*Duncan post hoc test,  $P < 0.001$ . Vertical bars denote the SEs.

group: nervousness ( $n = 1$ , 14.3%), anxiety ( $n = 1$ , 14.3%), nausea ( $n = 2$ , 28.6%), fatigue ( $n = 2$ , 28.6%). None of the participants (0%) experienced a manic/hypomanic episode (*DSM-IV* criteria) or YMRS scores higher than 8 at T1 or T2.

## DISCUSSION

Bupropion, as an add-on therapy to an MS in the treatment of acute BD, was reported to have good efficacy and a lower risk of treatment-emergent mania when compared with other ADs, such as venlafaxine and sertraline.<sup>36</sup> Our findings suggest that bupropion augmentation may be used as a promising augmentation strategy also in depressed BD-I patients with co-occurring CDD. Many studies focused on the causal relation between BD-I and SUD by examining the temporal sequence of onset of the 2 conditions.<sup>5,37</sup> Those patients in whom the onset of BD preceded or was concurrent with alcohol or drug abuse (“bipolar first”) were found to be more severe with respect to “alcohol or drug first” patients.<sup>38</sup> The majority of the patients included in our study were “bipolar first,” so a possible explanation for the lack of efficacy of the valproate/aripiprazole combination on the acute depressive symptomatology may be related to a high severity of the bipolar disorder, needing therefore an AD augmentation. Bupropion has also shown efficacy in reducing the cocaine craving; our results being in accordance with those reported in previous studies on dual heroine-cocaine addicts, especially in patients with depressive symptoms.<sup>32,39</sup> The chronic use of cocaine leads to a downregulation of dopaminergic systems,<sup>40</sup> so the efficacy of bupropion in reducing cocaine craving may be related to its action as a dopamine reuptake blocker.<sup>41</sup>

## Limitations of the Study

The results of this study need to be interpreted with caution because of its limitations, in particular, the very small sample size, the absence of a placebo group, the open-label design, and the brief duration of the study.

Moreover, our BD-I/CDD patients were hospitalized and, therefore, they were unable to use cocaine during the study

period, so we cannot be sure that the reduced DAST score in the bupropion add-on group could result in a reduced substance intake in an outpatient setting. The DAST score, however, is a measure of substance craving that is not directly influenced by concurrent use of cocaine and may, therefore, represent a tangible measure of decreased need for the substance.

## CONCLUSIONS

Our preliminary results suggest that adding bupropion to MSs and atypical antipsychotics may be a good therapeutic strategy in the short-term treatment of acute depression in those BD-I patients with comorbid cocaine dependence. Further studies, with larger sample sizes and double-blind design, are needed to confirm our findings.

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