Effects of Cigarette Smoking on Neuropsychological Performance in Mood Disorders: A Comparison Between Smoking and Nonsmoking Inpatients

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ABSTRACT

Objective: To investigate the effects of cigarette smoking on neuropsychological performance in patients with mood disorders.

Method: One hundred depressed patients with *DSM-IV-TR*–defined major depressive disorder (n = 61) or bipolar disorder (n = 39), hospitalized for a 4-week psychiatric rehabilitation program, were included. Forty-five were active regular smokers, and 55 were nonsmokers who had never smoked in their lifetime. At the beginning and the end of the hospitalization, patients were administered a comprehensive neuropsychological battery (evaluation of verbal and visual memory, working memory, attention, visual-constructive ability, language fluency, and comprehension) as primary outcome measures and psychometric scales (evaluation of depression and illness severity). Smoking status was assessed by personal interviews. Investigators were blind to the results of neuropsychological tests and to the smoking status of the patients. Data were collected from February 2011 to January 2012.

Results: At the beginning of the hospitalization, smokers showed significantly better performance in verbal memory, language fluency, and working memory (all *P* values < .01) than nonsmokers. No interaction between smoking and diagnosis was found. At the end of the hospitalization, the whole group of patients significantly improved in several cognitive domains, with smokers maintaining significantly better performance in verbal memory, language fluency, and working memory (all *P* values < .01) than nonsmokers.

Conclusions: Our preliminary results indicate a better performance by smokers in verbal memory and working memory domains than by nonsmokers, suggesting that a cognitive enhancement may be associated with nicotine use in depressed patients with MDD or bipolar disorder. Smoking may be a form of cognitive self-medication mediating the association between smoking and mood disorders. Further studies with larger samples are needed.

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The percentage of smokers is significantly higher among patients with various psychiatric disorders than among members of the general population.[1–3] The prevalence of current daily smoking is nearly 60% in patients with major depressive disorder (MDD) and 40% to 70% in patients with bipolar disorder.[1,4–7] The mechanisms underlying this association remain unclear, and different explanations have been proposed, such as common environmental/genetic risk factors[8–10] or a causal bidirectional relationship,[11–13] including the "self-medication hypothesis" related to potential mood-influencing properties of nicotine and/or other tobacco smoke ingredients.[6,14–16]

Recently, smoking patients with first-episode psychosis showed better cognitive performance than nonsmoking patients,[17] and preclinical evidence suggested beneficial effects of nicotine and subtype-selective nicotinic receptor agonists in schizophrenia-associated cognitive deficits[18]; similarly, nicotine may improve deficits on attention-related tasks in individuals with attention-deficit/hyperactivity disorder (ADHD).[19–21] These findings have suggested that cognitive enhancement associated with nicotine use may lead to smoking as another form of "self-medication" underlying the association between smoking and some psychiatric disorders.

Impairment on a range of cognitive domains, including executive functions, verbal and visual memory, attention, and psychomotor speed, is a well-documented finding in patients with MDD and bipolar disorder, both in acute phases and euthymia.[22–26] On these bases, we hypothesized that smoking might exert procognitive effects in patients with mood disorders, similar to those previously found in patients with psychosis or ADHD.

To our knowledge, studies primarily investigating the association between smoking status and cognitive performance in patients with mood disorders are lacking. Only 1 pilot study has found a beneficial effect of cigarette smoking on subjective but not objective measures of cognitive functions in a sample of euthymic patients with bipolar disorder.[25]

The main aim of our study was to investigate the effects of cigarette smoking on neuropsychological performance in depressed patients with MDD or bipolar disorder assessed at the beginning of a 4-week hospitalization for a brief psychiatric rehabilitation program. As a secondary aim, we investigated the influence of smoking on modifications of neuropsychological performance at the end of the hospitalization. We expected that smoking patients would show better performance than nonsmoking patients.

METHOD

Participants

One hundred subjects with MDD (n = 61) or bipolar disorder I or II (n = 39) according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[27] criteria who were in a depressive episode and without suicide risk were recruited from the inpatients consecutively referred to Villa San Benedetto Hospital, Albese

Clinical Points

- Smoking assessment and neuropsychological evaluation are recommended in the routine clinical approach to patients with mood disorders.
- The improvement of cognitive deficits by cognitive remediation treatments may also be useful in promoting smoking cessation in patients with mood disorders.
- Psychotropic medications with negative side effects on cognition may increase cigarette consumption in patients with mood disorders.

con Cassano, Como, Italy, to undergo a 4-week hospitalization for a psychiatric rehabilitation program. The program focused on promoting personal autonomy and abilities (self-care and house and financial management), social activities (development of communication and social interaction abilities), and physical activities by means of occupational and educational group interventions. All patients underwent a similar program. Exclusion criteria were relevant modifications of pharmacologic treatments within the 4 weeks preceding hospitalization or during the hospitalization including addition or discontinuation of drugs; any modification of dosage of the drugs in use that might influence the neuropsychological performances, according to the concordant clinical judgment of 2 psychiatrists expert in both psychopharmacology and neuropsychology; other concurrent Axis I diagnoses (*DSM-IV-TR* criteria); suspected or diagnosed (IQ < 70) mental retardation; electroconvulsive therapy in the preceding 6 months; lifetime neurologic diseases; history of neurologic trauma resulting in loss of consciousness; drug or alcohol abuse/dependence within the previous 6 months; or hypothyroidism or hyperthyroidism. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the Local Health Authority of the Province of Como, Italy; all participants voluntarily provided written informed consent after the procedure had been fully explained. Data were collected from February 2011 to January 2012.

Smoking Assessment

Psychologists, blind to the neuropsychological performance of the patients, evaluated by personal interviews the following variables: age at onset and duration of smoking, lifetime smoking habit, number of cigarettes smoked both in the 24 hours preceding the day of the neuropsychological assessment and on the day of the assessment, levels of nicotine dependence (by 6-item Fagerström test,[28] total score: 0–10, very low dependence–very high dependence). In this study, we included *nonsmokers*, ie, subjects who had never used cigarettes/other tobacco products in their lifetime, and *smokers*, ie, subjects with active cigarette use on a daily basis and with a regular smoking habit. *Regular smokers* were defined as subjects who had smoked on a daily basis for a period of at least 4 weeks continually[29,30] and had not quit smoking for a period longer than 3 months in the last 2 years. No restrictions on smoking were imposed during hospitalization.

Neuropsychological Assessment

Both at the beginning (within the first 2 days) and at the end (the day before discharge) of the hospitalization, as primary outcome measures, a standardized neuropsychological battery was performed by trained psychologists blind to the smoking habit of the patients. The neuropsychological battery took approximately 1 hour, with breaks to avoid fatigue, and was performed in the late morning. The results were expressed as scores corrected for age, schooling, and, when appropriate, sex, according to the Italian validation samples.[32] The higher the score, the better the performance.

Novelli's Story Recall Test. In Novelli's Story Recall Test,[31] the subject must recall and repeat as much information as possible about a short chronicle that has just been read aloud by the examiner. Then, the chronicle is immediately read again by the examiner, and the subject must recall and repeat as much information as possible after 10 minutes. The test evaluates short- and long-term verbal memory.

Attentional Matrices. The Attentional Matrices[32] test consists of 3 identical matrices of numbers disposed by rows, randomly interspersed with designated target numbers. The subject must cross out 1, 2, and 3 target numbers for each matrix, respectively, in 45 seconds for each matrix. The test evaluates the ability to maintain attention over time and spot specific elements among distracters.

Rey-Osterrieth Complex Figure Copy Test. In the Rey-Osterrieth Complex Figure Copy Test (ROCF-C),[33] the subject must copy, to the best of his or her ability, a complex abstract figure placed in front of him or her using paper and pencil. The test is not timed, but the time taken to copy the figure is observed. The test evaluates the ability of disposing and organizing visual elements in the space and maintaining spatial relations among them (visual-constructive ability).

Rey-Osterrieth Complex Figure Recall Test. The Rey-Osterrieth Complex Figure Recall Test (ROCF-R)[33] is administered 10 minutes after the ROCF-C Test. The subject must recall and reproduce, using paper and pencil and without seeing any stimulus, the complex abstract figure copied 10 minutes earlier during the ROCF-C Test. The test evaluates long-term visual-constructive memory.

Phonemic Fluency Test. In the Phonemic Fluency Test,[31] the subject must recite, in 60 seconds, as many words as possible that begin with a specific letter, such as *p*, announced by the examiner. The test requires the subject to list 3 series of words that start off with 3 different phonemic cues (*p*, *f*, and *l*). The test evaluates language fluency, such as ability to recall words, and frontal executive functions, such as working memory.

Semantic Fluency Test. In the Semantic Fluency Test,[31] the subject must recite, in 60 seconds, as many words as possible that belong to a specific semantic category, such as *animals*, announced by the examiner. The test requires the subject to list 3 series of words that belong to 3 different semantic cues (*animals*, *fruits*, and *car companies*). The test evaluates language fluency, such as ability to recall words.

Token Test. In the Token Test,[34] the subject must listen to, understand, and follow orders, read by the examiner, to touch, take, or move, in different combinations, some tokens having different shapes, sizes, and colors. The test evaluates the ability to understand and process semantic information.

Psychometric Assessment

Both at the beginning (within the first 2 days) and at the end (the day before discharge) of the hospitalization, the severity of clinical symptoms was evaluated by psychiatrist-rated psychometric scales: the 17-item Hamilton Depression Rating Scale (HDRS),[35] measuring the severity of depressive symptoms (range: 0–52, from *no depressive symptoms* to *very severe depression*) and the 18-item Brief Psychiatric Rating Scale (BPRS),[36] measuring several psychopathological symptoms including depression, anxiety, hallucinations, and unusual behaviors (range: 18–126, from *symptoms not present* to *extremely severe condition*).

Statistical Analyses

Continuous data, nominal data, and the association between variables were analyzed by *t* test, χ^2 analysis or Fisher exact test, and Pearson correlation statistics, respectively. Differences in neuropsychological performance between smokers and nonsmokers at the beginning of hospitalization were investigated by 7 factorial analysis of variance (ANOVA) models, including the results of neuropsychological tests as dependent variables and smoking status (smokers/nonsmokers) and diagnosis (MDD/bipolar disorder) as between-subjects factors. Both main effects and effects of interaction between factors were considered. Since the results of neuropsychological tests were expressed as age-, schooling-, and sex-corrected scores,[32,34] we did not include age, schooling, and sex as covariates in ANOVAs. The decision regarding inclusion of psychometric scale scores as covariates in ANOVAs was made according to results of preliminary analyses investigating both the association between the neuropsychological performance and the HDRS and BPRS scores and the difference between the compared groups.

The influence of smoking on modifications of neuropsychological performance during the hospitalization was investigated by repeated-measures ANOVAs including the results of neuropsychological tests as dependent variables, "time" (the beginning and the end of hospitalization) as the repeated-measures factor, and "smoking" and "diagnosis" as between-subjects factors. Both main effects and effects of interactions were considered. The same repeated-measures ANOVA models were performed with psychometric scale scores as dependent variables.

Because of the high number of statistical tests performed, we lowered the significance level (α) from .05 to .01 to account for the exploratory nature of the study and to maintain enough statistical power in the analyses.

The Statistical Package for Windows (Statistica 10.0, Statsoft Inc, Tulsa, Oklahoma) was used for statistical analyses.

RESULTS

Demographic and clinical characteristics of smokers and nonsmokers are presented in Table 1. No significant differences were found except for a significantly higher level of schooling ($P < .01$) and a trend toward younger age in smokers ($P = .012$). Smokers with MDD or bipolar disorder did not differ in psychotropic medication distribution or in any variables regarding smoking (Table 1).

Neuropsychological Performance and Smoking at the Beginning of the Hospitalization

Since preliminary analyses showed no significant correlations between neuropsychological performance and psychometric scale scores, we did not include these variables as covariates in the ANOVAs.

Smokers had significantly better performance on Novelli's Story Recall Test, on the Phonemic Fluency Test, and on the Semantic Fluency Test than nonsmokers (all *P* values < .01; Table 2). Patients with bipolar disorder showed significantly worse performance on the Semantic Fluency Test than patients with MDD ($P < .01$; Table 3). No other significant effects were found at the beginning of the hospitalization.

No significant correlations were found between neuropsychological performance and duration of smoking, levels of nicotine dependence, or the number of cigarettes smoked either in the 24 hours preceding the day of the neuropsychological assessment or on the day of the assessment.

Neuropsychological Performance and Smoking at the End of the Hospitalization

Between the beginning and the end of the hospitalization, the whole group of patients showed an improvement in performance on Novelli's Story Recall Test (mean ± SD scores = 10.39 ± 4.04 [beginning] and 13.16 ± 4.74 [end]; $F = 48.21$, $P < .001$), the ROCF-C (mean ± SD scores = 25.82 ± 9.13 [beginning] and 27.77 ± 8.44 [end]; $F = 11.68$, $P < .001$) and the ROCF-R (mean ± SD scores = 10.28 ± 5.83 [beginning] and 14.27 ± 7.06 [end]; $F = 33.63$, $P < .001$), and on the Semantic Fluency Test (mean ± SD scores = 32.89 ± 7.95 [beginning] and 36.00 ± 9.29 [end]; $F = 13.05$, $P < .001$); moreover, a trend toward improvement on the Attentional Matrices (mean ± SD scores = 37.86 ± 9.45 [beginning] and 40.19 ± 9.84 [end]; $F = 6.14$, $P = .015$) and on the Phonemic Fluency Test (mean ± SD scores = 28.41 ± 9.11 [beginning] and 30.74 ± 8.47 [end]; $F = 6.62$, $P = .011$) was found. Smokers had significantly better performance on the Phonemic Fluency Test ($F = 10.02$, $P < .01$), the Semantic Fluency Test ($F = 7.02$, $P < .01$), and Novelli's Story Recall Test ($F = 6.96$, $P < .01$) than nonsmokers. No other significant effects were found at the end of the hospitalization.

No significant correlations were found between neuropsychological performance at the end of hospitalization and the number of cigarettes smoked either in the 24 hours preceding the day of the neuropsychological assessment or on the day of the assessment.

Table 1. Demographic and Clinical Characteristics of Patients With Major Depressive Disorder or Bipolar Disorder

Characteristic	Smokers (n = 45)	Nonsmokers (n = 55)	Statistic	*P*
Major depressive disorder: bipolar disorder, n:n	27:18	34:21	$\chi^2 = 0.03$	.85
Female:male, n:n	31:14	46:9	$\chi^2 = 3.04$	.081
Age, mean (SD), y	54.87 (11.88)	62.88 (11.97)	$t = -3.34$	.012
Schooling, mean (SD), y	10.19 (3.51)	8.18 (3.80)	$t = 2.72$	< .01*
HDRS total score, mean (SD)	20.35 (8.54)	21.37 (4.63)	$t = 0.76$	.45
BPRS total score, mean (SD)	42.57 (8.72)	41.22 (7.23)	$t = -0.85$	.40
Medication, n (%)				
Serotonin reuptake inhibitors	20 (44.4)	25 (45.5)	$\chi^2 = 0.01$	.91
Serotonin and norepinephrine reuptake inhibitors	8 (17.8)	16 (29.1)	$\chi^2 = 1.74$	.18
Other antidepressants (agomelatine, bupropion, mirtazapine, trazodone)	7 (15.6)	14 (25.5)	$\chi^2 = 1.46$	.23
Tricyclic antidepressants	1 (2.2)	4 (7.3)	Fisher exact test	.37
Typical antipsychotics	8 (17.8)	11 (20.0)	$\chi^2 = 0.08$	.78
Atypical antipsychotics	13 (28.9)	17 (30.9)	$\chi^2 = 0.05$	.83
Mood stabilizers	21 (46.7)	16 (29.1)	$\chi^2 = 3.28$	.07
Benzodiazepines	33 (73.3)	42 (76.4)	$\chi^2 = 0.12$	.72
Age at onset of smoking, mean (SD), y				
Major depressive disorder	16.80 (5.42)		$t = 1.15$	.26
Bipolar disorder	18.73 (5.49)			
Duration of smoking, mean (SD), y				
Major depressive disorder	39.32 (9.07)		$t = 1.6$	.12
Bipolar disorder	33.90 (13.78)			
Cigarettes smoked in the 24 hours preceding the day of the NPA at BH, mean (SD), no.				
Major depressive disorder	15.60 (12.87)		$t = 0.22$	.82
Bipolar disorder	16.54 (14.50)			
Cigarettes smoked on day of the NPA at BH, mean (SD), no.				
Major depressive disorder	5.36 (4.65)		$t = 0.59$	.56
Bipolar disorder	4.64 (2.80)			
Cigarettes smoked in the 24 hours preceding the day of the NPA at EH, mean (SD), no.				
Major depressive disorder	17.31 (10.24)		$t = 0.75$	.46
Bipolar disorder	14.94 (10.68)			
Cigarettes smoked in hours preceding the NPA at EH, mean (SD), no.				
Major depressive disorder	5.79 (4.33)		$t = -0.26$	.79
Bipolar disorder	6.23 (5.96)			
Fagerstrom total score, mean (SD)				
Major depressive disorder	5.36 (2.54)		$t = 0.31$	.76
Bipolar disorder	5.09 (3.33)			

*Statistical significance: $P < .01$.
Abbreviations: BH = beginning of hospitalization, BPRS = Brief Psychiatric Rating Scale, EH = end of hospitalization, HDRS = Hamilton Depression Rating Scale, NPA = neuropsychological assessment.

Between the beginning and the end of the hospitalization, the whole group of patients showed an improvement in both HDRS scores (mean ± SD = 21.00 ± 6.27 [beginning] and 7.30 ± 4.57 [end]; $F = 131.93$, $P < .001$) and BPRS scores (mean ± SD = 41.79 ± 7.88 [beginning] and 29.02 ± 7.87 [end]; $F = 266.20$, $P < .001$). No other significant effects were found.

DISCUSSION

We investigated the effects of cigarette smoking on neuropsychological performance in depressed patients with MDD or bipolar disorder. Since, to our knowledge, no other published studies have investigated this issue, our results should be considered preliminary.

Overall, the scores of the neuropsychological tests in our sample indicated impairment in verbal memory, attention, visual-constructive ability and memory, language fluency, working memory, and ability to process semantic information, in accordance with previous studies.[22–24,37,38] Our results showed that, at the beginning of hospitalization, smoking patients with MDD or bipolar disorder had better performance in verbal memory, language fluency, and working memory than nonsmokers, without significant interactions between smoking status and diagnosis. Smokers and nonsmokers did not differ in clinical severity or sex and psychotropic medication distribution, although smokers showed significantly higher levels of schooling and a trend toward younger age than nonsmokers when the results of neuropsychological tests were corrected for age and schooling. Thus, it is unlikely that these variables accounted for the differences in neuropsychological performance between the 2 groups. At the end of the hospitalization, the whole sample of patients showed significant improvement in most cognitive domains, with smokers maintaining better performance in verbal memory, language fluency, and working memory than nonsmokers. Overall, our findings support the cognitive approach to the self-medication hypothesis in patients with MDD or bipolar disorder, similar to what has previously been suggested for patients with psychosis.[17] The high rate of smoking among patients with mood disorders may be related, at least partly, to an attempt at improving some of their cognitive deficits. Conversely, the lack of difference in clinical severity between smokers and nonsmokers in our sample does not support the idea of smoking as self-medication to ameliorate depressive symptoms, as suggested in other studies.[6,14–16] However this issue is still unclear, and controversial results have been reported.[1,39–44]

Our results differ from those obtained by Law and coworkers,[25] which did not find differences in cognitive performance between smoking and nonsmoking patients with bipolar disorder. However, there may be many reasons for this discrepancy. The Law et al study arose from a post hoc analysis of data collected during a separate study with different aims in euthymic bipolar patients, smoking status was determined by self-report, different cognitive tasks were performed, and subjects were asked not to smoke before testing. Thus, the results are hardly comparable.

Our findings may be explained by the beneficial procognitive effects of nicotine, an agonist of brain nicotinic acetylcholine receptors (nAChRs) and are consistent with the hypothesis that cholinergic dysfunctions may contribute to the development of cognitive deficits associated with mood disorders.[45,46] The cholinergic system modulates cognitive

Table 2. Neuropsychological Performance and Smoking at the Beginning of the Hospitalization

Test score, mean (SD)	Smokers (n = 45)	Nonsmokers (n = 55)	Analysis of Variance	
			F	*P*
Novelli's Story Recall Test	11.70 (4.88)	9.40 (3.31)	6.99	< .01*
Attentional Matrices	38.67 (9.78)	37.22 (9.21)	0.30	.58
Rey-Osterrieth Complex Figure Copy	26.59 (8.79)	25.19 (9.42)	0.18	.67
Rey-Osterrieth Complex Figure Recall	10.51 (6.80)	10.11 (5.01)	0.02	.88
Phonemic Fluency Test	31.07 (10.44)	25.69 (8.22)	7.91	< .01*
Semantic Fluency Test	35.71 (8.64)	30.66 (7.11)	10.78	< .01*
Token Test	29.41 (3.36)	28.26 (4.08)	2.05	.15

*Statistical significance: $P < .01$.

Table 3. Neuropsychological Performance in Patients With Major Depressive Disorder or Bipolar Disorder at the Beginning of the Hospitalization

Test score, mean (SD)	Patients With Major Depressive Disorder (n = 61)	Patients With Bipolar Disorder (n = 39)	Analysis of Variance	
			F	*P*
Novelli's Story Recall Test	10.45 (4.01)	10.43 (4.59)	0.002	.97
Attentional Matrices	37.65 (9.63)	38.19 (9.28)	0.03	.86
Rey-Osterrieth Complex Figure Copy	26.01 (9.11)	25.52 (9.26)	0.17	.68
Rey-Osterrieth Complex Figure Recall	10.66 (5.91)	9.71 (5.72)	0.73	.39
Phonemic Fluency Test	28.90 (8.62)	27.33 (10.97)	0.35	.55
Semantic Fluency Test	34.62 (7.98)	30.24 (7.84)	7.29	< .01*
Token Test	28.52 (3.92)	29.14 (3.64)	0.64	.42

*Statistical significance: $P < .01$.

processes by its projections to areas critically involved in cognitive function, such as the frontal cortex, hippocampus, and amygdala.[47] Experimental disruption of the cholinergic system, in both humans and animals, resulted in memory, working memory, and attention impairment; conversely, pharmacologic enhancement of cholinergic neurotransmission or acute/chronic nicotine administration obtained reverse effects[18,48,49] and nAChR agonists, especially those acting at α4β2 and α7 nAChRs, improved attentional and working memory deficits in preclinical animal models and in some clinical studies.[50–53]

Structural brain changes in the hippocampus, amygdala, prefrontal cortex, and basal ganglia of patients with mood disorders[54] may arise partly from cholinergic dysfunctions[45] and have been related to cognitive deficits in memory, attention, and executive function domains.[22,23,55–58] Accordingly, altered regulation of α7 nAChR expression in the prefrontal cortex and hippocampus of bipolar patients has been found,[59,60] and mice lacking the β4 subunit of nAChRs showed deficits in both hippocampus- and amygdala-dependent memory functions and depression-like behaviors.[61]

In line with these findings, smokers in our sample showed better performance, specifically in the verbal memory and working memory domains, than nonsmokers. Conversely, we found no effects of smoking on attention. However, since the Attentional Matrices Test requires both attentional abilities and efficient psychomotor speed to be efficiently performed, deficits in psychomotor speed, not assessed by our neuropsychological battery, might have masked the potential proattentive properties of smoking.[18,62,63] A limitation of our study is that the neuropsychological battery was not able to disentangle the different cognitive domains potentially involved in the results of each task. Future studies with more comprehensive batteries will be useful.

Finally, it should be noted that the procognitive activity of smoking may also be related to other mechanisms beyond nicotine's effects on the cholinergic system, such as the nicotine-mediated release of several neurotransmitters influencing cognitive functions, including dopamine, serotonin, norepinephrine, and glutamate,[18,62,63] or the potential effects of other bioactive ingredients contained in cigarette smoke.

We did not find correlations between the results of neuropsychological tests and variables regarding smoking, including the number of cigarettes smoked in the hours preceding the cognitive assessment. However, we cannot exclude an association between the amount of smoked nicotine and cognitive performance, since the total cigarette puff volume, as well as the nicotine content in the different types of cigarettes, may vary considerably among individuals. A limitation of our study is the fact that blood/saliva levels of nicotine and/or its metabolites were not measured before cognitive assessment, and further studies investigating the relationship between measured levels of nicotine and cognitive performance are needed.

Our study has other limitations. The sample size is relatively small, and our results should be confirmed in larger samples. Because of the preliminary nature of the study, we included only patients who had MDD or who were in the depressive phase of bipolar disorder and who were either active regular smokers or who had never smoked in their lifetime. Thus, further studies comprising subjects with other patterns of smoking and patients in different phases of bipolar disorder, including euthymia, are needed. We excluded from the study the patients who underwent relevant modifications of their pharmacologic treatments, and we found no significant differences in the distribution of psychotropic medications between smokers and nonsmokers; however, we cannot completely exclude an influence of pharmacotherapy on our results, related to interactions of medications with nicotine and/or to the potential effects of psychotropic medications on cognitive performance. Indeed, the impact of psychotropic medications on cognition is highly complex and, to date, not fully clarified, because, on the one hand, they may improve cognition by alleviating psychopathological symptoms but, on the other hand, they may exert their own cognitive side-effects. Effective antidepressant treatments improve cognitive functions in patients with mood disorders, but tricyclic antidepressants are more likely to induce cognitive deficits than selective serotonin reuptake inhibitors (SSRIs), while patients treated with serotonergic-noradrenergic inhibitors might have less

memory impairment than those treated with SSRIs.[64,65] Lithium appears to have subtle negative effects on neurocognition in patients with bipolar disorder that are more prominent compared to those of lamotrigine, while valproate, carbamazepine, and topiramate show worse cognitive effects than lithium, and antipsychotics show more negative effects on cognition than lithium and anticonvulsants.[65] Finally, benzodiazepines are associated with both transient and longer-lasting cognitive impairment.[66]

Keeping in mind these limitations, our preliminary findings suggest that a cognitive enhancement, mainly in verbal memory and working memory domains, may be associated with nicotine use in depressed patients with MDD or bipolar disorder, and smoking may be a form of cognitive self-medication mediating the association between smoking and mood disorders. Much more work is clearly required to clarify the neurobiological substrates underlying the comorbidity of mood disorders and smoking. A better understanding of this issue may be useful to improve therapeutic strategies for smoking cessation, mood disorders, and the comorbidity of these 2 conditions.

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