Does Negative Affectivity Predict Differential Response to an SSRI Versus a Non-SSRI Antidepressant?

Maria Lidia Gerra, MD; Carlo Marchesi, MD; Jose A. Amat, MD, PhD; Pierre Blier, MD, PhD; David J. Hellerstein, MD; and Jonathan W. Stewart, MD

ABSTRACT

Objective: This work tested the hypothesis that patients with high negative affectivity (NA) would have a better response to a serotonergic agent (escitalopram) than to one not thought to act directly on serotonin (bupropion).

Method: Data from a study conducted between August 2007 and July 2011 were reanalyzed retrospectively. Patients (N = 245) meeting criteria for major depressive disorder (MDD), diagnosed with *DSM-IV-TR*, were randomly assigned to double-blind treatment with bupropion extended-release, escitalopram, or the combination. Negative affectivity score was estimated using the guilt, hostility/irritability, and fear/anxiety items of the Hamilton Depression Rating Scale, the Montgomery-Asberg Depression Rating Scale, the Quick Inventory of Depressive Symptoms, and the Social Adjustment Scale. We felt that these items captured published descriptions of the NA construct. A Clinical Global Impressions-Severity of Illness (CGI-S) score ≤ 2 defined response. Because combined treatment addressed both serotonin and non-serotonin systems, patients treated with both medications did not test the hypothesis and so were excluded from the analyses.

Results: Analysis of covariance with treatment as a grouping variable, NA as covariate, and CGI-S as dependent variable showed a significant 2-way interaction between treatment and NA ($F_{1,156} = 4.82$, $P < .03$). In the low-NA group, response rates were similar between treatments (escitalopram: 28/42 [67%]; bupropion: 23/40 [58%]; NS), while there was a significant advantage for escitalopram in patients with high NA (escitalopram: 24/40 [60%]; bupropion = 14/41 [34%]; $P = .017$).

Conclusions: These data suggest that patients with high negative affectivity respond preferentially to antidepressants that selectively enhance serotonin neurotransmission. Although patients with low NA appear to benefit from serotonin enhancement as well, they also improved with bupropion, an antidepressant not thought to directly affect serotonin neurotransmission. These findings come from retrospective analyses using unproven approximation of NA, so no clinical inferences should be made before independent replication utilizing accepted NA measurement.

Trial Registration: ClinicalTrials.gov identifier: NCT00519428

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Corresponding author: *Maria Lidia Gerra, MD, Department of Neuroscience, Psychiatry Unit, University General Hospital, Braga Bldg, Via Gramsci 14, Parma, PR 43126, Italy (marialidia.gerra@studenti.unipr.it).*

The relationship between depression and anxiety has been controversial: some have argued that anxiety in the presence of depression is not a separate disorder, while others have argued that anxious depression should be considered separately from nonanxious depression.[1] Both epidemiologic and clinical studies report that MDD and the anxiety disorders are prevalent and more frequently comorbid than expected by chance: 50%–60% of individuals with a lifetime history of MDD report a lifetime history of at least 1 anxiety disorder.[2–4] At the symptom level, Fava et al[5] reported that 53% of a clinical sample of unipolar patients had "anxious" depression. The latter study, however, did not report on how many patients also met criteria for an anxiety disorder, and the former did not assess whether any without an anxiety diagnosis had "anxious" depression. Thus, it remains unclear how redundant major depression with comorbid anxiety and anxious depression are. Regardless of definition, Fava et al[6,7] argue that "anxious depression" is important due to its association with greater severity of illness, increased functional impairment, high chronicity, delayed and poorer response to antidepressant treatment, and an increased risk of suicidality relative to depressed patients who do not report prominent anxiety.[5,8–11] Both *DSM-5*[12] and *ICD-10*[13] use both approaches to patients who report co-occurring anxiety and depression; that is, one may diagnose either both disorders or depression "with anxious distress" (*DSM-5*) ("mixed anxiety and depression" in *ICD-10*).

An alternative to the *DSM*/*ICD* approach is the tripartite model of mood disorders proposed by Clark and Watson,[14] which provides a theoretical framework for testing the relationship between depressed and anxious moods. They observed that some symptoms are relatively specific to depressive disorders (eg, anhedonia and reduced positive affect) and others, to anxiety disorders (eg, anxious arousal and somatic anxiety), while others, such as general distress and increased negative affect, are common to both depressive and anxiety disorders. In this model, positive affectivity (PA) is defined in terms of enthusiasm, energy, mental alertness, and determination, while negative affectivity (NA) includes a broad range of aversive mood states, such as distress, nervousness, fear, anger, guilt, and scornfulness. Both dimensions of affectivity can be viewed either as traits (ie, persistent differences in general affective level) or as states (ie, transient fluctuations in mood).[15] The third dimension, anxious arousal (AA), primarily refers to the somatic components of anxiety resulting from acute physiologic responses to specific fearful environmental cues, including dizziness, chest pain, shaking hands, trouble swallowing, and shortness of breath.

In this model, MDD with anxious symptoms can be characterized by high NA and high AA. Nutt et al[16] and Stahl[17]

Clinical Points

- Our results suggest physicians take into account a dimensional approach to MDD that could identify a subgroup of MDD patients with high level of negative affectivity.
- If more rigorously replicated, these results suggest clinicians might consider use of a selective serotonin reuptake inhibitor over bupropion as first-line treatment for depressed patients with a high level of guilt, hostility/irritability, or fear/anxiety.

suggested that high NA results from serotonin deficiency and so should respond to antidepressants that specifically enhance serotonin neurotransmission, such as the selective serotonin reuptake inhibitors (SSRIs). Therefore, we hypothesized that patients high in NA would preferentially respond to an SSRI relative to a non-SRI while those having low NA would not show such differential response. Stahl[17] and Nutt et al[16] did not propose a neurotransmitter hypothesis for AA, so we ran similar but exploratory analyses investigating possible preferential treatment response for AA.

METHOD

Patient data came from a randomized controlled clinical trial that compared the effect of bupropion, escitalopram, or their combination in patients affected by MDD. The study characteristics are only briefly summarized here. More detailed information can be found in a previous publication.[18] This 2-site study was approved by the respective human subjects committees. The study is registered with ClinicalTrials.gov (identifier: NCT00519428).

Sample

Patients were selected from those affected by MDD who sought treatment at the Depression Evaluation Service, Columbia University (New York, New York), at the Hôpital de Hull (Gatineau, Quebec, Canada), and at the Royal Ottawa Hospital (Ottawa, Ontario, Canada) from August 2007 to July 2011. Study entry criteria included (1) MDD as the primary psychiatric diagnosis, as determined by the Structured Clinical Interview for *DSM-IV-TR*[19]; (2) a score of at least 22 at the Montgomery-Asberg Depression Rating Scale (MADRS)[20]; and (3) signed informed consent. Patients were excluded if they (1) had an unstable medical condition; (2) had a history of psychosis or bipolar disorder; (3) had current (past 6 months) substance abuse or dependence; (4) were taking psychoactive medications and did not have a history of allergy to, prior nonresponse to, or intolerance of either study medication; or (5) had a history of anorexia nervosa or bulimia nervosa.

Treatment

Following initial evaluation, patients who still met entry criteria at a second visit (generally 1–2 weeks following their initial evaluation and without a single-blind placebo lead-in) were randomly assigned to double-blind treatment with bupropion monotherapy (bupropion extended-release [XL] 150-mg pills plus a placebo matching the escitalopram), escitalopram monotherapy (escitalopram 10-mg pills plus a placebo matching the bupropion) or dual therapy (escitalopram 10-mg pills plus bupropion XL 150-mg pills). Maximum bupropion dosing was 150 mg/d for the first week, 300 mg/d for weeks 2 and 3, and 450 mg/d for the remainder of the 12-week study. Maximal escitalopram dosing was 10 mg for the first week, with weekly 10-mg/d dose increases to 40 mg/d at week 4 and beyond. All dose increases occurred only if the patient had not remitted (HDRS-17 score ≤ 7) and was tolerating the medication sufficiently that doctor and patient were comfortable raising the dose.

Assessment

Patients were evaluated at each study visit using the 17-item Hamilton Depression Rating Scale (HDRS-17),[21] MADRS,[20] Clinical Global Impressions scale (CGI),[22] and the Quick (16-item) Inventory of Depressive Symptoms (QIDS).[23] In addition, at randomization and every 4 weeks postrandomization, patients completed the Social Adjustment Scale (SAS).[24]

Negative affectivity was assessed using the guilt, hostility/irritability, and fear/anxiety items of the HDRS-17, MADRS, QIDS, and SAS, as suggested by Nutt et al[16] and Stahl[17] (Table 1). Several items in our rating scales addressed an aspect of NA, and therefore those items were converted to 7-point scales and added together, and the mean was taken to obtain a score for that NA aspect. Each patient's NA score was calculated by adding the resulting guilt, hostility/irritability, and fear/anxiety scores. Then, we cut the NA score at the sample median (2.08), producing a high-NA group and a low-NA group.

Anxious arousal was evaluated by the following 3 HDRS items: anxiety (somatic), somatic symptoms (gastrointestinal), and somatic symptoms (general). Each patient's AA score was calculated by adding the items. Then we cut the AA score at the median (1.067), creating high-AA and low-AA groups. Unfortunately, the available scales did not have items that we considered to reflect somatic anxiety. Therefore, it is possible that our estimation of AA is only a partial assessment of AA as described by Clark and Watson.[14] We found no items that seemed to reflect PA.

We also investigated the anxiety/somatization factor of the HDRS (HDRS-A/S), which was used to assess anxious depression in previous studies. This factor includes the following 6 items: anxiety (psychic), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), hypochondriasis, and insight,[5] and therefore it includes symptoms that are partially captured by NA and all of the symptoms of AA.

Outcome Measure

Because these analyses utilized several HDRS-17 items in the predictor variable, to avoid redundancy, we used CGI-Severity of Illness (CGI-S) as the outcome measure. A CGI-S score ≤ 2 at the end of the study constituted response.

Table 1. Negative Affectivity Score

Guilt	Hostility/Irritability	Fear/Anxiety
HDRS 2: Feeling of guilt	SAS 5: Did you have any open argument with your friends in the last 2 weeks?	HDRS 10: Anxiety psychic
MADRS 9: Pessimistic thoughts (guilt, inferiority, self-reproach, sinfulness, remorse, and ruin)	SAS 11: Did you have any open argument with your relatives in the last 2 weeks?	SAS 16: How often have you been worried about things happening to your relatives without good reason in the last 2 weeks?
QIDS-SR 11: (Negative) view of myself	SAS 15: How often have you wanted to do the opposite of what your relatives wanted in order to make them angry during the last 2 weeks?	SAS 25: Have you felt upset worried, or uncomfortable while doing your work during the last 2 weeks?
	SAS 24: Have you had any arguments with people at work in the last 2 weeks?	SAS 53: How often have you been worried about your partner or any of your children without good reason in the last 2 weeks?
	SAS 31: Have you had any arguments with people (salespeople/tradesmen/neighbors) in the last 2 weeks?	MADRS 3: Inner tension
	SAS 38: Have you had any arguments with your partner in the last 2 weeks?	QIDS 16: Feeling restless
	SAS 50: How have you been getting along with your children during the last 2 weeks? (Include only children over the age of 2 years)	

Abbreviations: HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptoms, QIDS-SR = Quick Inventory of Depressive Symptoms–Self-Report, SAS = Social Adjustment Scale.

Statistical Analyses

The data were analyzed using χ^2 for categorical variables and 2-tailed *t* tests and analysis of covariance (ANCOVA) for continuous variables, as appropriate. To test our hypothesis that subjects with high NA would preferentially benefit from an SSRI, we used an ANCOVA, with the endpoint CGI-S as dependent variable, treatment as a grouping variable, and baseline NA and CGI-S as covariates. Exploratory analyses replaced NA in the above analysis with AA. We first ran these analyses inserting all main effects and all levels of interaction, intending to decrease the level of interaction iteratively until finding a level of interaction at which at least 1 was significant. We set α to .05. While we present multiple tests, we did not correct for this because we had a single test for our hypothesis, with remaining tests being confirmatory or exploratory.

RESULTS

From the original sample (N = 245), 76 patients receiving both medications were not considered in the present analyses, as they could not contribute to testing whether some patients preferentially respond to one of the drugs. Thus, the analyses were limited to the patients treated with monotherapy (N = 169), of whom 6 patients were not included in the data analysis because they had no postrandomization CGI-S score.

Baseline Characteristics

The final sample comprised 163 patients, of whom 81 were treated with bupropion and 82, with escitalopram. There were 108 (66%) women and 55 men (34%), with a mean age of 40.4 ± 10.6 years. Mean ± SD time since the first episode of MDD was 12.7 ± 12.1 years, and mean age at onset was 28.1 ± 14.1 years. Age, age at onset, illness duration, severity of depressive symptoms at baseline, and NA level did not differ between treatments (Table 2). There was a significant difference in gender, with more men in the bupropion group, so gender was included as a covariate in our analyses.

Table 2. Demographic and Clinical Characteristics

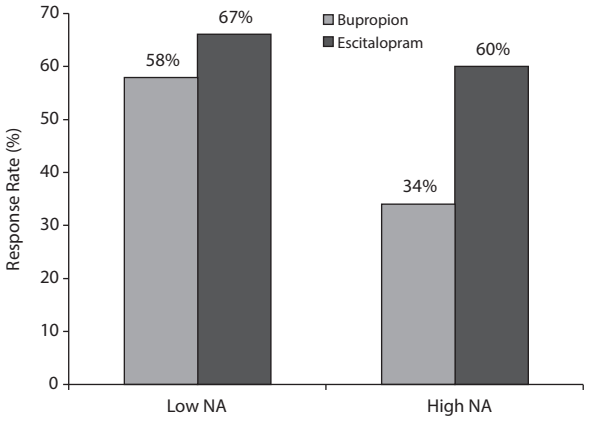
	Bupropion (n = 81)	Escitalopram (n = 82)	Statistic	*P* Value
Gender, male, n (%)	33 (40.7)	22 (26.8)	$\chi^2 = 3.5$	.04
Age, mean ± SD, y	40.5 ± 11.3	40.2 ± 10.0	$F = 0.94$	.30
Education, mean ± SD, y	14.5 ± 3.2	14.2 ± 3.0	$F = 0.21$	.65
Family status, n (%)				
Never married	33 (40.7)	26 (31.7)	$\chi^2 = 4.9$	.29
Married/living together	28 (34.5)	32 (39.0)		
Separated/divorced	18 (22.2)	22 (26.8)		
Widowed	2 (2.4)	2 (2.4)		
Occupation, n (%)				
Unemployed	23 (28.4)	23 (28.0)	$\chi^2 = 9.2$	.32
Employed	46 (60.4)	55 (67.0)		
Student	4 (4.9)	1 (1.2)		
Retired	1 (1.2)	1 (1.2)		
Other	4 (4.9)	2 (2.4)		
Race, n (%)				
Caucasian	64 (79.0)	57 (69.5)	$\chi^2 = 4.9$	.54
African American	3 (3.7)	2 (2.4)		
Other	14 (17.2)	23 (28.0)		
Age at onset, mean ± SD, y	28.6 ± 14.0	27.7 ± 12.9	$F = 0.48$	.49
HDRS-17 score at baseline, mean ± SD	19.7 ± 5.1	20.1 ± 4.1	$F = 4.1$	.04
HDRS-29 score at baseline, mean ± SD	29.3 ± 6.5	29.9 ± 5.5	$F = 5.0$	.03
NA score at baseline, mean ± SD	2.2 ± 0.8	2.2 ± 0.7	$F = 1.3$	.23

Abbreviations: HDRS = Hamilton Depression Rating Scale, NA = negative affectivity.

Response to Treatments

The analysis of all possible interactions among NA, treatment, baseline severity, and gender did not demonstrate a significant 4-way interaction, so this term was removed. The next analysis omitting the 4-way interaction did not show any of the four 3-way interactions to be significant, so these were removed. The next analysis found a significant 2-way interaction between treatment and NA ($F_{1,156} = 4.82$, $P < .03$), suggesting the treatments differed in likelihood of improvement in high- vs low-NA subjects. Inspection revealed that this interaction was due to differential effects of bupropion in the 2 NA groups (Figure 1). Thus, while responses to escitalopram did not differ significantly between

Figure 1. Comparison of Response Rates in Patients With High and Low Negative Affectivity (NA) Scores



low- and high-NA groups (67% vs 60%, NS), bupropion was significantly more effective for low-NA than high-NA patients (58% [23/40] vs 34% [14/41], $\chi^2_1 = 4.4$, $P < .03$). Also, escitalopram was significantly more effective than bupropion for high-NA patients ($\chi^2_1 = 5.40$, $P = .017$) but not low-NA patients ($\chi^2_1 = 0.50$, NS). Neither gender nor severity of depression, measured with HDRS-17 at randomization, was a significant covariate either alone (gender: $F_{1,146} = 2.29$, NS; severity: $F_{1,128} = 2.83$, NS) or in interaction with the other variables (gender: $F_{1,146} = 2.28$, NS; severity: $F_{1,128} = 3.55$, NS).

The same analysis using AA did not demonstrate a treatment-by-AA-by-outcome interaction at any level of interaction (eg, the analogous 2-way interaction between AA and treatment yielded $F_{1,154} = 0.017$, $P = .89$). A similar analysis utilizing the HDRS-A/S was also not significant ($F_{1,154} = 0.004$, $P = .94$).

DISCUSSION

The present study tested the hypothesis that patients with MDD and high NA would preferentially respond to escitalopram relative to bupropion. As hypothesized, patients with high NA were significantly more likely to benefit if treated with the SSRI, escitalopram, than with the non-SSRI, bupropion. Exploratory analyses of AA and the HDRS-A/S did not suggest a relationship between these and differential responsivity to escitalopram versus bupropion.

Other research suggests that antidepressants that act through the selective inhibition of the serotonin transporter modulate primarily the symptoms of negative affectivity and/or an anxious dimension of depression. Filteau et al,[25] for example, found that SSRI responders had greater baseline anxiety/agitation levels than responders to norepinephrine reuptake inhibitors; Bodkin and colleagues[26] reported that SSRIs significantly reduced symptoms of panic and anxiety in 18 of 20 patients with depression, while bupropion lacked such benefits; and Knutson et al[27] compared paroxetine 20 mg/d to placebo in normal volunteers, finding that the SSRI reduced negative affect relative to placebo, yet did not alter indices of positive affect.

However, to our knowledge, only 2 studies evaluated the specific effect of antidepressant treatment on NA. Tomarken et al[28] compared the efficacy of bupropion (300 mg/d) to placebo in 19 depressed outpatients; compared with placebo, bupropion produced a greater improvement in PA symptoms, but not those of NA or AA, in agreement with studies suggesting bupropion may be more effective for core symptoms of depression than for the anxiety that often accompanies depression.[26] Dichter et al[29] described the treatment outcome of 20 depressed outpatients randomly assigned to treatment with either venlafaxine extended release (XR) (225 mg/d) or paroxetine (30 mg/d) during a 12-week treatment trial, reporting that both venlafaxine XR and paroxetine produced more robust changes on NA than PA symptoms. As both venlafaxine and paroxetine are potent serotonin reuptake inhibitors, the Dichter study seems to confirm our findings. Together, these findings suggest that increased serotonin neurotransmission ameliorates NA, supporting the inference by Nutt et al[16] and Stahl[17] that decreased serotonin neurotransmission underlies the pathophysiology of NA.

Genetic studies support serotonergic dysfunction as an important component of the pathogenesis of NA. In particular, homozygotes for the long (*l*) allele of the serotonin transporter–linked polymorphic region (5-HTTLPR) have low negative emotionality (anxiety/neuroticism scores),[30] whereas the short (*s*) allele is associated with hypervigilance.[31] These studies suggest altered serotonin function in subjects who have high negative emotionality and predict that those with the short allele will have high NA.

Unlike NA, AA levels in our depressed patients did not predict treatment differences between escitalopram and bupropion. However, no previous studies have evaluated the effect of antidepressant treatment on AA, and our estimation of AA is partial because of missing items assessing all aspects of AA. Therefore, AA may have been poorly assessed rather than unimportant to differential treatment effects, and this finding needs to be replicated.

Previous studies evaluated the treatment effect on both psychic and somatic anxiety as measured by the HDRS-A/S, variously reporting a small difference or lack of difference between these medications in reducing anxiety symptoms. Rush et al[32,33] compared patients treated with bupropion (N = 234, N = 126) with patients treated with sertraline (N = 225, N = 122) for 16 weeks and found that baseline HDRS-A/S levels did not distinguish responders to bupropion vs sertraline. Papakostas et al[34] evaluated 10 double-blind, randomized studies among depressed patients who received treatment with either bupropion (N = 1,061) or an SSRI (N = 1,061), reporting that in depressed patients with high levels of anxiety the rate of response to an SSRI was slightly but significantly higher (6%) than to bupropion.

To compare our results with the above-mentioned studies, we also evaluated in our patients the effect of treatment on the HDRS-A/S factor and failed to find a significant HDRS-A/S–by-treatment interaction. Since psychic anxiety is considered part of the NA dimension, which we found

more likely to respond to an SSRI, while somatic anxiety is included in the AA dimension, which did not appear to require specifically improved serotonin neurotransmission, we attributed the lack of difference between drugs in anxious depressed patients to the fact that the HDRS-A/S measures not only psychic anxiety but also somatic anxiety. Therefore, our results suggest that NA may be a better measure to identify patients specifically responsive to SSRI, while the somatic components of anxious depression can be adequately treated by drugs that do not specifically boost serotonin.

The present study supports that a subgroup of MDD patients is characterized by high levels of general distress (NA) that, according to the *DSM-5* and *ICD-10*,[12,13] respectively, can be diagnosed as "MDD with anxious distress" or "mixed anxiety and depression." This subgroup may be better treated with a medication that enhances serotonergic neurotransmission than an antidepressant having a non-serotonin mode of action.

Limitations

This study is limited by being a retrospective reanalysis rather than a prospective test of the hypothesis. Because the available data did not include Watson and Clark's Mood and Anxiety Symptoms Questionnaire (MASQ; D. Watson, PhD; L. A. Clark, PhD; unpublished manuscript; 1991) or Positive and Negative Affect Scale (PANAS),[35] we approximated their NA and AA items with an ad hoc rating scale consisting of items chosen from other scales (HDRS-17, QIDS, MADRS, SAS) on the basis of face validity only, and therefore we could have oversampled some aspects of NA and underestimated others. Previous literature suggested that the majority of standard anxiety and depression rating scales are heavily weighted toward symptoms of general distress or negative affect,[36] so we used items from existing scales to approximate NA; ideally, an NA score would be determined directly by the MASQ or the PANAS, and our attempted approximation would be validated by comparing it with the MASQ or PANAS. For this reason, no clinical inferences should be made before independent replication utilizing accepted NA and AA measurements.

Another limitation is that the sample size may not have had the power to differentiate drug effects using AA and HDRS-A/S. The 6% difference between SSRI and bupropion reported by Papakostas and colleagues,[34] for example, would require 2,122 patients to have an 80% chance of demonstrating superiority of SSRI. Such a difference, however, is not clinically meaningful, as the number needed to treat would be 17 for the treatment choice to make a difference in 1 patient. A small effect may account for the inconsistent literature in which some studies find differential treatment effects between patients with and without anxious depression, while others do not.

Finally, biological studies suggest the effects of antidepressants on mood are complex, and there is considerable "cross-talk" between monoamine neurons and overlapping projection fields within the central nervous system. For example, serotonin regulates other neurotransmitters (eg, dopamine and norepinephrine) in a complex way, making the mood effects of various antidepressant strategies drugs difficult to predict since they all enhance serotonin transmission, albeit by different mechanisms.[36] Some antidepressant medications can also exert differential actions on the norepinephrine system. Specifically with regard to bupropion, norepinephrine neurons recover their mean firing rate and display more burst activity with prolonged administration, whereas both parameters remain attenuated and their mean firing rate is also dampened with noradrenergic regimens of venlafaxine.[37,38] Such attenuated norepinephrine activity could help explain the beneficial action of SSRIs and venlafaxine, but not bupropion, in panic symptoms.[26,39] Moreover, it is now thought that the increases in synaptic monoamines induced by prolonged administration of antidepressants result in secondary neuroplastic changes that occur on a more delayed timescale, quite likely involving transcriptional and translational changes that mediate molecular and cellular plasticity.[40,41] Therefore, the acute effects of antidepressants on monoamine systems on specific symptoms of major depression must be interpreted cautiously.

CONCLUSION

Our post hoc analyses of a previously reported study confirm that a non-serotonergic agent is less effective than a serotonergic drug in treating depressed patients with high NA, but just as effective in treating those with low NA. Contrariwise, we did not find support of differential response to an SSRI versus a non-SSRI agent to be dependent on AA scores or the HDRS-A/S factor. This supports the hypothesis that the NA symptoms of depression may result from inadequate serotonergic neurotransmission. Prospective treatment studies utilizing the MASQ while measuring central serotonin activity are indicated.

Author affiliations: Psychiatric Section, Department of Neuroscience, University of Parma, Parma, Italy (Drs Gerra and Marchesi); Depression Evaluation Service, New York State Psychiatric Institute, and Columbia University College of Physicians and Surgeons, New York (Drs Amat, Hellerstein, and Stewart); and Royal Ottawa Mental Health Care Center, Ottawa, Ontario, Canada (Dr Blier).

Potential conflicts of interest: **Dr Stewart** has served on advisory boards for Biovail, Alkermes, and Somerset; served on a data and safety monitoring board (DSMB) for Pfizer; and worked as consultant for Bristol-Myers Squibb. Dr Stewart's wife has served on advisory boards for Sanofi-Aventis and a DSMB for Novartis, was an expert witness for a Novartis presentation to the US Food and Drug Administration, and has received speaking honoraria from Merck, Boehringer-Ingelheim, and Sanofi-Aventis. **Dr Blier** has received research grants and received honoraria for giving lectures and/or participated in advisory boards for AstraZeneca, Biovail, Bristol-Myers Squibb, Eli Lilly, Euthymics, Forest, Janssen, Lundbeck, Otsuka, Pfizer, Servier, Takeda, and Valeant. He has also served as a consultant for Lundbeck and Valeant. **Dr Hellerstein** has received grant support from Eli Lilly and Pfizer. **Dr Marchesi** has received grant support from Eli Lilly. **Drs Gerra** and **Amat** report no potential conflict of interest.

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