BUPROPION NORMALIZES COGNITIVE PERFORMANCE IN PATIENTS WITH DEPRESSION

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Patients with mood disorders are known to have neurocognitive deficits in many, if not most, cognitive domains (1). In a recent paper, we showed that depressed patients on modern antidepressants had, in spite of successful treatment, residual deficits in tests of effortful attention, executive function and information processing speed (2). Although the cognitive impairments associated with depression are improved by effective antidepressant therapy, they do not tend to normalize (3,4,5,6).

This general rule has not been tested, however, in comparative studies of specific antidepressants. One might expect, for example that that antidepressants with potent noradrenergic (NE) effects would be cognitive enhancers (7,8,9,10). In contrast, antidepressants whose primary action is serotonergic would be expected to cognitively neutral, or less likely to "normalize" cognition in depressed patients (11,12,13,14,15,16,17).

We took the opportunity to examine this proposition in a naturalistic study of depressed patients who had been treated with seven different modern antidepressants. We wondered whether, in a real-world situation, could one demonstrate cognitive differences among patients taking different drugs? To address the question, we took advantage of a computerized neurocognitive screening battery that could administer seven neuropsychological tests in a short period of time, and generate results with millisecond accuracy. Because the test is easy to administer, it could be given, in our clinics, to virtually *every* patient on antidepressants.

METHODS & MATERIALS

SUBJECTS

The subjects of this investigation were outpatients at the NC Neuropsychiatry Clinics in Chapel Hill and Charlotte, age 18-65, with the diagnosis of major depressive disorder (MDD), unipolar, non-psychotic. The subjects were all in good health, with no concomitant neurocognitive disorders (e.g., attention deficit disorder, learning disability, chronic pain, mild cognitive impairment) and no comorbid psychiatric diagnoses. They were on no concomitant medications. Subjects were selected for inclusion in this investigation if antidepressant treatment led to optimal clinical response, in the opinion of the treating clinician, and if the patient had been discharged to routine, quarterly follow-up. All patients had to have been on a stable dose of drug for at least 4 weeks.

A search of a database of patients who had been tested with the CNS Vital Signs battery at the North Carolina Neuropsychiatry Clinics yielded no fewer than 541 patients who had been tested while on antidepressants. Eliminating patients who need not meet the above criteria, and matching patients as closely as possible for three equal groups on the basis of medication, age, race, and gender yielded a final sample of 81 patients (bupropion, 27; venlafaxine, 27; SSRI's, 27).

Twenty-seven controls were randomly selected from the CNS Vital Signs normal database. This database is comprised of individuals who are in good health, with no current or past psychiatric, neurological or cognitive disorder, and on no current centrally-active medications. The controls were matched as closely as possible for age, race and gender. (All of the Ss, patients and controls, were white.)

COGNITIVE EVALUATION

Patient's neurocognitive performance was measured on a computerized battery of tests, "CNS Vital Signs" (CNSVS). CNSVS is a PC-based neurocognitive screening battery, comprised of seven familiar neuropsychological tests: verbal and visual memory (VBM, VIM), finger tapping (FTT), symbol-digit coding (SDC), the Stroop test (ST), the shifting attention test (SAT) and the continuous performance test (CPT). The test battery is self-administered in the clinic on an ordinary PC, and takes about 30 minutes. CNS Vital Signs generates 5 cognitive domain scores and one summary score (the "neurocognition index", NCI). Group differences were assayed by MANOVA, taking as covariates patient age and gender. If significant between groups differences were detected, pairwise *t* tests were done to measure differences between the three antidepressant groups and normals.

RESULTS

In Table 1, columns 2-5 are the domain scores NCI scores for the three antidepressant groups and normal controls. F scores from MANOVA and significance levels are in columns 6 and 7. Significant group differences exist for 4 of 5 domain scores and for the NCI. The sources of these differences were established by pairwise t tests, and are presented in Table 2. The SSRI group scored significantly below normals in tests of psychomotor speed, cognitive flexibility and reaction time. The VEN group scored more poorly in than normal in reaction time, a measure of information processing speed derived from the Stroop test. The BP group did not differ from normals in any of the cognitive domains.

Table 1. Mean Test Scores and Difference from Normal

MEDICATION	SSRI	VEN	BP	NML	F	P<
N	27	27	27	27		
AGE	43.81	46.11	44.00	43.85		
MALE	11	11	7	10		
FEMALE	16	16	20	17		
NEUROCOGNITION INDEX	89.77	94.80	100.00	98.34	2.59	**0.023**
COMPOSITE MEMORY	96.56	95.50	100.81	97.70	2.18	0.051
PSYCHOMOTOR SPEED	145.23	161.45	166.92	171.76	4.91	**0.000**
REACTION TIME*	697.44	700.02	649.80	639.17	4.24	**0.001**
COGNITIVE FLEXIBILITY	32.04	38.89	45.07	43.27	4.24	**0.001**
COMPLEX ATTENTION*	11.42	8.92	7.48	8.38	3.26	**0.006**

NOTE, Table 1. An asterisk indicates that lower scores are better.

Table 2. Pairwise t Tests Comparing Antidepressant Groups to Normals

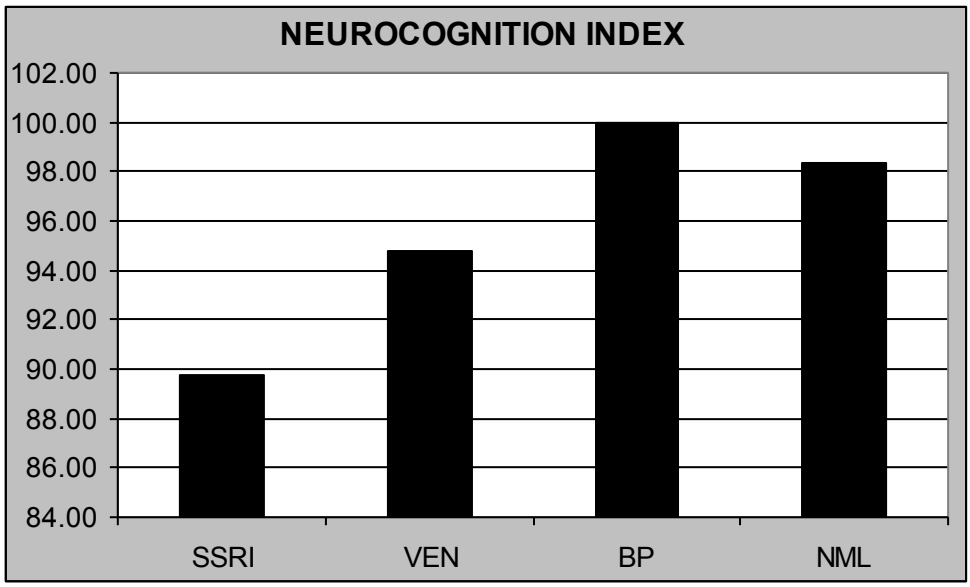
PAIRED t TEST	NMLvSSRI		NMLvVEN		NMLvBP	
	t	P<	t	P<	t	P<
NEUROCOGNITION INDEX	2.94	0.0049	1.26	0.2139	-1.05	0.2968
COMPOSITE MEMORY	0.49	0.6229	1.02	0.3144	-1.81	0.0768
PSYCHOMOTOR SPEED	3.93	0.0003	1.47	0.1483	1.01	0.3195
REACTION TIME	-1.94	0.0580	-2.03	0.0474	-0.46	0.6446
COGNITIVE FLEXIBILITY	3.29	0.0018	1.06	0.2922	-0.85	0.4009
COMPLEX ATTENTION	-1.76	0.0846	-0.34	0.7371	0.73	0.4659

DISCUSSION

Patients with depression are subject to neuropsychological deficits in attention, memory, psychomotor speed, processing speed and executive function. When they are treated, they perform better, but they do not perform as well as normal controls (1, 17). They improve, at least to a degree, but do not "normalize." The data reported here suggest that how well they perform on neurocognitive testing may be a function of the antidepressant with which they are treated. What our data show is that depressed patients on BP perform as well as normals do on a battery of neurocognitive tests. Patients on VEN and SSRI's do not.

These results are consistent with the hypothesis that cognitive benefit may occur relative to an antidepressant's norepinephrine activity, while lack of benefit may relate to its serotonergic activity. The noradrenergic/dopaminergic antidepressant, BP, is associated with normal function. The mixed serotonin/norepinephrine reuptake VEN performs less well than BP, but better than the SSRI's (Figure 1). This is consistent with the principle that enhanced norepinephrine metabolism is associated with better cognitive performance on a variety of neurocognitive tasks.

Figure 1. Relative Summary Performance of Antidepressants



A naturalistic, cross-sectional study is not an optimal environment for dealing with the complexities of the questions at hand. One would prefer to have data from a more controlled environment. The ideal way to examine drug-related changes in neurocognition is to test patients at baseline, and then to test them again after they have achieved a therapeutic result. It would also be useful to have a comparison group of patients who were treated with placebo. The severity of patients' depression at baseline and how well they have responded to treatment should have been calibrated with more precision than we have done. And the only unbiased way to compare one treatment to another is to use random assignment.

Patients were not randomly assigned to medication. Antidepressants were selected on the basis of clinicians' professional good judgment. This is a flaw, but not a fatal flaw. The choice of which antidepressant to use was made by 9 experienced clinicians, operating independently in two different clinics. No specific pattern was detected in the clinician's choice. If there was bias in drug selection, it would have worked against BP and VEN. Psychiatrists, aware of the beneficial neurocognitive effects of BP, sometimes prescribe the drug for depressed patients who complain of problems with concentration or memory. Psychiatrists often prescribe VEN for patients with more severe depression, or who have failed to respond to SSRI's. If either of these factors had been operative in this study, one would have expected patients on BP or VEN to do less well than patients on SSRI's.

The reason why it is important to report these data, in spite of the obvious shortcomings, is that the relative neurocognitive effects of antidepressants are rarely addressed in the medical literature, and when they are, the research has been done in laboratory settings. Not only is it important to address the issue of neurocognition with respect to the antidepressants, it is important to do so using practical tools in a real-world environment. Computerized testing allows clinicians to evaluate the cognitive effects of drug treatment in the clinic setting.

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