Bupropion and Venlafaxine Responders Differ in Pretreatment Regional Cerebral Metabolism in Unipolar Depression

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Background: *Pretreatment functional brain imaging was examined for never-hospitalized outpatients with unipolar depression compared with control subjects in a crossover treatment trial involving bupropion or venlafaxine monotherapy.*

Methods: *Patients (n = 20) with unipolar depression received baseline (medication-free) fluorine-18 deoxyglucose (FDG) positron emission tomography (PET) scan and then at least 6 weeks of bupropion or venlafaxine monotherapy in a single-blind crossover trial. Age-matched healthy control subjects (n = 20) also received baseline FDG PET scans. For each medication PET data from patients compared with control subjects was analyzed as a function of treatment response (defined as moderate to marked improvement on the Clinical Global Impression Scale).*

Results: *Treatment response rates were similar for buproprion (32%) and venlafaxine (33%). Compared with control subjects, responders but not nonresponders, to both drugs demonstrated frontal and left temporal hypometabolism. Selectively, compared with control subjects bupropion responders (n = 6) also had cerebellar hypermetabolism, whereas venlafaxine responders (n = 7) showed bilateral temporal and basal ganglia hypometabolism.*

Conclusions: *These data suggest that pretreatment frontal and left temporal hypometabolism in never-hospitalized depressed outpatients compared with control subjects is linked to positive antidepressant response and that additional alterations in regional metabolism may be linked to differential responsivity to bupropion and venlafaxine monotherapy.*

Key Words: Bupropion, depression, positron emission tomography, treatment response, unipolar, venlafaxine

Although effective medications exist for the treatment of depression, the degree, timing, and frequency of treatment response is unpredictable and varies widely. Functional neuroimaging linked to treatment trials for depression represents a promising approach to examine the underlying neurobiology of treatment response variability and may ultimately serve as a tool to help predict antidepressant treatment response. Using these methods, a growing literature is beginning to elucidate the functional neuroanatomy of depression and to link these findings to clinical treatment responsiveness.

Pretreatment functional neuroimaging with positron emission tomography (PET) has been used in this fashion for antidepressants, mood stabilizers, and experimental treatments such as sleep deprivation and repetitive transcranial magnetic stimulation (rTMS). For antidepressants, Buchsbaum and colleagues (1997) found that increased baseline metabolism in the left rectal gyrus of the frontal lobe was correlated with antidepressant response to sertraline. Mayberg and colleagues (1997) found that baseline rostral anterior cingulate hypermetabolism correlated with subsequent antidepressant treatment response, whereas hypometabolism was associated with nonresponse. In an outpatient study that used paroxetine for the treatment of depression, lower metabolism in the left ventral anterior cingulate gyrus was associated with better treatment response (Brody et al 1999). In a study of patients with refractory unipolar and bipolar mood disorders, baseline paralimbic and prefrontal hypermetabolism was linked with carbamazepine response, whereas baseline widespread hypometabolism was associated with nimodipine response (Ketter et al 1999).

For sleep deprivation, Wu et al (1999) found that higher baseline metabolic rates in medial prefrontal cortex, ventral anterior cingulate, and posterior subcallosal gyrus correlated to antidepressant response from sleep deprivation. Ebert et al (1994) replicated the correlation between increased cingulate activity at baseline and the antidepressant effects of subsequent sleep deprivation.

Better antidepressant effects of high versus low frequency repetitive transcranial magnetic stimulation (rTMS) have been reported in those with baseline hypometabolism versus hypermetabolism respectively (Kimbrell et al 1999; Speer et al 2000). Hence, these initial studies examining regional cerebral activity at baseline and treatment response are provocative because they suggest links between pretreatment regional brain activity and subsequent treatment response across multiple treatment modalities.

To further examine altered baseline prefrontal and paralimbic functioning in depressed patients in relation to antidepressant response specificity, we conducted a randomized, crossover study involving pretreatment functional neuroimaging with fluorine-18 deoxyglucose (FDG) PET followed by bupropion or venlafaxine monotherapy. These two drugs were chosen because of their contrasting presumed mechanisms of action involving dopamine (and norepinephrine) for bupropion (Ascher et al 1995; Richelson 1996; Stahl et al 2004) and serotonin and norepinephrine for venlafaxine (Richelson 1996; Thase 1996; Frazer 2001). Preliminary FDG PET data in 11 of these patients have been reported elsewhere (Little et al 1996). We now report how pretreatment FDG PET data in the completed clinical trial of

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23 patients relates differentially to bupropion and venlafaxine antidepressant response.

Methods and Materials

Subjects

Through local newspaper advertisements in the Washington, D.C., metropolitan area, the study recruited 23 outpatients with unipolar depression (11 women, 12 men; mean age 46.3 ± 12.9 SD) and no history of psychiatric hospitalization and 20 healthy control subjects (11 women, 9 men; mean age 46.6 ± 13.1 SD) without personal or first-degree relative history of psychiatric illness. After a complete description and discussion of the study including the possible risks and benefits of participation, written informed consent was obtained. Patients were not paid for their participation. The study procedures were approved and monitored by the committee on human experimentation of the Intramural Research Program of the National Institute of Mental Health (NIMH).

Patients met criteria for a current episode of major depression ($n = 14$), major depression plus dysthymia ($n = 8$), or dysthymia ($n = 1$) by clinical interview using DSM-IV (American Psychiatric Association 1994) and the Structured Clinical Interview for DSM-IV Axis I Disorder, Patient Edition (SCID; First et al 1995). Subjects were determined to be physically healthy by history, physical and laboratory examinations (including comprehensive urine drug screen and human immunodeficiency virus testing), and brain magnetic resonance imaging. Data on cerebrospinal fluid amine metabolites of this same group has been previously reported (Little et al 1999), and these subjects were also included in the large group of patients with unipolar depression in whom severity of depression and cerebral glucose utilization has been reported (Kimbrell et al 2002).

Paid healthy control subjects were determined to have never been mentally ill by the Schedule for Affective Disorders and Schizophrenia—Lifetime Anxiety Version (SADS-L; Endicott and Spitzer 1978) and underwent the same medical screening procedures as the patients (Ketter et al 1999, 2001; Kimbrell et al 2002).

Clinical Trial

These patients were randomized to single-blind treatment with bupropion or venlafaxine monotherapy for a minimum of 6 weeks with the option of a subsequent crossover to the other medication for inadequate response or side effects. The crossover phase included the tapering of the first medication and a placebo period for up to 2 weeks. Medications were clinically titrated by a research psychiatrist (JTL) based on clinical response and side effects to the maximum dose tolerated, or up to 450 mg of bupropion or 375 mg of venlafaxine daily. All patients were blind as to which medication they were receiving during the study. Of these 23 patients, 20 (11 women, 9 men; mean age 46.7 ± 12.6 SD) also volunteered to receive a baseline (medication-free) FDG PET scan prior to bupropion or venlafaxine monotherapy.

Each patient was seen weekly by the research psychiatrist (JTL) and a blinded, trained rater. The observer-rating packet, administered weekly by the same rater for each patient, included the extended (28-item) Hamilton Depression Rating Scale (HAM-D, Hamilton 1960; Williams et al 1988), the Global Assessment Scale (GAS, Endicott et al 1976), and the Zung Anxiety Status Inventory (ZAS; Zung 1974). Interrater reliability for the weekly ratings between the five blinded raters was established using Inter-Class Correlations (ICC; Bartko and Carpenter 1976); ICC scores ranged from .67 to .98 for the HAM-D, from .88 to .89 for the GAS, and from .92 to .96 for the ZAS.

Patient self-ratings completed on a weekly basis included the Beck Depression Inventory (BDI; Beck et al 1961) and the Zung Self-Rated Anxiety Scale (1971). Retrospective life charting with the NIMH—Life Chart Method (LCM; Leverich et al 1998, 2001) and weekly prospective self- and observer-rated life charting (Denicoff et al 1997) was also conducted for each patient.

The primary clinical outcome measure was the Clinical Global Impressions Scale, Bipolar Version (CGI, Guy 1976; National Institute of Mental Health 1985; Spearing et al 1997). The CGI, completed at the end of each medication phase, used all available information for each patient by the blind rater in consensus with the research psychiatrist, both of whom were without knowledge of the brain imaging results. The CGI determinations of "much improved" or "very much improved," but not "mildly improved," were used as clinically meaningful responses to treatment.

Imaging Methods

Subjects were on a low-monoamine diet for 7 days (including no alcohol) before receiving the PET scan. Patients were imaged at baseline while free of psychotropic medication for at least 2 weeks (or 6 weeks in the case of prior fluoxetine treatment). Subject preparation on the day of the PET scan included insertion of an indwelling radial artery catheter to permit measurement of the arterial input function and insertion of an intravenous catheter in the other arm for injection of the radiotracer.

Patients and control subjects were scanned using a Scanditronix PC2048-7B scanner, with an in-plane resolution of 6 mm and an axial resolution of 10 mm at the center of the gantry. A transmission scan was obtained using a 68Ge/68Ga source rotated around the subject's head to correct the emission scans for photon attenuation by the skull and scalp and to verify correct head positioning for the emission scan.

Head movement was restricted with an individually molded thermoplastic mask. After the subjects' eyes were covered and headphones placed over their ears, 4–5 mCi of FDG was administered intravenously. During the FDG uptake period, subjects performed an auditory continuous performance task for 30 min (Cohen et al 1988; Kimbrell et al 2002). At the end of this 30-min period, the headphones were removed, and four emission scans were acquired over 7.5-min. Each emission scan consisted of 7 slices, yielding 28 interleaved slices parallel to the canthomeatal line.

Radial arterial blood sampling allowed determination of time-blood activity curves for dynamic tracer kinetic modeling that generated the image voxel intensity. The conversion of image voxel values from nanocuries per cubic centimeter to milligrams of glucose per 100 mg tissue per min (mg/hg/min; hg = 100 mg of tissue) was performed using methods described by Sokoloff (1981) and others (Brooks 1982; Huang et al 1980), generating regional cerebral glucose metabolic rate (rCMRglu).

Statistical Analysis

Image processing and analysis were performed on Sun Unix workstations (Sun Microsystems, Mountain View, California) using Matlab (Mathworks, Sherborn, Massachusetts) and Statistical Parametric Mapping software (SPM, courtesy of Functional Imaging Laboratory, Wellcome Department of Cognitive Neurology, London, United Kingdom). ANALYZE (Mayo Foundation, Rochester, Minnesota, 1991) and National Institutes of Health and NIMH–developed software were also used in the analysis.