
Cerebral Blood Volume and Clinical Changes on the Third Day of Placebo Substitution for SSRI Treatment

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Background: *Interruptions in SSRI treatment have been associated with adverse effects that can resemble depressive illness. We hypothesized that brain regions implicated in depression, with extensive serotonergic innervation, would exhibit changes in activity associated with emergence of symptoms following drug discontinuation.*

Methods: *Subjects meeting DSM-IV criteria for remitted major depression on 20 mg/day of either fluoxetine or paroxetine were recruited into this 6-week study. During weeks 2 and 6, subjects underwent a 3-day period in which either active drug or placebo was substituted for their medication under double-blind conditions. Cerebral blood volume (CBV) maps were obtained via dynamic susceptibility magnetic resonance imaging at the end of each double-blind period.*

Results: *In the paroxetine group, change in CBV in left medial superior frontal region and left caudate nucleus correlated significantly with change in Discontinuation Emergent Symptom Scale and Hamilton Depression Rating Scale (HDRS; $R^2 = 0.66$, $p = .0007$; $R^2 = 0.51$, $p = .006$; and $R^2 = 0.43$, $p = .015$; $R^2 = 0.32$, $p = .043$, respectively).*

Conclusions: *These data demonstrate that changes in regional CBV of left prefrontal cortex and left caudate nucleus correlate with the emergence of discontinuation symptoms and increased HDRS after interruption of paroxetine treatment. Biol Psychiatry 2003;53:100–105 © 2003 Society of Biological Psychiatry*

Key Words: SSRI discontinuation, MRI, CBV changes, prefrontal cortex, caudate nucleus

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of antidepressant medications in the United States (Delgado 2000). Although these agents are effective, patients taking antidepressants frequently have difficulty with medication compliance (Delgado 2000; Demyttenaere et al 1998). Little is understood about the effects of medication noncompliance on patients and on the metabolic activity of brain regions associated with depression. Recently, it has been recognized that interruptions in SSRI treatment are associated with unwanted effects, which can be somatic (e.g., dizziness, gastrointestinal symptoms) or can resemble some features of depressive illness including depressed mood and anxiety (Rosenbaum et al 1998). These symptoms are most commonly associated with SSRIs that have shorter half-lives, no active metabolites, and nonlinear elimination kinetics (Haddad 1997).

The SSRIs predominantly act on serotonergic neurons, and it is likely that homeostatic disruptions in these pathways related to abrupt interruption of treatment mediate the adverse events observed with treatment interruption. Although depressive symptoms could represent recurrence of the underlying disorder, the fact that such symptoms appear to resolve within 1–2 weeks in most patients (Michelton et al 2000; Rosenbaum et al 1998) suggests that they are not true relapses, but rather temporary perturbations of serotonergic pathways important in affective regulation.

Currently, depression is thought to reflect dysfunction in a mood circuit that includes prefrontal cortex, brain-stem nuclei, the caudate nuclei, thalamus, and hypothalamus (Ahearn et al 2001). Studies of depressed patients, with some exceptions, have reported decreased cerebral blood volume and metabolism, most commonly in the left prefrontal cortex (Bench et al 1995; Bremner et al 1997; Brody et al 1999; Bushsbaum et al 1997; Delgado et al 1999). Studies that have examined the effects of SSRI treatment have shown increased pretreatment cingulate activity in SSRI responders and a tendency to normalize

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both frontal and cingulate metabolic activity with treatment response (Brody et al 1999; Buchsbaum et al 1997; Mayberg et al 1999). Conversely when serotonergic neurotransmission was reduced by tryptophan depletion, Bremner et al (1997) found that patients who experienced relapses in depressive symptoms exhibited decreased metabolism in the middle frontal cortex, orbitofrontal cortex, thalamus, and caudate nucleus. In addition, the changes in the middle frontal cortex, orbitofrontal cortex, and thalamus showed a positive correlation with change in depressive symptoms.

In light of the data from these studies, we hypothesized that 11 brain regions, six left prefrontal cortex regions, cingulate gyrus, thalamus, and the caudate nucleus, all of which have extensive serotonergic innervation (Arato et al 1991; Flor-Henry 1985), would exhibit decreases in cerebral blood flow associated with the emergence of clinical symptoms following discontinuation of paroxetine. To test this hypothesis, remitted depressed patients treated with a relatively short-acting SSRI, paroxetine, underwent two 3-day periods of double-blind treatment during which they received either placebo interruption or continued drug therapy. At the end of each period, changes in regional brain activity under both active drug and placebo conditions were measured using dynamic susceptibility (DSC) magnetic resonance imaging (MRI). This method produces detailed maps of cerebral blood volume (CBV), permitting determination of cerebral hemodynamics with high anatomic and temporal resolution similar to emission tomography (Henry et al 2001; Levin et al 1995), without exposing subjects to repeated doses of ionizing radiation. To provide a control condition, the same procedures were carried out on a group of patients being treated with fluoxetine, a longer acting SSRI that has been associated with a low incidence of new symptoms during brief treatment interruptions (Coupland et al 1996; Michelson et al 2000; Rosenbaum et al 1998).

Methods and Materials

This study was reviewed and approved by the McLean Hospital Institutional Review Board. Written informed consent was obtained from each subject before entering into the study protocol. Subjects meeting DSM-IV criteria for major depression in remission on 20 mg/day of either fluoxetine ($n = 15$) or paroxetine ($n = 14$) were recruited into this 6-week study. Diagnosis was verified during a semistructured interview by a board certified psychiatrist (MEH) and was confirmed by the Structured Clinical Interview for DSM-III-R (First et al 1997). Subjects had been maintained on a stable 20-mg dose of medication for a minimum of 6 months and a maximum of 36 months. Patients meeting criteria for bipolar disorder, schizophrenia, or schizoaffective disorder or who were actively abusing substances, taking centrally active medications except thyroid

hormone, or who had a known contraindication to MRI were excluded from the study.

For 4 of the 6 study weeks, subjects continued their own medication. During week 2 and week 6, subjects underwent a 3-day period of double-blind treatment. In one of these periods, placebo was substituted for active medication; during the other, medication was continued as usual in an order-randomized fashion. On the third day of each double-blind period, rating scales were completed and subjects underwent an MRI procedure as described below.

To increase the likelihood of identifying atypical depressive symptoms, a 31-item version of the Hamilton Depression Rating Scale (HDRS) was used, including the conventional 21 items of the HDRS, plus a 10-item extension consisting of items assessing helplessness, hopelessness, worthlessness, hypersomnia (early), hypersomnia (oversleeping), hypersomnia (napping), increased appetite, weight gain, psychic retardation, and motoric retardation (Hamilton 1967; Williams 2001), was administered at weekly clinic visits, together with the Discontinuation Emergent Symptom Scale (DESS; Rosenbaum et al 1998). Primary outcome measures for the study were changes in scores on these two instruments, with change on these scales calculated by subtracting the score on the last day of substitution with blinded medication (during the scanning visit, day 7 of weeks 2 and 6) from the score obtained at the clinic visit of the preceding week.

Scanning Procedures

Subjects presented to the imaging suite 30 min before their scan time. Subjects were fitted with an 18G antecubital angiocatheter for contrast administration and were placed in the scanner in the supine position, with their heads secured with surgical tape. We performed the MRIs on a 1.5-Tesla General Electric Sigma Scanner (Milwaukee, WI) retrofit with a whole body echo planar gradient set (Advanced NMR Systems, Wilmington, MA). The examination consisted of several elements, including anatomic imaging (consisting of a T_1 sagittal series and a T_2 axial series), a proton magnetic resonance spectroscopy study (findings to be reported elsewhere), and the CBV measurement. The total examination time was approximately 1.5 hours. Two female fluoxetine subjects were unable to complete both scanning sessions because of inability to obtain intravenous access. One female fluoxetine subject and one male paroxetine subject could not be scanned according to schedule because of equipment malfunction. The paroxetine subject agreed to go back on active drug and then undergo a repeat of blinded medication, at which time the scanning was completed. The fluoxetine subject declined. One male fluoxetine subject was excluded from the analysis because his DESS and HDRS increased by 5 and 11 points, respectively, while on active blinded medication and did not change while on placebo. One male paroxetine subject was excluded because of a history of alcohol withdrawal seizures. With these exclusions, there were 13 paroxetine and 11 fluoxetine subjects included in the analysis.

Sagittal and axial localizer images acquired on study day 1 were used to realign head position on study day 2. For CBV measurements, echo planar images were collected with the standard quadrature head coil using a spin-echo sequence. The

Table 1. Demographic Description of Subject Population

	Fluoxetine <i>n</i> = 11 Male Subjects <i>n</i> = 2 (18%)			Paroxetine <i>n</i> = 13 Male Subjects <i>n</i> = 4 (30%)		
	Mean	SD	Range	Mean	SD	Range
Age	40	13	23–60	38	11	21–67
Baseline HDRS	1.7	1.4	0–4	1.5	2	0–6
Baseline DESS	.2	.4	0–1	.3	.6	0–2
Months on drug before entering the study	22.8	8.8	9–36	20.7	10.1	8–35

DESS, Discontinuation Emergent Symptom Scale; HDRS, Hamilton Depression Rating Scale.

midsagittal image from the T₁ sagittal image series was used to prescribe 10 axial brain slices (7 mm thick, 3 mm skip) for CBV determinations. The following parameters were used: Time Repetition (TR) = 2000 msec, Time Echo (TE) = 100 msec, field of vision = 40 × 20 cm, matrix = 256 × 128, in-plane resolution, 1.5 mm × 1.5 mm. Gadoteridol (ProHance, Bracco Diagnostics, Princeton, NJ), 0.2 mmol/kg was administered as a bolus via the intravenous catheter over 4 sec, beginning 20 sec into the scan. These imaging parameters weight blood volume measurement toward small vessels (<100 μm in diameter; Boxerman et al 1995).

Data were transferred offline for processing. A motion correction algorithm was applied to detect and correct translational and rotational motion during image acquisition (Maas et al 1997). Image-intensity data were acquired from three contiguous axial slices chosen for each patient such that the middle slice allowed for the best visualization of the head of the caudate nucleus. Cortical regions were defined using a semiautomated cortical profiling algorithm to define 12 equiangular regions of interest (ROI) per slice that spanned the width of the cortical gray matter (1 ROI: 30° arc, 9 mm width). In keeping with our a priori hypotheses, data from the six left-sided prefrontal regions (two per slice) were used for the cortical analysis. In addition, five hand-drawn ROIs—anterior cingulate, right and left caudate nucleus, and right and left thalamus—were defined for each subject by a research assistant who was blind to treatment condition (Henry et al 2001). The CBV change was determined by calculating the ratio of each subject's on-drug to their off-drug CBV measurement for each ROI.

Statistical Methods

The HDRS change from baseline, DESS change from baseline, and regional average (median) CBV ratios were determined as described above. Regression analyses comparing change in mean CBV for each ROI to change in DESS and HDRS for each treatment group were conducted. These regression results are

reported in terms of R^2 with associated p values. Data analyses were restricted to the five hand-drawn regions and the six left prefrontal cortical regions defined by the cortical profiling algorithm. Analyses were done separately for paroxetine and fluoxetine subjects. Statistical significance required $p < .05$. Statistical analyses were conducted using Statview version 4.5.

We hypothesized that following antidepressant discontinuation, we would observe the following changes in prefrontal cortex, cingulate gyrus, thalamus, and the caudate nucleus: 1) HDRS and DESS scores would increase, and these changes would be greater for paroxetine subjects than for fluoxetine subjects. 2) In subjects who exhibited symptoms with placebo substitution, CBV would decrease in the left prefrontal cortex, the left caudate nucleus, and the left thalamus and increase in the cingulate gyrus and therefore correlate with change in clinical state as measured by the DESS and HDRS.

Results

The study sample characteristics are summarized in Table 1. As noted, at baseline, both fluoxetine and paroxetine subjects had low HDRS scores, reflecting remission status.

The changes in DESS and HDRS for the fluoxetine and paroxetine subjects in the imaging data set are shown in Table 2. As noted, the paroxetine group had larger changes in HDRS and DESS scores than the fluoxetine group, but this difference did not reach statistical significance. The change in HDRS among paroxetine patients was highly correlated with changes in DESS ($R^2 = 0.84$; $p < .001$). Three of the paroxetine patients had an increase of 10 or more symptoms on the DESS under placebo substitution, whereas none of the fluoxetine patients had an increase of more than five symptoms.

In the paroxetine group, consistent with our hypothesis that brain regions associated with depression and with

Table 2. Change from Baseline on HDRS and DESS

	Fluoxetine <i>n</i> = 11			Paroxetine <i>n</i> = 13		
	Mean	SD	Range	Mean	SD	Range
Change in HDRS ^a	1.27	2.41	(−3) −7	3.08	5.04	(−2) −13
Change in DESS ^a	1.54	2.02	(−1) −5	3.85	7.19	(−4) −22

DESS, Discontinuation Emergent Symptom Scale; HDRS, Hamilton Depression Rating Scale.

^aA negative change indicates a decrease in symptoms.

Table 3. Regression Analysis for Change in HDRS and DESS Ratings with CBV in ROI.^a

	HDRS			DESS		
	<i>R</i> ²	<i>F</i>	<i>p</i>	<i>R</i> ²	<i>F</i>	<i>p</i>
Left caudate nucleus	.32	5.215	.04	.432	8.38	.015
Right caudate nucleus	.02	.20	.66	.01	.13	.72
Left thalamus	.001	.02	.90	.02	.28	.61
Right thalamus	.01	.14	.72	.02	.24	.63
Cingulate gyrus	.04	.49	.50	.12	1.47	.25
Left prefrontal cortex						
Medial orbital	.14	1.80	.21	.09	1.13	.31
Lateral orbital	.11	1.42	.26	.14	1.75	.21
Medial middle	.01	.16	.70	.01	.07	.80
Lateral middle	.01	.12	.73	.08	.89	.37
Medial superior	.51	11.53	.006	.66	21.27	.0007
Lateral superior	.16	.27	.61	.07	.82	.39

CBV, cerebral brain volume; DESS, Discontinuation Emergent Symptom Scale; HDRS, Hamilton Depression Rating Scale; ROI, region of interest.

^aResults shown for Paroxetine subgroup only (*n* = 13).

known serotonergic innervation would show changes in regional CBV, the change in CBV in the left medial superior frontal region correlated significantly with changes in DESS and HDRS ($R^2 = 0.66$, $p = .0007$; $R^2 = 0.51$, $p = .006$, respectively) (Table 3, Figure 1). Similarly, the change in CBV in the left caudate nucleus correlated significantly with changes in DESS and HDRS ($R^2 = 0.43$, $p = .015$; $R^2 = 0.32$, $p = .043$, respectively; Table 3, Figure 1). Also, the change in CBV in the left caudate nucleus correlated with the change in the medial superior frontal region ($R^2 = 0.517$, $p = .0056$). There were no significant changes in CBV with placebo substitution for fluoxetine in any of the target brain regions.

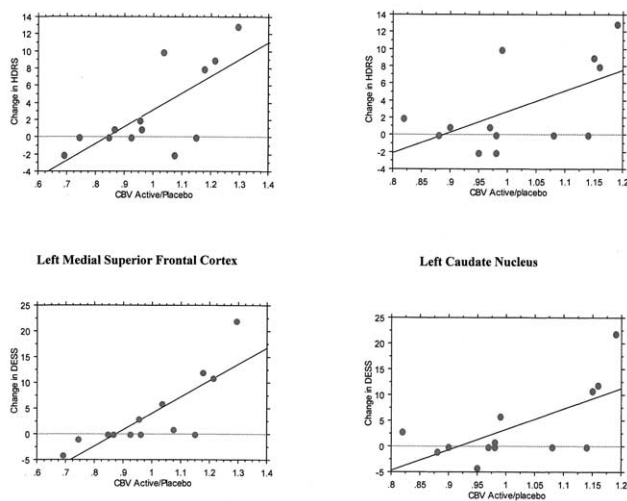


Figure 1. Regression analysis between Hamilton Depression Rating Scale (HDRS), Discontinuation Emergent Symptom Scale (DESS), and change in cerebral blood volume (CBV; regional CBV on active drug/regional CBV during placebo substitution).

Discussion

In 2 of 11 ROIs examined, DESS and HDRS change scores were strongly correlated with change in CBV in remitted paroxetine-treated depressed patients. In the other nine ROIs in the paroxetine patients, and in all 11 ROIs in the fluoxetine patients, these correlations did not reach statistical significance. These correlations of HDRS and DESS change scores with changes in CBV in the left medial superior frontal cortex and the left caudate nucleus, suggest alterations in the activity of brain circuits that have been implicated in the pathophysiology of depression.

These findings suggest that regardless of whether the symptoms are temporary perturbations or would herald a relapse if untreated, pathophysiologically they may be consistent with those associated with depression. The CBV and clinical findings in the paroxetine group are consistent with the brain imaging findings reported by Bremner et al (1997) who used fluorodeoxyglucose (FDG) positron emission tomography to study 21 SSRI responders undergoing tryptophan depletion. As described above, patients who experienced relapses in depressive symptoms exhibited decreased metabolism in the middle frontal cortex, orbitofrontal cortex, thalamus, and caudate nucleus. The changes in the middle frontal cortex, orbitofrontal cortex, and thalamus also showed a positive correlation with change in depressive symptoms. These findings are also consistent with the work of Kennedy and colleagues (Kennedy et al 2001), who, based on SSRI treatment effects, proposed a mood circuit consisting of the frontal lobe, the caudate nucleus, and other subcortical structures. Thus, despite significant differences in the resolution of the two imaging methodologies, it appears that SSRI treatment, tryptophan depletion, and abrupt interruption of treatment with paroxetine have

a great deal of overlap in the brain regions in which these factors affect metabolism.

Several factors limit the interpretation of these results. The number of patients studied was small, and therefore these results must be regarded as preliminary. In this regard, although the ROIs were defined a priori, this was an exploratory study, and we did not correct for multiple comparisons. Another potential confound of these data are that echo planar imaging techniques are vulnerable to susceptibility artifacts in brain regions that are close to sinuses, such as the frontal lobes; however, a spin–echo sequence such as that used in this study refocuses the dephasing of the signal caused by susceptibility gradients and significantly reduces the loss of signal from dephasing compared with gradient echo sequences. Although gradient echo Echo Planar Imaging (EPI) is often used for DSC studies because of the larger magnitude of the change in signal intensity caused by the contrast bolus, the spin–echo method also provides a desirable increase in sensitivity to the microvasculature (Boxerman et al 1995). In addition, although DSC CBV was chosen for its lack of ionizing radiation in this crossover design and because it has a greater signal-to-noise ratio than blood oxygen level–dependent functional MRI, it may be vulnerable to changes in vascular tone that do not directly reflect changes in metabolic activity (e.g., changes in serotonin activity; Scanley et al 2001).

A third potential limitation of these data are that the subjects were mostly premenopausal women, and we did not take into account phase in the menstrual cycle or use of oral contraceptives when planning scanning times (Lancaster 1994); however, the time between blood volume mapping for the placebo and active drug conditions was 28 days. In addition, the scans were scheduled at the same time of day to minimize differences due to circadian rhythms. The two groups of patients studied, although not intentionally matched to each other, were highly comparable on several key variables, including gender, age, and duration of therapy. In addition, their clinical state, as measured by the HDRS at study entry, demonstrates that both groups responded well to the medication (or placebo effect of medication) and were clinically stable at time of entry into the study. The randomization of the timing of the placebo substitution and crossover within the same individual allowed each person to be treated as his or her own control. In a pilot study with relatively small numbers of patients in each group, such as this study, this design significantly enhances statistical power. The changes in clinical rating scales observed are consistent with earlier reports of SSRI discontinuation (Coupland et al 1996; Ellenbogen et al 1996; Kennedy et al 2001), both in terms of the number of patients experiencing adverse effects and the number of events reported. The strong correlation

between the increase in depressive symptoms and discontinuation symptoms supports the hypothesis that the depressive symptoms observed represent a change in brain function related to treatment interruption. It is not possible, however, to determine whether these changes represent relapse or a temporary perturbation because all patients resumed treatment following drug interruption. To test this question, it would be necessary to follow the course of symptoms off medication for an extended period.

In conclusion, these data demonstrate that changes in the activity of the left prefrontal cortex and the left caudate nucleus correlate with the emergence of discontinuation symptoms and increased HDRS after interruption of paroxetine treatment. When viewed from the perspective of studying acute changes associated with depressive relapse, these findings indicate that depressionlike symptoms occurring after relatively rapid perturbations of serotonergic circuitry may be confounded by the equivalent of symptoms associated with abrupt paroxetine discontinuation. This, in turn, suggests that gradual tapering of longer acting agents may have significant advantages over paradigms that involve abrupt changes in serotonergic tone when studying depressive relapse.

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