A Magnetic Resonance Imaging Study of Regional Cortical Volumes Following Stereotactic Anterior Cingulotomy

By Scott L. Rauch, MD, Nikos Makris, MD, PhD, G. Rees Cosgrove, MD, Hackjin Kim, MA, Edwin H. Cassem, MD, Bruce H. Price, MD, Lee Baer, PhD, Cary R. Savage, PhD, Verne S. Caviness, Jr., MD, Dphil, Michael A. Jenike, MD, and David N. Kennedy, PhD

ABSTRACT

The purpose of this study was to test the hypothesis that orbitofrontal cortical volume would be reduced following anterior cingulotomy for obsessive-compulsive disorder (OCD). Whole brain cortical parcellation was performed on magnetic resonance imaging (MRI) data from nine patients, before and 9 (±6) months following anterior cingulotomy. No significant volumetric reductions were found in the orbitofrontal cortex. Exploratory findings of reduced volume in ventral temporo-fusiform and posterior cingulate regions were consistent with chance differences, in the face of multiple comparisons. Therefore, though the circumscribed lesions of anterior cingulotomy have recently been associated with corresponding volumetric reductions in the caudate nucleus, no comparable volumetric reductions are evident in cortical territories. Taken together, these results are most consistent with a model of cingulo-striatal perturbation as a putative mechanism for the efficacy of this procedure. While limitations in sensitivity may have also contributed to these negative findings, the methods employed have previously proven sufficient to detect cortical volumetric abnormalities in OCD. The current results may reflect a relatively diffuse pattern of cortico-cortical connections involving the neurons at the site of cingulotomy lesions. Future functional neuroimaging studies are warranted to assess possible cortical or subcortical metabolic changes associated with anterior cingulotomy, as well as predictors of treatment response.

CNS Spectrums *2001;6(3):214-222*

INTRODUCTION

Bilateral stereotactic anterior cingulotomy is a procedure that is currently performed in cases of severe and otherwise treatment-refractory obsessive-compulsive disorder (OCD) or major depressive disorder.[1] Though research in this area has suggested modest efficacy and relative safety,[2-6] little is known about the mechanism by which this or other neurosurgical procedures for psychiatric indications have their beneficial or adverse effects. In particular, there is a relative dearth of literature pertaining to the structural and functional neuroanatomical consequences of contemporary neurosurgical treatments for psychiatric diseases.

Recently, we assessed subcortical changes in brain volume associated with anterior cingulotomy, by conducting a morphometric magnetic resonance imaging (MRI) examination of pre-operative and post-operative data from nine patients who had undergone neurosurgical treatment for OCD at Massachusetts General Hospital (MGH).[7] Consistent with a prior hypotheses, we found bilateral reduction in caudate volume post-operatively, the magnitude of which was correlated with cingulotomy lesion volume. In the current study, we sought to extend those findings by performing an analogous assessment of change in regional cortical volumes using cortical parcellation methods[8,9] applied to the same MRI data sets.

We reasoned that regions that share dense connections with the site of the anterior cingulotomy would be most likely to exhibit reductions in volume post-operatively.[7,10] Among cortical regions, the orbitofrontal cortex is purported to share such dense connections with the anterior cingulate.[11-14] Moreover, the orbitofrontal cortex is principally implicated in the pathophysiology of OCD,[15,16] and successful treatment of OCD is associated with metabolic reductions within the orbitofrontal cortex.[17,18] Therefore, we predicted that, in comparison with pre-operative MRI, post-

Dr. Rauch is psychiatrist and radiologist; Drs. Kim, Cassem, Baer, Savage, and Jenike are psychiatrists; Dr. Kennedy is radiologist; Drs. Makris, Price, and Caviness are neurologists; and Dr. Cosgrove is neurosurgeon, all at the Massachusetts General Hospital and Harvard Medical School in Boston. Dr. Price is also a member of the Department of Neurology at McLean Hospital in Belmont, MA.

Acknowledgments: The authors acknowledge H.Thomas Ballantine, Jr., for his pioneering efforts regarding cingulotomy at Massachusetts General Hospital, as well as Andy Nierenberg, Darin Dougherty, Valerie Giorgione, and Ida Giriunas for their contributions to the Cingulotomy Assessment Committee. Further, the authors wish to thank David Shera for his statistical consultation and Peter Manzo and Linda Leahy for their technical assistance. This research was supported by the Massachusetts General Hospital Psychosurgery Research Fund and the David Judah Research Fund. Support was also received from National Institute of Mental Health grants RO1 MH 60219 (Dr. Rauch), NS 34189 (Dr. Kennedy) and DA 09467 (Drs. Kennedy and Makris); The Fairway Trust (Dr. Kennedy); and the Giovanni-Armenise-Harvard Foundation for Advancement of Scientific Research (Drs. Caviness and Kennedy).

Please direct correspondence to: Scott L. Rauch, MD, Department of Psychiatry, Massachusetts General Hospital–East, 9th Floor, Bldg. 149, 13th Street, Charlestown, MA 02129. Fax: 617 726 4078; Tel: 617 724 9553; e-mail: rauch@psych.mgh.harvard.edu

operative MRI would show significant volume reductions within the orbitofrontal cortex.

MATERIALS AND METHODS

Clinical Material

This study was conducted with the approval of the Subcommittee on Human Studies of MGH. Clinical data including demographics, diagnostic information, and brain MRI were obtained retrospectively from the hospital records of nine patients (five male, four female) who received bilateral stereotactic anterior cingulotomies at MGH between 1990 and 1997 for the indication of severe, treatment-refractory OCD. Of note, approximately 40% of patients who receive anterior cingulotomy at MGH return for a second surgical procedure[2,3]; consequently, a series of patients has accrued for which initial pre-operative and ~9-month post-operative data (ie, obtained immediately prior to the second operation) are available. For this cohort, mean (±SD) age at first cingulotomy was 35 (±16) years, and time between pre-operative and post-operative MRI was 9 (±6; range 4–23) months. All patients had comorbid major depression, were on a variety of psychotropic medications, and were otherwise without major neurological disorders. In particular, all of these patients were free of histories of significant head trauma, stroke, or other known organic brain lesions. It is critical to appreciate that this select cohort, who returned for a second operation, is skewed with respect to outcome after first cingulotomy. Specifically, whereas ~30% of patients who undergo cingulotomy for OCD ultimately meet clinical criteria as "responders" (eg, a 35% reduction in Yale-Brown Obsessive-Compulsive Scale scores[2,19]), none of the patients in this cohort met such criteria at the time of their return for a second operation.

Neurosurgical Lesions

The procedure for bilateral stereotactic anterior cingulotomy has been described in detail previously.[1,20] Briefly, a pair of burr holes (1.2 cm in diameter) are made bilaterally 9.5 cm posterior to the nasion and 1.5 cm lateral to the midline. Electrically insulated thermistor electrodes are positioned stereotactically with MRI guidance. The initial targets are located 0.7 cm lateral to the midline, 2 cm posterior to the most anterior aspect of each frontal horn, and 1 mm above the roof of the ventricles. Lesions are created by heating the uninsulated tip (1 cm in length) to 80–85°C for 100 seconds by radiofrequency current. The electrode is then withdrawn 1 cm and another lesion is made immediately dorsal to the first. The procedure is then repeated on the contralateral side. Thus, this operation is intended to produce lesions of approximately 1x1x2 cm within the anterior cingulate cortex of each hemisphere (ie, total lesion volume=~4 cc).[7]

MRI Acquisition and Morphometry

The clinical MRI data that were subjected to morphometric analysis had been obtained between 1990 and 1997 with a 1.5 Tesla MR scanner (General Electric, Milwaukee, Wisconsin). The acquisition protocol entailed routine sagittal scout scans, followed by a three-dimensional T1-weighted spoiled gradient echo sequence (TR=50 msec, TE=9 msec, flip angle=50°, field of view=24 cm, matrix=256x256, averages=1) to obtain contiguous coronal slices (3 mm thick) covering the entire brain.

MRI data were harvested retrospectively and assigned random identification numbers so that the investigators performing the segmentations and parcellations could remain blind to any correspondence between images and subjects. The investigators performing the segmentations and parcellations were also blind to our *a priori* hypotheses.

Following image acquisition, the images underwent positional normalization, general anatomic segmentation, cortical parcellation, and subcortical gray matter parcellation. These procedures are summarized briefly here. Positional normalization entails the reformatting of the original coronal volumetric image dataset so that the interhemispheric fissure is within the sagittal plane and the anterior commissure-posterior commissure (AC-PC) line is perpendicular to the coronal plane.[21] General anatomic segmentation involves identifying the boundaries of the principal gray and white matter structures of the cerebrum based upon the natural gray or white matter boundaries as distinguished by differential signal intensities in the T1-weighted images.[21] These demarcations are made in a semi-automated fashion guided by landmark conventions and signal intensity histograms.

Subdivision of the cortical ribbon into gyral-based subdivisions (cortical parcellation) follows the scheme originally developed

"All patients had comorbid major depression, were on a variety of psychotropic medications, and were otherwise without major neurological disorders. In particular, all of these patients were free of histories of significant head trauma, stroke, or other known organic brain lesions."

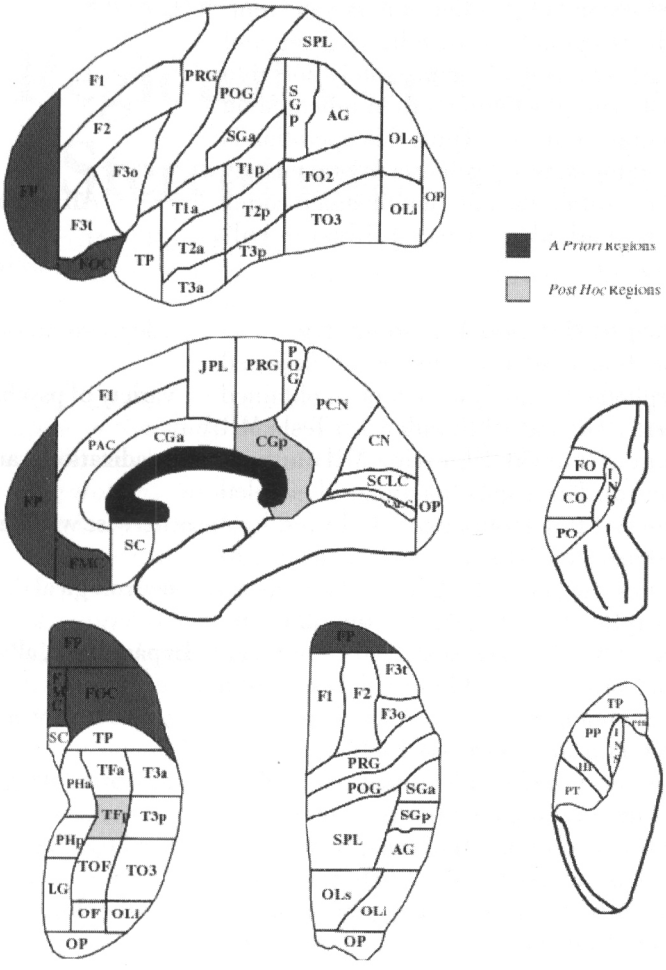


FIGURE.
Parcellation units (PU) are shown, shaded to highlight territories corresponding to our *a priori* hypothesis pertaining to the orbitofrontal cortex (dark gray) as well as regions where *post hoc* findings were noted (light gray). Abbreviations for the various parcellation units are as follows:
Frontal Lobe: FP, frontal pole; F1, superior frontal gyrus; F2, middle frontal gyrus; F3t, inferior frontal gyrus; F3o, inferior frontal gyrus; PRG, precentral gyrus; SMC, supplementary motor cortex; FMC, frontomedial cortex; FOC, frontoorbital cortex; FO, frontal operculum; CO, central operculum.
Temporal lobe: TP, temporal pole; T1a, superior temporal gyrus (anterior); T1p, superior temporal gyrus (posterior); T2a, middle temporal gyrus (anterior); T2p, middle temporal gyrus (posterior); TO2, middle temporal gyrus; T3a, inferior temporal gyrus (anterior); T3p, inferior temporal gyrus (posterior); TO3, inferior temporal gyrus; TFa, temporal fusiform gyrus (anterior); TFp, temporal fusiform gyrus (posterior); TOF, temporooccipital fusiform gyrus; PP, planum polare; INS, insula; H1, Heschl's gyrus; PT, planum temporale.
Parietal lobe: POG, postcentral gyrus; SPL, superior parietal lobule; SGa, supramarginal gyrus (anterior); SGp, supramarginal gyrus (posterior); AG, angular gyrus; PCN, precuneus; PO, parietal operculum.
Occipital lobe: OLs, occipital lateral gyri (superior); OLi, occipital lateral gyri (inferior); OP, occipital pole; CN, cuneus; LG, lingual gyrus; OF, occipital fusiform gyrus.
Medial paralimbic cortices: SC, subcallosal cortex; PAC, paracingulate cortex; CGa, anterior cingulate gyrus; CGp, posterior cingulate gyrus (includes retrosplenial cortex); PHa, parahippocampal gyrus (anterior); PHp, parahippocampal gyrus (posterior).

Rauch SL, Makris N, Cosgrove GR, et al. *CNS Spectrums.* Vol 6, No 3. 2001.

by Rademacher and colleagues[8] and subsequently refined by Caviness and colleagues[9] (see Figure). This procedure results in the identification of 48 parcellation units (PUs) per hemisphere and involves: (1) identification of a set of 42 anatomic landmarks that delimits the anterior and posterior boundaries, and (2) identification of the idealized courses of 31 prominent fissures that provide the medial-lateral boundaries of the cortical regions.

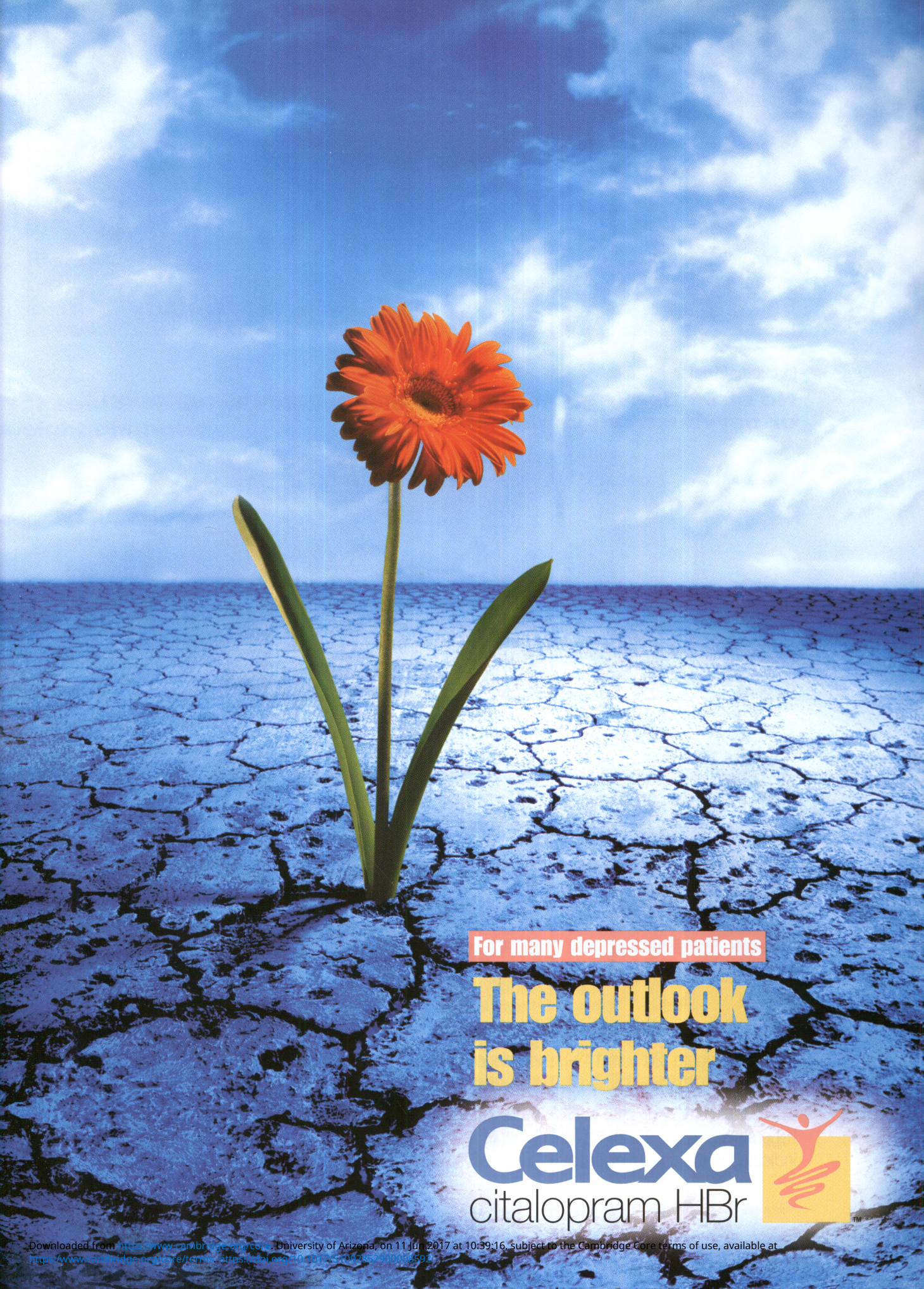
Hypotheses and Statistical Analyses

We hypothesized that comparisons between the pre-operative and post-operative MRI data would show volumetric reductions in specific frontal cortical regions that are believed to communicate with the territory of the anterior cingulate that is lesioned during cingulotomy; specifically, the PUs corresponding with the orbitofrontal cortex (frontoorbital cortex [FOC], frontomedial cortex [FMC], and frontal pole [FP]) were principally assessed. Paired *t*-tests were performed using a significance threshold of 0.05 (uncorrected for multiple comparisons). Following assessment of the three predicted PUs, pre-operative and post-operative volumes for the remaining 45 PUs were also compared, in an exploratory fashion.

For the purposes of this initial study, total (ie, right+left) volumes were used. Given that cingulotomy lesions are made bilaterally (and approximately symmetrically), bilateral cortical volume changes were predicted. This approach conferred several benefits: by using total volumes (rather than separately comparing each side), the number of multiple comparisons and the variance for each PU were minimized, while power was presumably optimized. Finally, *a priori*, we planned to follow up any significant differences in regional total volumes with separate comparisons of right and left components of the corresponding PU; thus, positive findings would be most compelling in cases where differences in total regional volume could be attributed to bilateral changes.

RESULTS

The comparison of post-operative with pre-operative volumes yielded no significant difference in orbitofrontal cortex (all $P>0.3$). Our statistical power to detect a "large" effect size (Cohen's [22] convention of 0.8 SD) between pre-operative and post-operative volumes by paired *t*-test was 0.77 for $P<0.05$ and 0.88 for

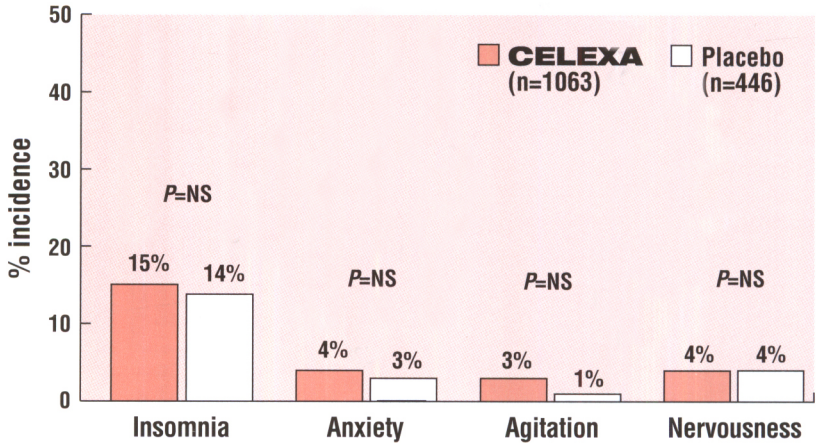


Celexa™
for depression

Effective first-line SSRI therapy with a favorable side-effect profile

In clinical trials*

No statistically significant insomnia, anxiety, agitation, or nervousness vs placebo[1]



No statistically significant fatigue vs placebo

■ CELEXA 5% vs 3% placebo

Significantly reduces anxiety symptoms in depressed patients vs placebo[2]

Weak inhibition of P450 isozymes†

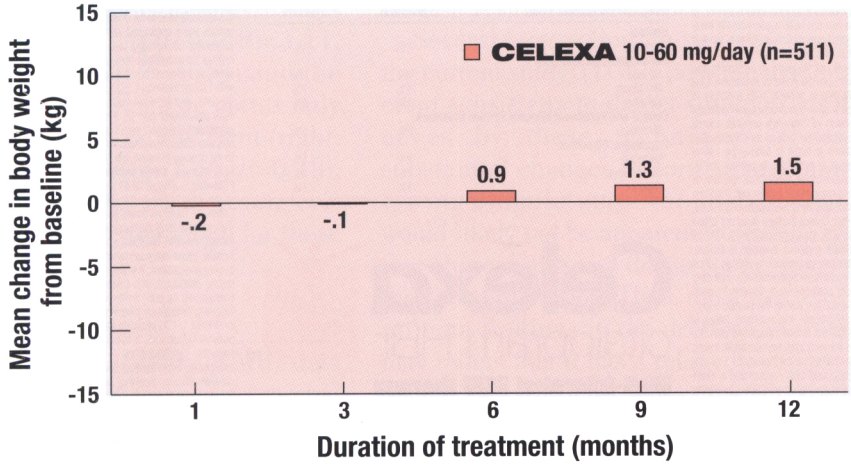
† The clinical significance of *in vitro* data is unknown.

The most frequent adverse events reported with CELEXA vs placebo in clinical trials were nausea (21% vs 14%), dry mouth (20% vs 14%), somnolence (18% vs 10%), insomnia (15% vs 14%), increased sweating (11% vs 9%), tremor (8% vs 6%), diarrhea (8% vs 5%), and ejaculation disorder (6% vs 1%).

CELEXA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients with a hypersensitivity to citalopram HBr or any of the ingredients in CELEXA. As with other SSRIs, caution is indicated in the coadministration of TCAs with CELEXA.

*Pooled data from placebo-controlled depression trials.

Not associated with clinically significant long-term weight changes[1]



Study design: 1-year, open-label, CELEXA treatment trial. Depressed patients were given CELEXA in a dose range of 10 to 60 mg/day.[1]

- CELEXA therapy was associated with a mean weight increase of only 1.5 kg after 12 months[1]

Once-daily 20 mg starting dose for all patients

- 20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients
- Now available in a sugar-free, alcohol-free oral solution — 1 tsp contains 10mg

Celexa™
citalopram HBr

Well-tolerated SSRI therapy

Visit the CELEXA Web site at http://www.celexa.com

Please see brief summary of prescribing information on last page of this advertisement.

References: 1. Data on file, Forest Laboratories, Inc. **2.** Flicker C, Tsay J-Y. Citalopram treatment of depression with anxiety. Poster presented at the 38th Annual Meeting, New Clinical Drug Evaluation Unit, 1998; Boca Raton, Florida.

FOREST PHARMACEUTICALS, INC.
Pharmaceuticals · Therapeutics · Managed Care · Specialty Sales

10/00

Brief Summary: For complete details, please see full prescribing information for Celexa.
INDICATIONS AND USAGE Celexa (citalopram HBr) is indicated for the treatment of depression. The efficacy of Celexa in the treatment of depression was established in 4- to 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation. The antidepressant action of Celexa in hospitalized depressed patients has not been adequately studied. The efficacy of Celexa in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials. Nevertheless, the physician who elects to use Celexa for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. **CONTRAINDICATIONS** Concomitant use in patients taking monoamine oxidase inhibitors (MAOI's) is contraindicated (see WARNINGS). Celexa is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in Celexa. **WARNINGS Potential for Interaction with Monoamine Oxidase Inhibitors In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRI's and MAOI's suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Celexa should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Celexa before starting an MAOI. PRECAUTIONS General** Hyponatremia Several cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Celexa treatment. All patients with these events have recovered with discontinuation of Celexa and/or medical intervention. Activation of Mania/Hypomania In placebo-controlled trials of Celexa, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with Celexa and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants. As with all antidepressants, Celexa should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of citalopram have been observed in animal studies, Celexa has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Celexa, seizures occurred in 0.3% of patients treated with Celexa (a rate of one patient per 98 years of exposure) and 0.5% of patients treated with placebo (a rate of one patient per 50 years of exposure). Like other antidepressants, Celexa should be introduced with care in patients with a history of seizure disorder. Suicide The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Celexa should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Interference With Cognitive and Motor Performance In studies in normal volunteers, Celexa in doses of 40 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgement, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities. Use in Patients With Concomitant Illness Clinical experience with Celexa in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Celexa in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Celexa has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 1116 patients who received Celexa in clinical trials were evaluated, and the data indicate that Celexa is not associated with the development of clinically significant ECG abnormalities. In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Celexa in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended. Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Celexa, however, it should be used with caution in such patients. **Drug Interactions** CNS Drugs – Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol – Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking Celexa is not recommended. Monoamine Oxidase Inhibitors (MAOI's) – See CONTRAINDICATIONS and WARNINGS. Cimetidine – In subjects who had received 21 days of 40 mg/day Celexa, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin – In subjects who had received 21 days of 40 mg/day Celexa, combined administration of Celexa and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium – Coadministration of Celexa (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalopram, caution should be exercised when Celexa and lithium are coadministered. Sumatriptan – There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (eg, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised. Warfarin – Administration of 40 mg/day Celexa for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine – Combined administration of Celexa (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered. CYP3A4 and CYP2C19 Inhibitors – *In vitro* studies indicated that CYP3A4 and CYP2C19 are the primary enzymes involved in the metabolism of citalopram. As data are not available from clinical pharmacokinetic studies, the possibility that the clearance of citalopram will be decreased when citalopram is administered with a potent inhibitor of CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, or erythromycin) or a potent inhibitor of CYP2C19 (eg, omeprazole) should be considered. Metoprolol – Administration of 40 mg/day Celexa for 22 days resulted in a two-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Celexa and metoprolol had no clinically significant effects on blood pressure or heart rate. Imipramine and Other Tricyclic Antidepressants (TCA's) - *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of Celexa (40 mg/day for 10 days) with the tricyclic antidepressant imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCA's with Celexa. Electroconvulsive Therapy (ECT) – There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and Celexa. **Pregnancy** Pregnancy Category C - There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of Celexa on labor and delivery in humans is unknown. **Nursing Mothers** As has been found to occur with many other drugs, citalopram is excreted in human breast milk. The decision whether to continue or discontinue either nursing or Celexa therapy should take into account the risks of citalopram exposure for the infant and the benefits of Celexa treatment for the mother. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** Of 4422 patients in clinical studies of Celexa, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with Celexa in clinical trials received daily doses between 20 and 40 mg. In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively. 20 mg/day is the recommended dose for most elderly patients. **ADVERSE REACTIONS** The premarketing development program for Celexa included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Celexa varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Findings Observed in Short-term, Placebo-Controlled Trials** Adverse Events Associated With Discontinuation of Treatment Among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (ie, associated with discontinuation in at least 1% of Celexa-treated patients and at a rate at least twice that of placebo) are shown in **TABLE 1**. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in this table.

TABLE 1.
Adverse Events Associated With Discontinuation of Treatment in Short-term, Placebo-Controlled Depression Trials

	Percentage of Patients Discontinuing Due to Adverse Event	
Body System/Adverse Event	**Celexa (N=1063)**	**Placebo (N=446)**
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomiting	1%	0%
Central and Peripheral Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Adverse Events Occurring at an Incidence of 2% or More Among Celexa-Treated Patients **TABLE 2** enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with Celexa and for which the incidence in patients treated with Celexa was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence rate in the population studied. The only commonly observed adverse event that occurred in Celexa patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see **TABLE 2**).

TABLE 2.
Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Celexa (N=1063)**	**Placebo (N=446)**
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central & Peripheral Nervous System Disorders		
Tremor	8%	6%
Gastrointestinal Disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%
Vomiting	4%	3%
Abdominal Pain	3%	2%
General		
Fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea[†]	3%	2%
Libido Decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation Disorder[†,‡]	6%	1%
Impotence[‡]	3%	<1%

*Events reported by at least 2% of patients treated with Celexa are reported, except for the following events which had an incidence in placebo ≥ Celexa: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain. †Denominator used was for females only (N=638 Celexa; N=252 placebo). ‡Primarily ejaculatory delay. §Denominator used was for males only (N=425 Celexa; N=194 placebo). Dose Dependency of Adverse Events The potential relationship between the dose of Celexa administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or Celexa 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response ($p<.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning. Male and Female Sexual Dysfunction With SSRI's Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence. The table below displays the incidence of sexual side effects reported by at least 2% of patients taking Celexa in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	Celexa (425 males)	Placebo (194 males)
Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
Decreased Libido	3.8% (males only)	<1% (males only)
Impotence	2.8% (males only)	<1% (males only)

In female depressed patients receiving Celexa, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively. There are no adequately designed studies examining sexual dysfunction with citalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRI's, physicians should routinely inquire about such possible side effects. Vital Sign Changes Celexa and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Celexa treatment. In addition, a comparison of supine and standing vital sign measures for Celexa and placebo treatments indicated that Celexa treatment is not associated with orthostatic changes. Weight Changes Patients treated with Celexa in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients. Laboratory Changes Celexa and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Celexa treatment. ECG Changes Electrocardiograms from Celexa (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals. **Other Events Observed During the Premarketing Evaluation of Celexa** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by patients treated with Celexa at multiple doses in a range of 10 to 80 mg/day during any phase of a trial within the premarketing database of 4422 patients. All reported events are included except those already listed in **TABLE 2** or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasize that although the events reported occurred during treatment with Celexa, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Cardiovascular – *Frequent:* tachycardia, postural hypotension, hypotension. *Infrequent:* hypertension, bradycardia, edema (extremities), angina pectoris, extrasystoles, cardiac failure, flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. *Rare:* transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block. Central and Peripheral Nervous System Disorders – *Frequent:* paresthesia, migraine. *Infrequent:* hyperkinesia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. *Rare:* abnormal coordination, hyperesthesia, ptosis, stupor. Endocrine Disorders – *Rare:* hypothyroidism, goiter, gynecomastia. Gastrointestinal Disorders – *Frequent:* saliva increased, flatulence. *Infrequent:* gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. *Rare:* colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups. General – *Infrequent:* hot flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms. *Rare:* hayfever, Hernic and Lymphatic Disorders – *Infrequent:* purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. *Rare:* pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding. Metabolic and Nutritional Disorders – *Frequent:* decreased weight, increased weight. *Infrequent:* increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. *Rare:* bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration. Musculoskeletal System Disorders – *Infrequent:* arthritis, muscle weakness, skeletal pain. *Rare:* bursitis, osteoporosis. Psychiatric Disorders – *Frequent:* impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. *Infrequent:* increased libido, aggressive reaction, paroniria, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. *Rare:* catatonic reaction, melancholia. Reproductive Disorders/Female* – *Frequent:* amenorrhea. *Infrequent:* galactorrhea, breast pain, breast enlargement, vaginal hemorrhage. *% based on female subjects only: 2955 Respiratory System Disorders – *Frequent:* coughing. *Infrequent:* bronchitis, dyspnea, pneumonia. *Rare:* asthma, laryngitis, bronchospasm, pneumonitis, sputum increased. Skin and Appendages Disorders – *Frequent:* rash, pruritus. *Infrequent:* photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. *Rare:* hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani. Special Senses – *Frequent:* accommodation abnormal, taste perversion. *Infrequent:* tinnitus, conjunctivitis, eye pain. *Rare:* mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss. Urinary System Disorders – *Frequent:* polyuria. *Infrequent:* micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare:* facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain. **OVERDOSAGE Human Experience** Although there were no reports of fatal citalopram overdose in clinical trials involving overdoses of up to 2000 mg, postmarketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920 mg and 2800 mg), as well as nonfatal overdoses of up to 6000 mg. Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, and sinus tachycardia. In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of Torsades de pointes).

Rx only

Mfg. by:
Forest Laboratories Ireland Ltd.
Clonshaugh Industrial Estate
Dublin 17 Ireland
Made in Ireland

Distributed by:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045 USA

Marketed by:

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

Licensed from H. Lundbeck A/S Rev. 5/00

40-310072(4AFB) 12/00

$P<0.10$; N=9 and assuming $r=0.70$ between pre-operative and post-operative measures.

Next, an exploratory analysis of all other PUs found only two (of 45) comparisons that achieved the statistical threshold of $P<0.05$, uncorrected for multiple comparisons. Specifically, statistical evidence of volume reductions were found within the posterior temporal fusiform gyrus (PU=TFp; $t(8)=3.57$, $P=0.007$) and the posterior cingulate cortex (PU=CGp; $t(8)=2.50$, $P=0.04$). As noted, this number of comparisons would be expected to yield ~2–3 findings of $P<0.05$ by chance alone. However, for bona-fide lesion-related volume reductions, we should expect bilateral findings in corresponding PUs. Here, when each side was assessed separately, the finding in the posterior temporal fusiform gyrus was significant only on the left (left: $t(8)=3.11$, $P=0.01$; right: $t(8)=1.67$, $P=0.13$) and the finding in the posterior cingulate cortex only approached significance on the right (right: $t(8)=2.03$, $P=0.08$; left: $t(8)=1.46$, $P=0.18$). Thus, in neither case was there strong evidence of bilateral volume reduction for these cortical regions.

DISCUSSION

Previously, in an initial study of MRI data from this same cohort of patients, we reported the results of subcortical segmentation and parcellation.[7] The results of that analysis revealed significant bilateral volumetric reduction of the caudate nucleus that was significantly correlated with total cingulotomy lesion volume. In the current study, we performed a complementary assessment of volumetric changes within cortical regions. Here we report that, in contrast to the subcortical findings, no significant volumetric changes were found by parcellation in the orbitofrontal cortex following cingulotomy. Exploratory findings of mean volume reduction in the posterior temporal fusiform gyrus and the posterior cingulate cortex may well be due to chance, in the face of multiple comparisons. Taken together, morphometric MRI studies of cingulotomy demonstrate gross structural modification of cingulo-striatal circuitry, in the absence of detectable changes in the orbitofrontal cortex.

Post hoc findings of volume changes in other cortical regions should not be taken as compelling, pending replication. However, the observation of volume reduction in the posterior cingulate cortex is most intriguing given the recent preliminary finding that pre-operative metabolic rates within the posterior cingulate cortex correlate with subsequent treatment response in patients undergoing cingulotomy for OCD.[23] Volumetric reductions in the posterior cingulate cortex following cingulotomy are consistent with the fact that these regions are purported to share dense connections with one another.[24] Moreover, although contemporary neurocircuitry models of OCD have emphasized the role of the orbitofrontal cortex, the anterior cingulate cortex, and the caudate nucleus,[15,16] several functional imaging studies have also pointed to a role for the posterior cingulate cortex in OCD.[25,26] Consequently, these unanticipated yet convergent results merit further investigation.

"Here we report that, in contrast to the subcortical findings, no significant volumetric changes were found by parcellation in the orbitofrontal cortex following cingulotomy."

Several factors limit the interpretations of the current study: (1) it is possible that insufficient sensitivity to detect volumetric differences by these techniques obscured substantial changes in cortical anatomy following cingulotomy. Volumetric changes would likely not be apparent except in regions that share direct and dense connections with the site of the lesion. Thus, the absence of significant findings in the orbitofrontal cortex may reflect that it has a relatively diffuse pattern of connections, as is characteristic of higher-order associative regions. In addition, it is possible that regional effects were more circumscribed than those encompassed by a single parcellation unit. In this regard, however, it is important to note that similar methods were of sufficient sensitivity to detect cortical volumetric abnormalities in OCD,[27] even in the context of between-group comparisons that necessarily confer lesser statistical power. Furthermore, in the current data set, none of the orbitofrontal PUs exhibited changes that even approached statistical significance (all $P>0.3$), indicating exceedingly small effect sizes. (2) Nonetheless, it is possible that the neuroanatomical effects observed in this cohort, who all returned for a second operation following insufficient response to an initial cingulotomy, are not generalized to patients who derived benefit from the operation. For instance, it is conceivable that a cohort of patients whose OCD improved following cingulotomy would exhibit reduced orbitofrontal cortical volumes. (3) Finally, it is likely that significant changes in brain function may have occurred following cingulotomy in regions where gross changes in brain vol-

ume are not evident by morphometric MRI techniques. For these reasons, it will be important to extend these initial findings with further studies of consecutive cases and analysis of functional as well as structural neuroimaging data.

In conclusion, the current study found no significant frontal cortical volumetric reductions following cingulotomy, beyond the site of the lesions. In contrast, our prior study of subcortical structures showed bilateral and specific volumetric reductions of the caudate nucleus following cingulotomy. Taken together, these findings are consistent with disruption of cingulo-striatal circuitry as one possible mechanism for the purported efficacy of anterior cingulotomy. Technical limitations of the current study prevent a high degree of confidence that cortico-cortical perturbations are not also a major consequence of this procedure. Future studies using functional imaging methods will be crucial for definitively delineating the functional consequences of anterior cingulotomy. In addition, we propose that the analysis of pre-operative functional imaging data together with clinical outcome measures may provide neuroimaging predictors of treatment response to guide future patient selection for this extraordinary clinical intervention.[23] Likewise, analogous studies of other neurosurgical procedures for psychiatric illness are also warranted.[28] Finally, the development of alternative, non-ablative somatic treatments, such as deep brain stimulation[29,30] or transcranial magnetic stimulation,[31] for refractory psychiatric diseases may be facilitated by improved understanding of contemporary neurosurgical interventions and their consequences. CNS

REFERENCES

1. Cosgrove GR, Rauch SL. Psychosurgery. *Neurosurg Clin N Am.* 1995;6:167-176.
2. Baer L, Rauch SL, Ballantine HT, et al. Cingulotomy for intractable obsessive-compulsive disorder: prospective long-term follow-up of 18 patients. *Arch Gen Psychiatry.* 1995;52:384-392.
3. Spangler WJ, Cosgrove GR, Ballantine HT, et al. Magnetic resonance image-guided stereotactic cingulotomy for intractable psychiatric disease. *Neurosurgery.* 1996;38:1071-1076.
4. Cohen RA, Kaplan RF, Moser DJ, Jenkins MA, Wilkinson H. Impairments of attention after cingulotomy. *Neurology.* 1999;53:819-824.
5. Corkin S, Twitchell TE, Sullivan EV. Safety and efficacy of cingulotomy for pain and psychiatric disorder. In: ER Hitchcock, HT Ballantine, BA Meyerson, eds. *Modern Concepts in Psychiatric Surgery.* New York, NY: Elsevier/North-Holland; 1979:253-272.
6. Ochsner KN, Kosslyn SM, Cosgrove GR, et al. Deficits in visual cognition and attention following bilateral anterior cingulotomy. *Neuropsychologia.* In press.
7. Rauch SL, Kim H, Makris N, et al. Volume reduction in caudate nucleus following stereotactic lesions of anterior cingulate cortex in humans: a morphometric magnetic resonance imaging study. *J Neurosurg.* 2000;93:1019-1025.
8. Rademacher J, Galaburda AM, Kennedy DN, et al. Human cerebral cortex: localization, parcellation, and morphometry with magnetic resonance imaging. *J Cog Neurosci.* 1992;4:352-374.
9. Caviness VS, Kennedy DN, Richelme C, Rademacher J, Filipek PA. The human brain age 7-11 years: a volumetric analysis based upon magnetic resonance images. *Cereb Cortex.* 1996;6:726-736.
10. Dejerine J. *Anatomie Des Centres Nerveux.* Vol 2. Paris, France: Rueff et Cie; 1895.
11. Kaada BR. Cingulate, posterior orbital, anterior insular and temporal pole cortex. In: Magoun HW, ed. *Neurophysiology.* Baltimore, Md: Waverly Press; 1960:1345-1372.
12. Kaada BR, Pribram KH, Epstein JA. Respiratory and vascular response in monkeys from temporal pole, insular, orbital surface and cingulate gyrus. *J Neurophysiol.* 1949;12:348-356.
13. Pandya DN, Van Hoesen GW, Mesulam MM. Efferent connections of the cingulate gyrus in the rhesus monkey. *Exp Brain Res.* 1981;42:319-330.
14. Yakovlev PI, Locke S. Limbic nuclei of thalamus and connections of limbic cortex: Corticocortical connections of the anterior cingulate gyrus, the cingulum, and the subcallosal bundle in monkey. *Arch Neurol.* 1961;5:34-70.
15. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *Br J Psychiatry Suppl.* 1998;35:26-37.
16. Rauch SL, Whalen PJ, Dougherty DD, Jenike MA. Neurobiological models of obsessive compulsive disorders. In: Jenike MA, Baer L, Minichiello WE, eds. *Obsessive-Compulsive Disorders: Practical Management.* Boston, Ma: Mosby; 1998:222-253.
17. Baxter LR, Schwartz JM, Bergman KS, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Schizophr Bull. Arch Gen Psychiatry.* 1992;49:681-689.
18. Schwartz JM, Stoessel PW, Baxter LR, Martin KM, Phelps ME. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1996;53:109-113.
19. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale: Part I. Development, use, and reliability. *Arch Gen Psychiatry.* 1989;46:1006-1011.
20. Ballantine HT, Giriunas IE. Treatment of intractable psychiatric illness and chronic pain by stereotactic cingulotomy. In: Schmidek HH, Sweet WH, eds. *Operative Neurosurgical Techniques.* New York, NY: Grune & Stratton; 1982:1069-1075.
21. Filipek PA, Richelme C, Kennedy DN, Caviness VS. The young adult human brain: an MRI-based morphometric analysis. *Cereb Cortex.* 1994;4:344-360.
22. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* New York, NY: Lawrence Ehrlbaum; 1988.
23. Rauch SL, Dougherty DD, Cosgrove GR, et al. Cerebral metabolic predictors of response to anterior cingulotomy for obsessive-compulsive disorder [abstract]. *Biol Psychiatry.* In press.
24. Vogt BA, Pandya DN. Cingulate cortex of the rhesus monkey: II. Cortical afferents. *J Comp Neurol.* 1987;262:271-289.
25. Busatto GF, Zamignani DR, Buchpiguel CA, et al. A voxel-based investigation of regional cerebral blood flow abnormalities in obsessive-compulsive disorder using single photon emission computed tomography (SPECT). *Psychiatry Res.* 2000;99:15-27.
26. McGuire PK, Bench CJ, Frith CD, Marks IM, Frackowiak RS, Dolan RJ. Functional anatomy of obsessive-compulsive phenomena. *Br J Psychiatry.* 1994;164:459-468.
27. Grachev ID, Breiter HC, Rauch SL, et al. Structural abnormalities of frontal neocortex in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1998;55:181-182.
28. Lippitz BE, Mindus P, Meyerson BA, Kihlstrom L, Lindquist C. Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: relevance of the right hemisphere. *Neurosurgery.* 1999;44:452-460.
29. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet.* 1999;354:1526.
30. Nuttin B, Gabriels L, Cosyns P, Gybels J. Electrical stimulation of the brain for psychiatric disorders. *CNS Spectrums.* 2000;5:35-39.
31. Greenberg BD, George MS, Martin JD, et al. Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. *Am J Psychiatry.* 1997;154:867-869.