Bipolar Brains Exhibit Structural Abnormalities

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

STOCKHOLM — The brains of bipolar patients show specific regional abnormalities that may be associated with the neurocognitive deficits that bipolar patients exhibit, Jair Soares, M.D., said at the annual meeting of the European College of Neuropsychopharmacology.

It is worth noting, however, that some of these anatomic abnormalities are seen even in the brains of pediatric bipolar patients, so it's unclear whether the changes are neurodevelopmental or neurodegenerative, said Dr. Soares of the University of Texas, San Antonio.

He has collaborated on several brain imaging studies that have consistently identified structural changes in the bipolar brain. Although these studies are small and must be interpreted cautiously, he said, taken together, they paint a picture of a brain that may be fundamentally different from childhood on.

His recently published study of 27 adult bipolar patients (11 untreated and 16 on lithium monotherapy) and 39 healthy controls showed the relationship between the illness, lithium treatment, and cingulate volume. The 11 untreated patients had significantly decreased left anterior cingulate volumes, compared with both the healthy controls and the treated bipolar patients. The cingulate volumes of the treated patients were not different from those of controls (Biol. Psych. 2004;56:467-75).

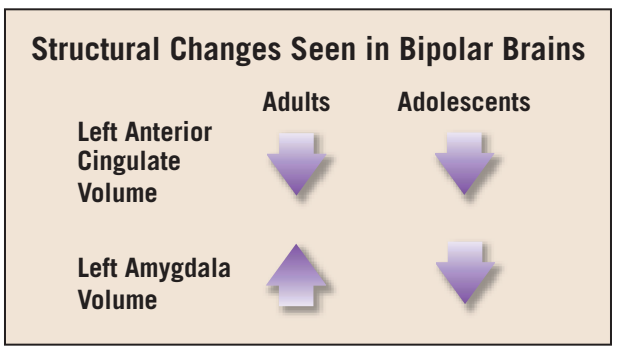
The cingulate is not the only abnormal area that has been documented in the brains of bipolar patients, Dr. Soares said. The volume of the amygdala and conductivity of the corpus callosum are also abnormal.

In another study of brain anatomy in bipolar subjects, he and his associates examined 24 bipolar patients and 36 healthy controls. Bipolar patients had significantly larger left amygdala volumes compared with controls (J. Psychiatr. Res. 2003;37:287-95).

A 2004 study in which Dr. Soares was involved found lower MRI signal intensity in the corpus callosa of 29 bipolar patients, compared with those of 23 unipolar patients and 36 healthy controls (J. Neurol. Neurosurg. Psych. 2004;75:221-5). "This suggests that there are abnormalities that might reflect abnormal myelination," he said.

"And this could be responsible for some of the neurocognitive abnormalities that bipolar patients display."

Bipolar patients also show increased areas of hyperintense abnormalities on MRI scans. "These are very nonspecific abnormalities that are often related to vascular changes. They are very prevalent in late-life depression and in patients with bipolar disorder. These might represent disruptions of specific brain pathways that interconnect areas involved in mood regulation," he suggested.



Bipolar brains seem to lose gray matter at an accelerated rate.

"We all lose gray matter as we age, but bipolar patients seem to start losing this much earlier," Dr. Soares said. A 2004 study of 22 bipolar patients and 22 healthy controls, all of middle age, found that age was not associated with gray matter volume in the controls.

In the bipolar patients, however, gray matter volume was inversely related to age (Neuropsychobiology 2001;43:242-7).

"They were losing it at a faster rate as they got older. Because the groups were similar in age this suggests there is a neurodegenerative mechanism in bipolar patients," he said.

Bipolar brains seem to lose gray matter at an accelerated pace. 'We all lose gray matter as we age, but bipolar patients seem to start losing this much earlier.'

Changes are evident even in the brains of adolescents with bipolar disorder. In a recent study on which he collaborated, investigators measured temporal lobe structures in 16 adolescents with bipolar disorder and 21 healthy controls and found decreased cingulate volumes in the left anterior, left posterior, and right posterior quadrants.

"This is interesting because in the adult study, we only found a change in the left anterior," Dr. Soares said. "The pediatric study found more extensive cingulate changes." These results might have been confounded by selection bias, he noted. The bipolar patients in the pediatric study represented early-onset disease, and so might have had a more severe form of the disorder.

Although the brains of adult bipolar patients display an increased amygdala volume, adolescent bipolar brains display a smaller volume, according to a study of both bipolar adolescents and healthy controls (Biol. Psychiatry 2004;56:399-405).

In this study, the left amygdalas of the subjects with bipolar disorder were smaller than those of the controls, a finding that has been replicated in two additional recent studies.

"Why is the amygdala smaller in bipolar children and larger in bipolar adults?" Dr. Soares asked. "What is it in the developmental years that causes this to happen?"

One explanation is that the bipolar brain may fail to control amygdala growth. "In controls, there is an inverse relation in size as the child increases in age.

This might reflect some kind of pruning mechanism in those years" that does not occur in people with bipolar disorder, he said.

There is mounting evidence that lithium treatment may prevent or even reverse some of these changes. The study that showed normal cingulate volumes in bipolar adults on lithium monotherapy and decreased volume in untreated bipolar adults showed lithium's association with an improved anatomic profile.

An earlier study by other investigators looked at the levels of N-acetyl aspartate, a marker of neuronal viability, before and after 4 weeks of lithium therapy both in 12 untreated bipolar patients and 9 healthy controls.

The study found a 5% increase in N-acetyl aspartate concentrations after therapy in both study groups (Biol. Psychiatry 2000;48:1-8).

"Although the studies are small, they do suggest that perhaps lithium has neurotrophic properties that could be preventing or reversing these changes," he said. ■

New Drugs Curb 'Off' Episodes in Advanced Parkinson's

BY BRUCE JANCIN
Denver Bureau

SAN FRANCISCO — A single dose of subcutaneous apomorphine rapidly and effectively reverses for at least 90 minutes the hypomobility, or "off," episodes that are common in patients with advanced Parkinson's disease, William C. Koller, M.D., said at the annual meeting of the American Academy of Neurology.

This injectable dopamine agonist, known as Apokyn, has received Food and Drug Administration approval as the first and only acute or rescue therapy for off episodes in Parkinson's disease patients.

Apokyn, which has orphan drug status, will be commercially available in July, with distribution to be handled through a specialty pharmacy network, according to a spokesperson for Mylan Laboratories Inc.

Parkinson's patients consider off episodes to be among the most frustrating aspects of the disease. Off episodes occur in about 50% of patients after 5 years of levodopa therapy.

The off episodes become increasingly frequent as the disease continues to progress.

Off episodes, which occur because of a shortage of dopamine in the brain's movement centers, are among the most frustrating aspects of Parkinson's.

These debilitating periods of loss of motor control are of two types: those that occur when a patient's oral Parkinson's disease medication wears off at the end of a dose, and those that occur unpredictably, according to Dr. Koller, who is with Mt. Sinai Medical Center, New York.

Off episodes occur because of a shortage of dopamine in movement centers in the brain. These episodes respond to oral dopamine agonists, but only after a roughly 90-minute delay during which patients may encounter great difficulty in walking, eating, and talking.

An alternative to Apokyn in approaching the problem of off episodes is rasagiline, a potent once-daily second-generation MAO type-B inhibitor.

Rasagiline reduces the frequency of such episodes by blocking dopamine breakdown, although it's not useful as rescue therapy during an episode, Dr. Koller said.

In addition, rasagiline has been shown in randomized trials to significantly improve motor function in general, and the disabling symptom known as freezing of gait in particular, in patients who have advanced Parkinson's disease, explained Nir Giladi, M.D., who is with Tel Aviv University.

Teva Neuroscience has filed a new-drug application with the Food and Drug Administration seeking two indications for rasagiline: as monotherapy in early Parkinson's disease and as an adjunct to levodopa in moderate to advanced disease.

Dr. Giladi reported on 454 levodopa-treated patients with advanced Parkinson's disease and motor fluctuations who participated in a double-blind, randomized 18-week trial of 1 mg/day of rasagiline, 200 mg of entacapone taken three to eight times daily as an active comparator, or placebo.

The primary study end point was change in the Freezing of Gait Questionnaire from baseline to week 10. Patients who were in the rasagiline group showed a significant mean 1.17-point improvement from a baseline of 11.9 on the 24-point scale, while improvement in the entacapone group did not reach significance.

The study was part of a larger trial in which the addition of 1 mg/day of rasagiline in levodopa-treated patients reduced the total daily time that Parkinson's symptoms weren't controlled by 1.2 hours, or 21%.

Postural hypotension was the only adverse event more common with rasagiline than placebo, he added. ■