Jeffrey Lieberman, MD, is a strong believer in accountability and in balancing risk, benefit, and cost. He therefore was concerned about the absence of data comparing the relative effectiveness and safety of the newer atypical antipsychotic drugs with those of first-generation agents like haloperidol and perphenazine. After all, the newer atypicals were developed in response to perceived limits in the efficacy of the earlier agents and the side effects associated with them, and as such they promised enhanced activity and safety.

Yet, according to Dr. Lieberman, “evidence of superior efficacy with the atypicals has not been established in the literature, while all but 10% of schizophrenics treated today are receiving the newer drugs … and this change has been at substantially increased cost.” To address the question of whether the newer drugs indeed deliver superior efficacy and safety, Dr. Lieberman and colleagues initiated the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).

“CATIE was the largest formal treatment trial ever sponsored by the National Institute of Mental Health,” explained Dr. Lieberman, “and was exceptionally long—18 months—to provide the opportunity to really measure treatment effects over time.” Furthermore, it was a novel concept—a hybrid study designed as a rigorous, large-scale comparative treatment trial but with many practical, real-world elements not traditionally included in clinical trials. For instance, it did not have stringent inclusion or exclusion criteria; rather, unselected patients (excluding only those with first episodes of schizophrenia or with proven treatment resistance) were recruited from a range of clinical settings. Patients with comorbidities and those receiving other medications were eligible. The trial design also allowed re-randomization in the event of poor efficacy or
intolerable side effects. These modifications permitted investigators to gauge real differences in outcomes achieved during actual practice experience.

The CATIE investigators enrolled 1,500 patients with schizophrenia at 57 sites in the United States. In Phase I, patients were randomly assigned to one of the atypical antipsychotic agents, olanzapine, quetiapine, risperidone, or ziprasidone (at physician-guided doses), or to low-dose perphenazine as the representative first-generation agent; they were then followed for 18 months or until treatment was discontinued. The primary endpoint was discontinuation of treatment drug for the entire 18 months.

“Although antipsychotics are effective in individual patients for the control of schizophrenia,” Dr. Lieberman explained, “as a class they are substantially limited, as reflected by a high rate of switching for reasons of inadequate efficacy or intolerable side effects.” Furthermore, the study data indicated that the most effective agent was clozapine, followed by olanzapine, as indicated by the lowest rates of discontinuation during the 18-month trial. “The improved efficacy of these drugs, however, comes at the cost of more significant side effects,” said Dr. Lieberman. Because these side effects, including metabolic and hematologic changes, are often asymptomatic, they do not cause patients to switch medications, but they may carry substantial health risks.

Perhaps most interesting was the finding that the rates of extrapyramidal side effects were low (<10%) in all study groups, including the perphenazine group. This suggests, according to Dr. Lieberman, “that the first-generation agents, if dosed properly, can be effective, safe, and potentially cost-effective options for the long-term treatment of schizophrenia.”

“Although antipsychotics are effective in individual patients for the control of schizophrenia,” Dr. Lieberman explained, “and we hope it will set a precedent to be followed in other therapeutic areas to ensure that patients are treated for all conditions based on sound experimental data and not simply on new drug marketing.”

Although all of the agents tested relieved the symptoms of schizophrenia, only 18% to 34% of patients in each treatment group continued their initial drug for the entire 18 months.

“This study was a landmark clinical trial of the comparative effectiveness of marketed treatments,” Dr. Lieberman explained, “and we hope it will set a precedent to be followed in other therapeutic areas to ensure that patients are treated for all conditions based on sound experimental data and not simply on new drug marketing.”

Jeffrey A. Lieberman, MD

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As neuroimaging methods continue to improve, the number of psychiatric disorders that scientists can characterize with imaging has grown exponentially, and collaboration among many fields has become the key to success. The Functional Neuroimaging Laboratory (FNL) at NewYork-Presbyterian Hospital/Weill Cornell Medical Center epitomizes this trend. Its researchers work together to develop novel imaging techniques, identify and characterize abnormal patterns of brain activity, and contribute to translational research.

“We do a lot of methodological development,” said David Silbersweig, MD. This is relatively rare among psychiatry labs. “We believe strongly that neuropsychiatric questions have their own challenges.” To meet these challenges, he added, the FNL depends on the multidisciplinary nature of its research team, which spans psychiatry, neurology, radiology, behavioral neuroscience, cognitive psychology, neuropsychology, physics, mathematics and statistics, and computer engineering.

In recent years, for example, the team has developed and validated new imaging methods to identify abnormalities within frontolimbic circuitry that are associated with psychosis in schizophrenia. Its researchers have also improved upon the widely used technology of blood oxygen level–dependent functional MRI (BOLD fMRI), gaining the ability to measure functional signals from a region at the bottom front of the brain that could not be imaged before because of ephemeral interference (so-called susceptibility artifacts). This region has turned out to be very important in the study of psychiatric patients.

The FNL’s interdisciplinary approach extends to its breadth of research projects. “Many of the same regions and circuits are implicated in a number of different disorders. We need to study them in parallel to try to tease this apart,” Dr. Silbersweig said. As part of the Center for the Neuroscience of Fear and Anxiety—a multi-institutional research center in New York City funded by the National Institute of Mental Health (NIMH)—the FNL is conducting imaging on patients with anxiety disorders to test hypotheses concerning the functioning of abnormal limbic fear circuitry in conditions such as panic disorder and post-traumatic stress disorder.

Other FNL research, currently in press at the American Journal of Psychiatry, takes a creative approach to investigating major depression. Rather than focus on the negative emotional circuitry of the brain, as is the case with most studies of major depression, the researchers tested reward circuitry in the ventral striatum associated with the ability to experience pleasure. Compared to control subjects, patients with major depression showed a significant reduction in the activation of that brain region to positive emotional stimuli. The results provide support for a circuit model of the disorder.

The FNL has also begun studying gender differences in psychiatric disorders. “There’s a different incidence of particular psychiatric disorders between the sexes,” said Emily Stern, MD, citing how women are more likely to be affected by depression and anxiety disorders, while men are more prone to attention-deficit disorder and Tourette’s syndrome.

The research team reported in Proceedings of the National Academy of Sciences USA (2005 Nov 1;102(44):16060-16065) on how the menstrual cycle can alter brain activity related to emotional processing. The study focused on women who had no premenstrual symptoms at all, but still found that during the premenstrual phase, activity in the medial orbitofrontal cortex increased in response to negative emotional linguistic stimuli and demands for behavioral inhibition. Follow-up studies are looking at the 2% to 10% of women who experience premenstrual dysphoric disorder.

The FNL has also introduced a Web site at www.functionalneuroimaging.org.

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Research has shown that children of depressed parents have high rates of mood, anxiety and disruptive disorders. The onset of these disabling conditions often begins before puberty and continues throughout adulthood. New evidence from Columbia University Medical Center and the New York Psychiatric Institute highlights the potential for reducing or preventing depression in children by successfully treating maternal depression.

A three-month study of children, aged 7 to 17, showed a relationship between remission of maternal depression and the child’s clinical state. The mothers were enrolled in the multistate Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial. The STAR*D study was designed to explore what to do if the first treatment for depression did not produce a remission. Children in the study were assessed, but not treated, for selected psychiatric disorders by trained child evaluators blind to the mothers’ response to treatment.

“Having a parent who is depressed is a serious environmental stress for a child,” explained Myrna Weissman, PhD, Professor of Epidemiology in Psychiatry at Columbia University College of Physicians and Surgeons and the lead author of the STAR*D Child Report. “If you could relieve the parent’s depression, you might have some impact on the child. This is the question we studied.”

Mothers in the study had a diagnosis of nonpsychotic major depressive disorder (MDD) and were being treated with antidepressant medication at 7 regional centers around the country. The mothers’ remission rate was 33% over 12 weeks, which was consistent with the STAR*D trial’s overall results for initial treatment. Remission is defined as the absence of depressive symptoms at the end of 3 months.

Children whose mothers’ depression remitted over this short time also showed significant improvement. If a mother’s depression remitted over the three months, there was an 11% overall decrease in the child’s psychiatric disorders. If the mother’s depression did not remit, there was an 8% overall increase in the child’s disorders. Maternal remission reduced the rates of children’s depressive and disruptive behavior disorders, but did not impact significantly on children’s anxiety.

Another important finding of the STAR*D Child Study is that successful treatment of maternal depression may prevent or delay the onset of a diagnosis in children. Children without a diagnosis at the mother’s initiation of her treatment remained well if the mother remitted, whereas 17% of these children developed a diagnosis if the mother did not remit.

“We’re not curing depression [in children], but we may prevent its onset by helping reduce the parent’s depression,” said Dr. Weissman, who described depression as a “mostly genetic disorder with strong environmental triggers.” Dr. Weissman believes that the results for children would be similar if her team had studied depression in fathers and regardless of the type of treatment the parent received, as long as it was effective. “We would have liked to have studied fathers, but we couldn’t for two reasons: rates of depression are higher in women, and women are more likely to bring their children in for assessment.”

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For adults who have mastered reading, words flow seamlessly across the page in an automatic, nearly instantaneous process. But such skills emerge through years of specialized learning and effort that, along the way, are associated with changes in neurologic function within specific brain structures. Now, by applying the latest technology, researchers at the Sackler Institute for Developmental Psychobiology can investigate the cognitive and neurobiological mechanisms of reading, as well as those behind reading disabilities such as dyslexia, in the hope of developing interventions tailored to the needs of individual children.

One recent study, published in *Neuropsychologia* (2006;44:2178-2188), investigated the association between reading ability and white matter tract microstructure during the early years of reading development. In a group of 31 children who were either reading disabled or nonimpaired, researchers Sumit N. Niogi and Bruce D. McCandliss used diffusion tensor imaging to show that the white matter in two left temporoparietal regions—the superior corona radiata and centrum semiovale—was denser among those with stronger reading skills.

“We discovered that white matter tracts in the left hemisphere specifically relate to reading, as opposed to IQ and short-term memory,” said Dr. McCandliss. “The regions act as connecting networks within the brain,” he explained, adding that the researchers had observed structural rather than functional differences. The study also documented that white matter differences are already present during the early years of reading acquisition, rather than emerging in adulthood.

This research confirms earlier work but possesses distinct advantages, since it is the first study to include a significant number of children with clear evidence of dyslexia, and measured a broader range of reading skills. Taken together, white matter tract differences account for nearly 40% of the disparity in reading skills among children.

Dr. McCandliss and his colleagues are also examining the brain’s electrophysiology by measuring high-density event-related potentials (ERPs) across an array of locations around the head. For this research, they are currently enrolling children aged 7 through 12. “With 129 sensors, we look at how signals vary during elementary cognitive acts, such as listening to or reading a word. And we’re able to look at how the electrical signals unfold over time,” he said.

This approach may eventually link with research on white matter tracts. A previous study using ERPs, published last year in *Behavior and Brain Functions* (2005 Apr 22;11[1]:4), demonstrated that adult English speakers experience an increase in activity over the left posterior visual regions about 170 milliseconds after reading a word. “This activity is critical in the brain’s automatic ability to recognize visual words,” explained Dr. McCandliss. “We’re now looking at this quality in children to uncover the physiologic development of white matter tract differences.”

Dr. McCandliss hopes that cognitive neuroscience research may ultimately have therapeutic applications. Among his many projects is an outreach program conducted in collaboration with New York City public elementary schools, called Reading Works, which uses computer software to teach reading skills to weak readers.

But many other factors, including the home literacy environment and degree of early print exposure, can affect reading. In an upcoming study to be published in *Developmental Science*, he joined with researchers at the University of Pennsylvania to test 150 healthy, socioeconomically diverse first-graders for language, visuospatial skills, memory, working memory, cognitive control, and reward processing. They found that socioeconomic status explained over 30% of the variance in language skills.

“As we start to understand what the different problems are in learning to read, we can begin to find interventions that target them. Understanding that profile of a child’s neurocognitive difficulties, and how they are mediated by other factors, could have a big impact.”

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Hippocampal Neurogenesis Found Key to Antidepressant Efficacy

The hippocampus has long been recognized as a key mediator of learning and memory in humans, but recent evidence suggests that it might also play an important role in the brain’s response to psychosocial stress and the development of depression. Chronic anxiety and depression have been linked to the loss of hippocampal neurons, and long-term treatment with antidepressant medications has been found to increase neurogenesis.

René Hen, PhD, and his colleagues at the New York State Psychiatric Institute are using genetic and radiological manipulation in mouse and rat models of stress to elaborate on the role of antidepressant-induced neurogenesis and the behavioral effects of these drugs.

Neurogenesis in human adult brains is an ongoing process in which progenitor cells from the subgranular zone of the dentate gyrus differentiate into granular neurons upon passage into the granule cell layer, and ultimately integrate into the functional circuitry of the hippocampus. According to Dr. Hen, “The assimilation of neophyte neurons into hippocampal processing has been illustrated in models in which new neurons have been shown to respond to environmental—eg, enrichment and learning—or pharmacologic—eg, antidepressant—stimulation by extending axonal projections to relevant target areas.”

In contrast, the human brain—and the hippocampus, specifically—in stressed settings is known to shrink through cell death, dendritic shrinkage, and neuronal atrophy, a condition predisposing depression in humans.

Dr. Hen’s own research employs a murine behavioral model of stress. The mice are offered food in a stressful environment and assessed for any feeding delay, which serves as a marker of anxiety. In a preliminary trial, the group found that mice treated for 5 days with the antidepressants fluoxetine or imipramine showed no improvement in the time to feed compared with control animals. However, those treated for 28 days demonstrated a significant decrease in the time to feed.

According to Dr. Hen, the delayed onset of antidepressant activity parallels that observed in humans and may directly correspond with the neurogenesis believed to underlie antidepressant efficacy. “The theoretical process of drug-induced neurogenesis would involve proliferation of neuronal progenitors, differentiation and migration of new neurons, and subsequent integration with pre- and postsynaptic targets, all of which would logically take several weeks.” In another study, Dr. Hen’s group showed a 60% increase in labeled progenitor cells in the dentate gyri of mice treated with fluoxetine for 11 or 28 days but not those treated for 5 days.

The team then used irradiation-induced reductions in cellular proliferation to further assess the role of neurogenesis in antidepressant actions. After delivering fractionated, low doses of X-rays directly to the hippocampus, the investigators noted an 85% reduction in precursor cells in the subgranular zone of the dentate gyrus. This decrease in neurogenesis, furthermore, was associated with the elimination of antidepressant-induced improvements in behavior otherwise observed in fluoxetine- or imipramine-treated mice. Similarly, a strain of serotonin-receptor “knockout” mice that exhibits elevated anxiety did not respond to fluoxetine with a reduction in the delay to feed or with increased neurogenesis; on the other hand, neurogenesis was increased and anxiety improved in knockouts treated with the tricyclic antidepressant imipramine, which works via an alternative pathway.

According to Dr. Hen, “Evidence that 5-HT1A-receptor knockout interferes with both the behavioral and neurogenic effects of fluoxetine suggests that these two effects may be causally related.” If so, it might be inferred that the presence and proper function of hippocampal neurogenesis are required elements for antidepressant drug activity.

Dr. Hen warns that these exciting results “remain correlative and the exact mechanism and relationship of antidepressant drugs to hippocampal neurogenesis remains to be defined.”

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As a postdoctoral fellow in schizophrenia treatment and research, Yulia Landa, PsyD, became interested in delusional thinking. This prompted her to investigate the range of available interventions at the time, including the concept of cognitive-behavioral therapy (CBT) for psychosis.

Based on the principles of cognitive therapy originally developed by Aaron Beck, MD, CBT for psychosis focuses on the psychotic experience and the patient’s attempts to understand his/her symptoms, and particularly the thoughts, images, and internal communication that define one’s reaction to the event. The patient is encouraged to consider an alternative view, discuss the consequences of holding onto the belief, and set up behavioral experiments to test the validity of the delusion.

Dr. Landa has taken this approach a step further and combined CBT with the benefits of group therapy. According to Dr. Landa, “In a group, patients can learn how to process information more effectively, become aware of and discuss cognitive biases contributing to delusional beliefs, and reality-test their beliefs.”

Results of numerous controlled trials have demonstrated an improvement in drug-resistant psychotic symptoms and associated distress resulting from CBT adjunctive treatment for schizophrenia. The group therapy setting, Dr. Landa explained, “provides an excellent psychoeducational venue in which patients can discuss symptoms, decrease their sense of isolation, improve interpersonal skills, and build ego function.”

Dr. Landa began her quest to incorporate CBT into the schizophrenia management paradigm by contacting international leaders in the field of CBT research, including Dr. Beck in the United States. She then worked with her Cornell mentor, Steven M. Silverstein, PhD, and colleagues Fred Schwartz, PhD, and Adam Savitz, MD, PhD, to identify patients with a primary DSM-IV diagnosis of schizophrenia or schizoaffective disorder. The patients were enrolled in a pilot trial of the new combined-therapy approach, termed Group Cognitive Behavioral Therapy (GCBT) for Delusions.

In the *Journal of Contemporary Psychotherapy* (2006;36[1]:9-17), Dr. Landa and colleagues described their success with GCBT in this population. The 6 patients who had been stabilized on antipsychotic medications but who retained psychotic delusions underwent 13 one-hour GCBT sessions, during which the individuals in the group worked on self-identified delusional beliefs that they perceived as stressful and wanted to explore and change. At the end of the intervention period, the investigators noted a significant reduction in delusional conviction (*P*<.03) and a significant increase in the ability to dismiss delusional thoughts (*P*<.002). The patients’ self-assessment of distress also improved significantly over the study period.

Dr. Landa, recipient of a 2006 NARSAD Young Investigator award, believes this technique might be a key to improved functioning in refractory schizophrenics. “The group CBT format,” Dr. Landa explains, “provides patients the opportunity to observe the irrationality and inconsistencies of other group members’ beliefs and to share feedback in a safe and supportive environment. The group promotes coping strategies to deal with symptoms, encourages interaction, and permits more patients to receive treatment.”

The success of Dr. Landa’s work positioned her to be NewYork-Presbyterian/Weill Cornell’s Department of Psychiatry host for the 7th International Annual Research Conference on CBT in Psychosis. This program, held in May, was a particularly exciting moment in her career, as it was chaired by Dr. Beck, the inspiration for her interest in CBT. She was also recently named a Beck Institute for Cognitive Therapy and Research Scholar for the 2006-07 academic year.

Currently, Dr. Landa is extending her work on CBT by initiating a formal, randomized, controlled clinical study of GCBT that will focus on patients with paranoid delusions. Her partner for this study will be David Silbersweig, MD, of NewYork-Presbyterian/Weill Cornell.

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The STAR*D Child Study Team has completed 1- and 2-year assessments of these children, and the data are currently being analyzed. Significantly, mothers whose depression remitted at 3 months were more likely to be better educated and have higher incomes than mothers whose depression did not remit.

While the STAR*D Child Study results are encouraging for clinicians, the number of mothers enrolled in the study was lower than what was hoped based on the demographics of the patients. Of the 808 women in their childrearing years, aged 25 to 60, screened at the participating STAR*D outpatient clinics, only 22% (177) had at least one child in the age range of 7 to 17. According to Dr. Weissman, this suggests that mothers are less likely than women without children to seek treatment for depression.

Dr. Weissman has been documenting depression in 3 generations of families since the late 1970s. She has shown that depression is highly inheritable, running strongly through families. She and her colleagues are currently researching genetic markers in family members with MDD. Participants are currently being recruited for the Genetics of Recurrent Early Onset Major Depression (Gen-RED) study. Persons aged 21 and older, who have had onset of depression before age 30, and have had two or more major depressive episodes and who also have a family member with depression are eligible. (For more information, contact sib-health@childpsych.columbia.edu.)

Dr. Weissman concluded, “The implications of the STAR*D Child Study are that if you are depressed and have children, get treatment.” She added, “If the first treatment doesn’t work, try another treatment or increase the dose because eventually most people get better. If a mother gets better, it’s a twinner.”

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