

NOVEMBER/DECEMBER 2014

Jeffrey A. Lieberman, MD

Psychiatrist-in-Chief
NewYork-Presbyterian/
Columbia University
Medical Center
Director, New York State
Psychiatric Institute
jl2616@columbia.edu

Jack D. Barchas, MD

Psychiatrist-in-Chief
NewYork-Presbyterian/
Weill Cornell Medical Center
jbarchas@med.cornell.edu

Electroconvulsive Therapy: A Potent Therapy for Major Depressive Disorder

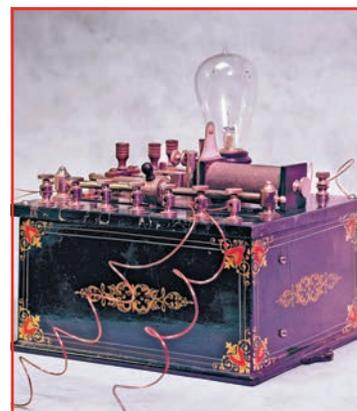
Over the years public perception and understanding of electroconvulsive therapy (ECT) have been influenced by its frightening depiction in movies, such as *One Flew Over the Cuckoo's Nest*, and the earlier primitive methods by which it was administered. However, ECT has advanced considerably since its introduction in 1938, and, despite some controversy surrounding its efficacy versus side effects, it is today well established as a safe, effective, and even lifesaving treatment for certain psychiatric disorders.

“ECT has undergone a lot of changes and improvements since the late 1930s,” says **Joan Prudic, MD**, Medical Director, Electroconvulsive Therapy Service, NewYork-Presbyterian/Columbia University Medical Center. ECT is now employed for relieving symptoms of major depressive disorder, bipolar disorder, schizophrenia, and non-psychiatric medical conditions, including Parkinson’s disease.

“Eighty-five percent of our patients have depression, which often is treatment-resistant,” says Dr. Prudic. “While ECT looks like a last resort when you’re dealing with treatment-refractory depression, if the person is psychotically depressed or extremely suicidal, this level of severity can be an indicator to give ECT as a first-line treatment.”

Dr. Prudic, who is also Director of the Clinic for Innovations in Treatment Resistant Depression and a research psychiatrist at the New York State Psychiatric Institute, has participated in pioneering research in

(continued on page 2)



ECT technology has come a long way since its early days.

**CONTINUING
MEDICAL EDUCATION**

For all upcoming education events through NewYork-Presbyterian Hospital, visit www.nyp.org/pro.

Brain Stimulation Therapy for Treatment-Resistant Depression

Major depressive disorder is one of the most common psychiatric disorders in the United States, each year affecting some 6.7 percent of adults. For those individuals who have failed to respond to traditional treatments – antidepressants and psychotherapy – the use of brain stimulation therapies, including repetitive transcranial magnetic stimulation (rTMS), promises to be an effective therapy.

Marc J. Dubin, MD, PhD, a psychiatrist at NewYork-Presbyterian/Weill Cornell Medical Center, specializes in the evaluation of patients with mood disorders who are treatment-resistant. Dr. Dubin combines psychopharmacology treatment with psychotherapy and, when appropriate, employs the use of rTMS. This breakthrough depression treatment – which was FDA approved for adults in 2007 – uses highly focused, brief electromagnetic pulses administered through an electromagnetic coil to non-invasively stimulate function in a targeted brain region. The magnetic field is similar to the strength of an MRI scan.

(continued on page 3)



Dr. Marc J. Dubin

NewYork-Presbyterian Psychiatry
ranks #2 in the nation.



Electroconvulsive Therapy: A Potent Therapy for Major Depressive Disorder (continued from page 1)

ECT throughout her career, and she and her Columbia colleagues continue to develop clinical trials for other innovative treatments for depression, particularly in the area of brain stimulation. She has been principal investigator on grants from the National Institute of Mental Health and the National Alliance for Research on Schizophrenia and Depression, receiving continuous support since 1985. Her research and clinical interests focus on the diagnosis and treatment of depression, including geriatric depression, ECT, and the improvement of community treatment in these areas through dissemination of research findings to clinical practice.



Dr. Joan Prudic

“When my division embarked on this work in the late 1970s we understood ECT differently from how we understand it now,” says Dr. Prudic, who is also President of the International Society for ECT and Neurostimulation. “We’ve improved ECT quite a bit since then and it remains the most powerful antidepressant.”

Clinical Indicators

In determining which patients would benefit most from ECT, Dr. Prudic weighs several factors. “The primary diagnostic indicator is major depression,” she says. “We also look for clinical indicators – the severity of the depression, or if the patient is psychotic, suicidal, or has stopped eating or drinking. The depression may also be less severe, but the individual has failed a significant number of medication trials. Severe depressions that go on for too long are not only very impairing, they can be life-threatening. We don’t want somebody to suffer if there is a treatment available that can end that depression. We want to restore them to health and better functioning.”

Dr. Prudic and Columbia colleague **Nancy A. Kerner, MD, PhD**, have reviewed ECT practice in the geriatric population as well and note that studies have shown it is the most successful and rapid treatment for elderly patients with depression, bipolar disorder, and psychosis. “For patients who suffer from intractable catatonia and neuroleptic malignant syndrome, ECT can be lifesaving,” says Dr. Prudic. “And for older patients who cannot tolerate or respond poorly to medications and who are at a high risk for drug-induced toxicity or toxic drug interactions, ECT can be the safest treatment option.”

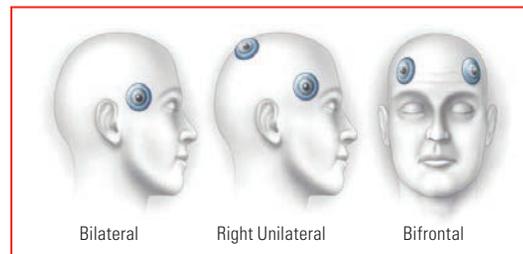
The Method

With advances in both anesthesia and technology, ECT today is very safe. The patient is sedated using general anesthesia with a short-acting anesthetic agent followed by a muscle relaxant. The ECT device is connected to two small electrodes, which are placed on the scalp. A small electrical current is then delivered to the scalp through the paddles, which causes a short – usually 20 to 60 seconds – controlled seizure. The treatment, from the time the patient is asleep to the time the patient wakes up, is about five to 10 minutes. Treatments range from four to 20, but most patients require six to 12, given once every two to three days.

Several aspects of the ECT method – particularly the selection of electrode placement – are subject to varying opinions. “When ECT was first developed we knew nothing about pathophysiology or neuronal circuitry of depression or ECT. We know more now, and it appears that many of the areas of interest in depression are interior; they’re not on the surface of the brain,” says Dr. Prudic. “What we try to do is to reach those areas. I think that’s in part why ECT is such an effective treatment – the stimulus can be transmitted to those areas.”

If a patient is in good health, treatment risks are minimal, says Dr. Prudic. “Any disorientation tends to be time-limited. Once the patient is fully awake, it will abate with our current techniques. Even anterograde memory problems, which can develop over the course of treatment, will generally subside within a few weeks after treatment is completed.”

According to Dr. Prudic, there are multiple



Standard electrode placement for ECT

hypotheses as to why ECT is effective. “Our current theory is that it releases most of the neurotransmitters that we think are important in the treatment of depression. In addition, ECT induces brain growth factors that are restorative. There has also been some volumetric work that indicates that there is even an increase in tissue – particularly in the hippocampus. There really is no scientifically substantial evidence that indicates that there is destruction of tissue.”

Advancing the Understanding of ECT

In conjunction with initiatives from the National Institute of Mental Health, Dr. Prudic and her colleagues seek to identify treatment targets through fMRI pilot work. “The hope is that by making the treatment more targeted, you can mitigate cognitive side effects associated with electroconvulsive therapy.”

The researchers are also conducting EEG-related testing looking at evoked potentials to better understand cognitive circuit integrity. With funding from the NIH, they are seeking to develop cognitive remediation as prevention and treatment for cognitive issues.

Dr. Prudic notes that it is critical to continue to elucidate the pathophysiology of depression and the ways in which ECT alters that pathophysiology. “Currently, our major instrument to study this is brain imaging,” she says. “The question remains ‘What exactly is ECT doing?’ It’s clearly doing something that all of our other treatments for depression don’t do. We need to improve our technology and persevere in these efforts.”

Reference Articles

Kerner N, Prudic J. Current electroconvulsive therapy practice and research in the geriatric population. *Neuropsychiatry* (London). 2014 Feb;4(1):33-54.

Elias A, Chathanchirayil SJ, Bhat R, Prudic J. Maintenance electroconvulsive therapy up to 12 years. *Journal of Affective Disorders*. 2014 Mar;156:228-31.

For More Information

Dr. Joan Prudic • jp33@columbia.edu

Brain Stimulation Therapy for Treatment-Resistant Depression *(continued from page 1)*

“One theory is that stimulating the brain repeatedly enhances long-term potentiation, which leads to stronger connections between neurons in the area that is being stimulated and other areas in the same network. In turn, those stronger connections may normalize the function of the underlying neural network,” says Dr. Dubin. “There is also belief that the process enhances network plasticity that can help the psychotherapeutic process, making the brain more receptive to change that could come through psychotherapy.” Dr. Dubin also notes that there has been evidence that stimulating the sensory motor cortex can improve stroke symptoms and play a role in rehabilitation.

Deciding to Use rTMS

Prior to recommending rTMS, Dr. Dubin takes a detailed clinical history of a patient’s past and current depressive episodes. “I first explore other kinds of psychopathology that might explain why the patient hasn’t responded to treatments for depression,” says Dr. Dubin. “Sometimes people are misdiagnosed with depression when they really have a personality disorder or bipolar disorder. These disorders may have been misdiagnosed, which is why they haven’t responded.”

After consulting with the patient’s psychiatrist who may have treated the individual for some time, Dr. Dubin is then able to confirm the diagnosis of depression. “I verify that they’ve either tried a number of therapies that haven’t worked, or that they haven’t been able to tolerate those treatments,” he says. “At that point I’ll talk with the patient about the risks and benefits of rTMS.”

According to Dr. Dubin, the main benefit is, obviously, the treatment of depression, and the risks are minimal. “There is a risk of seizure, but that is considered to be extraordinarily small,” he says. “There are no cognitive side effects. There is a risk of mild headache and scalp irritation that are generally managed with over-the-counter medications.”

Patients undergo treatment Monday through Friday for five to six weeks, with each rTMS session lasting 40 minutes. “A high intensity magnet is positioned over their left frontal lobe that has been found to be underactive in major depression,” says Dr. Dubin. Patients are comfortably seated in a reclining chair during the treatment.

“Throughout the process we observe the patient closely for symptoms of depression using established depression rating scales,” he says. “We’re mindful that individuals with severe symptoms of depression are at risk for suicide, and monitor them very closely. If we have concerns and find that it is necessary, we can bring them to our psychiatric emergency room. We also make sure that they have adequate follow-up with their outpatient psychiatrist.”

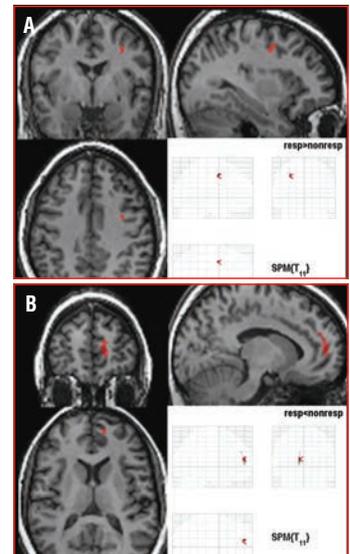
Understanding rTMS Treatment and Response

Dr. Dubin combines his scientific interest in neurophysiology with his clinical concern in helping people with depression. “My research centers on using different imaging modalities, including MRI and functional MRI, to try to better define what happens to the brain during a course of rTMS in people who respond versus people who do not respond,” he says. “Some of my current research involves using different kinds of MRI prior to treatment to help define precisely where to position the magnet.”

While rTMS is effective for treatment-resistant major depressive disorder, the response rate for depression is modest, which led

Dr. Dubin and **Nora Weiduschat, MD, MPH**, Assistant Professor of Neuroscience in Radiology at Weill Cornell Medical College, to search for biomarkers predictive of treatment response. In 2013, they undertook a study of 13 patients with major depression resistant to at least two antidepressants in the current episode who were treated with a 25-day course of rTMS over the left dorsolateral prefrontal cortex (DLPFC).

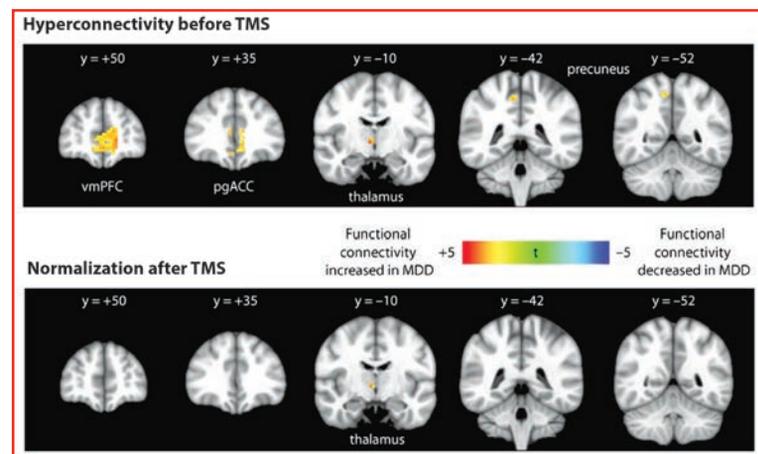
The results of this study, believed to be the first investigation to compare pre-treatment brain perfusion patterns of depressed individuals who responded to rTMS to those who did not, were published in the *Journal of Affective Disorders*. Six individuals responded to rTMS, with greater resting state blood flow in the target site at baseline compared to non-responders who showed greater baseline activity in the left medial frontal cortex.



Following treatment with rTMS, regional perfusion in (A) responders and in (B) non-responders at baseline shows increased dorsolateral prefrontal cortex activity in responders and increased mediofrontal activity in non-responders.

The researchers determined that these results, which suggested a stronger DLPFC perfusion in responders and stronger medial prefrontal perfusion in non-responders both at baseline and post-treatment, require confirmation in a larger, prospective placebo controlled study.

In another study of 17 patients with depression and a cohort of 35 healthy control subjects, the results of which were published in the October 2014 issue of *Biological Psychiatry*, Dr. Dubin, **Conor Liston, MD, PhD**, Assistant Professor of Neuroscience and Psychiatry, and colleagues used functional MRI to study the effect of TMS on two networks important in emotional



TMS normalized depression-related hyperconnectivity between the subgenual cingulate and several areas of the default mode network, including the ventromedial prefrontal cortex (vmPFC), pregenual cingulate (pgACC), thalamus, and precuneus.

regulation and cognition. Functional MRI was used to measure connectivity between the frontoparietal central executive network (CEN) and the medial prefrontal-medial parietal default mode network (DMN) both before and after a 25-day course of TMS. TMS normalized depression-related hyperconnectivity between the subgenual cingulate – an important target for other antidepressant modalities – and medial prefrontal areas of the DMN, but did not alter connectivity in the CEN. In addition, individuals with greater baseline connectivity with the subgenual anterior cingulate cortex were more likely to respond to TMS. The results indicate that TMS may act, in part, by selectively regulating network-level connectivity and also highlight potential neuroimaging biomarkers for predicting treatment response.

“In people who respond to TMS, we’re looking to see if networks that regulate emotion show distinctive abnormalities at baseline compared to people who don’t respond to TMS,” says Dr. Dubin. “If we can somehow use that information when a patient first comes to us for treatment, it will help us decide whether or not they are an appropriate candidate and whether or not they are likely to respond.”

“I see transcranial magnetic stimulation not presently as a cure, but as a potential and extremely valuable treatment that is in evolution,” adds Dr. Dubin. “Most people in this field believe that it has considerable efficacy right now, but there is a lot of room to optimize it – to improve it – by more accurately defining and personalizing the target location according to each individual patient’s underlying pathology. As we learn more about targeting and how to optimize the stimulus parameters, it will be an even more effective treatment.”

Reference Articles

Liston C, Chen AC, Zebly BD, Drysdale AT, Gordon R, Leuchter B, Voss HU, Casey BJ, Etkin A, Dubin MJ. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biological Psychiatry*. 2014 Oct 1;76(7):517-26.

Weiduschat N, Dubin MJ. Prefrontal cortical blood flow predicts response of depression to rTMS. *Journal of Affective Disorders*. 2013 Sep 5;150(2):699-702.

For More Information

Dr. Marc J. Dubin • mrd9035@med.cornell.edu

Research Innovations

Human Neurobiology

Addressing Depression in the Very Elderly

Studies of the Weill Cornell Institute of Geriatric Psychiatry by George S. Alexopoulos, MD, Faith M. Gunning-Dixon, PhD, Sarah Shizuko Morimoto, PsyD, Patrick J. Raue, MD, and others have been the first to identify that structural and functional abnormalities of the brain’s cognitive control network predict poor response of late-late life depression to antidepressant drugs. They used their findings to develop two distinct approaches to novel treatment development:

- Targeted problem solving therapies imparting skills that enable patients to overcome behavioral problems related to cognitive control network dysfunction
- A computerized cognitive remediation designed to generate neuroplasticity and improve the function of the cognitive control network

Both approaches have improved depression in patients at risk for failing antidepressant drugs. Findings of these studies have been published in prestigious journals, including *Molecular Psychiatry*, *American Journal of Psychiatry*, *Archives of General Psychiatry*, *Nature Communications*, and the *Journal of Affective Disorders*.



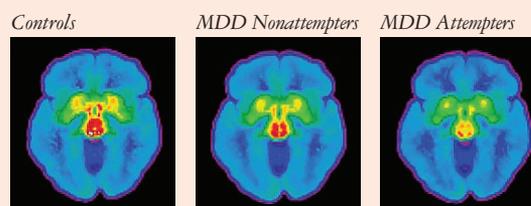
Depressed older adults have lower functional connectivity in the cognitive control network and higher connectivity in the default mode network than normal adults.

Functional connectivity in the cognitive control network but not in the default mode network predicts response to an antidepressant.

Molecular Imaging and Neuropathology

Investigating Biological Factors in Suicide Susceptibility

Suicidal behavior has previously been linked to mood disorders, in particular major depressive disorder (MDD) and bipolar disorder (BPD). But not all patients with MDD and BPD are suicidal. Faculty in the Molecular Imaging and Neuropathology Division in the Department of Psychiatry at New York-Presbyterian/Columbia and the New York State Psychiatric Institute have been examining the biological substrates of mental illness with an emphasis on mood disorders and suicide behavior. Several lines of evidence implicate abnormal serotonergic function in suicidal behavior and completed suicide. Recent work by Jeffrey M. Miller, MD, Natalie Hesselgrave, MEd, R. Todd Ogden, PhD, Gregory M. Sullivan, MD, Maria A. Oquendo, MD, and J. John Mann, MD, using PET imaging with ¹¹C-DASB to quantify *in vivo* regional brain serotonin transporter binding has shown that depressed suicide attempters had lower serotonin transporter binding in the midbrain compared with depressed nonattempters. Additionally, low midbrain serotonin transporter binding appears to be related to the pathophysiology of suicidal behavior rather than of MDD. The results have been published in *Biological Psychiatry*.



Low serotonin transporter binding in MDD quantified by PET with ¹¹C-DASB distinguishes suicide attempters.

Notable Achievements

Mental Health Foundation Honors Dr. Jeffrey Lieberman

The Mental Health Foundation's Second Annual Special Evening in New York honored **Jeffrey A. Lieberman, MD**, Psychiatrist-in-Chief at NewYork-Presbyterian/Columbia University Medical Center and Director of the New York State Psychiatric Institute, for his years of leading work in the field of mental illness. Matilda Raffa Cuomo, former First Lady of New York State, presented the award to Dr. Lieberman at the Columbus Citizens Foundation townhouse in New York City.



Dr. Jeffrey A. Lieberman

In his acceptance remarks, Dr. Lieberman, who is the Immediate Past President and Trustee of the American Psychiatric Association, noted that although mental illness, like cancer or diabetes, is endemic to the country's population, it has historically been ignored or discriminated against. He also emphasized that the early identification of mental illness in young people will afford them the chance to get on the right course in life and also save the healthcare system the expense of what would be lifelong care for their disease. "The best way to make progress is through organizations like this that bring people together, forge a commitment to a common agenda, and to basically move the ball down the field with respect to this cause," said Dr. Lieberman.

Dr. Catherine Lord Elected to Prestigious Institute of Medicine

Catherine Lord, PhD, Director of the Center for Autism and the Developing Brain at NewYork-Presbyterian Hospital, has been elected to the Institute of Medicine (IOM). Election to the IOM is considered to be one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.



Dr. Catherine Lord

"It's a privilege to be elected into the Institute of Medicine, and I couldn't be more honored," said Dr. Lord. "I've spent my career working to transform the way we understand and treat autism spectrum disorders, and membership provides me with an opportunity to have a greater voice for patients and their families around the country."

Dr. Lord, a psychologist nationally known for groundbreaking longitudinal studies of children with autism, was among 70 new members and 10 foreign associates to join the Institute at its 44th Annual Meeting. "These leaders' tremendous achievements have contributed significantly to advancing health and medicine.

The expertise and knowledge they bring to the IOM will encourage and enhance its success," said IOM President Victor J. Dzau.

New members are elected by current active members through a selective process that recognizes individuals who have made major contributions to the advancement of the medical sciences, health care, and public health. With their election, members make a commitment to volunteer their service on IOM committees, boards, and other activities. Projects during the past year include studies on meeting the needs of those nearing the end of life, determining what is known about and how to reduce sport-related concussions in youth athletes, analyzing the treatment of post-traumatic stress disorder in military and veteran populations, enhancing governance and accountability in graduate medical education, and examining long-term health effects of blast exposures.

Dr. Herbert Pardes Awarded Inaugural Humanitarian Prize by Brain & Behavior Research Foundation

The Brain & Behavior Research Foundation has honored **Herbert Pardes, MD**, President of the Foundation's Scientific Council and Executive Vice Chair of the Board of Trustees at NewYork-Presbyterian Hospital, with its inaugural Humanitarian Prize at the Foundation's 27th Annual National Awards Dinner in October.



Dr. Herbert Pardes

Dr. Pardes, a noted psychiatrist and outspoken advocate for the mentally ill, is the first recipient of the Humanitarian Prize, which will bear his name and honor individuals who have made significant contributions to the field of mental health through education, prevention, treatment, research, health policy, administration, clinical care, mentoring, and advocacy.

The Brain & Behavior Research Foundation raises funds to invest in cutting-edge research projects to understand, treat, and ultimately prevent and cure mental illness. Since 1987, it has awarded over \$320 million in research grants to more than 3,800 scientists around the world.

"We are proud to bestow our inaugural Humanitarian Prize to Dr. Pardes for a lifetime of achievement in the field of mental health, including his contributions as the founding president of the Scientific Council," said Jeffrey Borenstein, MD, the Foundation's President and CEO. "Dr. Pardes sets the standard and exemplifies the qualities we will look for in future recipients."

"Eradicating mental illness has been something I've worked toward my entire career, and we've made great strides in the diagnosis and treatment of mental illness," said Dr. Pardes. "But much remains to be done. We must ensure that the Foundation continues to support the work of innovative scientists to discover the root cause of these conditions so they can be treated more effectively and, ultimately, be prevented or cured."



Advances in Psychiatry

NewYork-Presbyterian Hospital
525 East 68th Street
New York, NY 10065

www.nyp.org

NON-PROFIT ORG.
US POSTAGE
PAID
STATEN ISLAND, NY
PERMIT NO. 169

