

## Clinical Trials Data

### New Antidepressants and Mania

As noted in previous issues of the *BNN*, the Stanley Foundation Bipolar Network (SFBN) is conducting a randomized, double-blind clinical trial comparing three different antidepressants—bupropion (Wellbutrin®), sertraline (Zoloft®), and venlafaxine (Effexor®)—in patients with bipolar disorder who experience a depression that breaks through ongoing pharmacoprophylaxis. Over 100 patients have been randomized in the clinical trial. Although the trial is ongoing, and the blind has not been broken, several interesting findings can be reported. There appears to be a moderate rate of antidepressant response to these agents as a group (33%), and of particular note, a lower than expected rate of inducing (i.e., “switching” into) mania (12%) during the 10-week acute trial phase. In addition, in the 1-year continuation phase (for acute antidepressant responders), a relatively low rate of switching into mania (also 12%) was observed.

These data are in general agreement with other studies indicating that with the newer (or “second generation”) antidepressants, when used as adjuncts to mood stabilizers, their proclivity to induce mania may not be as great as with the first generation tricyclic (TCA) and monoamine oxidase inhibitor (MAOI) antidepressants. The current literature on these older agents appears divided into two sets of observations, with many investigators reporting low switch rates (10% or below) and another group reporting relatively high switch rates (25–50%) in response to antidepressant treatment of bipolar depression.

### Rapid Cycling?

It is unclear as to what to attribute the difference in these very discordant rates of switching into mania, but one possibility is the initial cycle frequency of the patients being studied. There appears to be a rough correlation between those who study a higher percentage of rapid cycling patients ( $\geq 4$  episodes/year) and their observations of a greater likelihood of a switch into mania. This relationship, however, is not true for all the studies and is not consistent with the data just cited from the SFBN. Suppes et al. (2000; *J Affect Disord*, in press) reported that over 50% of the patients in the SFBN had a history of rapid cycling, including 10% who had a history of ultra-rapid cycling (rapid mood shifts within a month), and 20%

who had a history of ultradian cycling (rapid mood shifts within a day). Thus, even in this population characterized by relatively high rates of rapid cycling, the switch rates on bupropion, sertraline, or venlafaxine when used as adjuncts to previously inadequate mood stabilizers still remained relatively low. The only discriminating variable between those in the SFBN who switched on antidepressants and those who did not was that those with a history of 20 or more prior episodes of mania were more likely to switch than those without this history. These data would be partially convergent with the belief that those patients with a greater vulnerability to mania prior to institution of an antidepressant might be at greater risk for such a future switch into mania.

The role of the concurrent use of one or more mood stabilizers with an antidepressant in preventing the antidepressant-induced switch into mania also remains to be further explored. The SFBN data and those from other investigators suggest that the newer antidepressants may have a better therapeutic index in bipolar depression (degree of efficacy compared to side effects, including the induction of switching) than had previously been realized.

Altshuler et al. (1999) recently reported data indicating that patients with bipolar illness who discontinued their antidepressant were three times more likely to relapse into another depression than those who maintained their antidepressant in long-term prophylaxis (see last issue of *BNN*). Altshuler’s data were not collected as part of a controlled study, and whether these two groups were matched for

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**Clinical Trials Data**

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equal baseline severity and vulnerability remains to be determined. Nevertheless, the data from these and other sources suggest that using the newer antidepressants earlier to supplement mood stabilizers should be considered. ■

**//www: bipolar**

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

This new National Institutes of Health website has information on over 5,000 NIH-funded clinical trials nationwide, including whether or not the studies are recruiting patients and whom to contact for participation. Explore this website if you would like to participate in research and are looking for a study in your area.

**Bipolar Network News**

**Editors-in-Chief:**

Robert M. Post, MD  
Gabriele S. Leverich, MSW

The *BNN* is published four times a year by an international group of investigators working with patients with bipolar disorder to better understand the long-term course and treatment of the illness. The goal of the Network is to help develop new and more effective treatments for bipolar disorder.

Publication of the *BNN* is made possible by an unrestricted grant from Janssen Pharmaceutica (<http://us.janssen.com>), a division of the Johnson and Johnson company.



Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in summary or prepublication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact, omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the *BNN*.

For any comments or suggestions you may have, or to be placed on the mailing list, please contact us at:

**Bipolar Network News**

NIMH  
10 Center Drive  
Bldg. 10, Room 3S239  
Bethesda, MD 20892

Telephone: (800) 518-SFBN (7326)  
Fax: (301) 402-0052  
Website: [www.bipolarnetwork.org](http://www.bipolarnetwork.org)  
E-mail: [info@bipolarnetwork.org](mailto:info@bipolarnetwork.org)

**Research Update:**

**Placebo in Psychiatric Research**

The National Depressive and Manic-Depressive Association recently convened a consensus conference on the use of placebo in clinical trials of mood disorders (September 14–15, 1999). Clinicians, scientists, patient advocates, and experts in bioethics and biostatistics met to address many issues in the use of placebo in clinical trials. Recent newspaper articles and television reports have questioned the ethics of giving people with serious mental illnesses a placebo trial, thereby denying them the opportunity to receive a medication that might improve their illness. The *BNN* has also addressed this topic (see *BNN* Vol. 4, Issue 2, 1998, p. 2). The journal *Biological Psychiatry* recently published an issue (Vol. 47, Issue 8, April 15, 2000) entirely devoted to the findings and presentations of this conference. Below are some excerpts from that issue:

“A basic principle inherent to all research is that the patient experience no ‘unacceptable’ harm...This means that protocols including placebo control groups should provide for close monitoring, and if the patient does poorly study treatment should immediately be terminated and rescue treatments instituted. (p. 687)

“I recommend that free care be provided, equal in time to study duration, to patients who were terminated from the study due to side effects or lack of efficacy.” (p. 688)

- **Dennis S. Charney**, Yale University School of Medicine: *“The Use of Placebos in Randomized Clinical Trials of Mood Disorders: Well Justified, but Improvements in Design are Indicated”*

“...in mental disorders...there have been apparently well-designed trials in which the response to placebo was not only robust, but statistically indistinguishable from the response to the active compound....Thus, a new compound might look equivalent to an established medication, but without a placebo control one does not know whether the particular population enrolled in that particular trial would have improved in any event. (p. 689)

“NIMH-sponsored trials should include placebo conditions when alternative designs would not provide replicable and generalizable results. (p. 690)

“If symptoms have worsened or remained unimproved in people on placebos, then why not rerandomize such placebo nonresponders to standard or experimental treatment as soon as is reasonably appropriate?” (p. 690)

- **Steven E. Hyman, David Shore**, National Institute of Mental Health: *“An NIMH Perspective on the Use of Placebos”*

“...50 years of experience speak to the unique value and utility of placebo-controlled trials. There is little room for doubt that the continued use of placebo control groups is vital to the protection of the drug supply. Although respect for the interests of individual patients requires that placebo not be used in every setting and when used, used prudently, nothing requires that its use be proscribed absolutely.” (p. 705)

- **Paul Leber**, Neuro-Pharm Group LLC: *“The Use of Placebo Control Groups in the Assessment of Psychiatric Drugs: An Historical Context”*

“The ethical opposition to the use of placebos in clinical trials is based on the norm of medical ethics that physicians have an obligation to promote benefit to individual patients by providing optimal medical care....I contend that time-limited periods of treatment withholding in placebo-controlled trials of new psychiatric treatments may be ethically justifiable, provided that the design and conduct of these studies satisfy stringent ethical standards and guidelines. (p. 711)

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## Meeting Highlights

Society of Biological Psychiatry  
Chicago, Illinois, May 11–13, 2000



The Annual Meeting of the Society of Biological Psychiatry, held from May 11–13, 2000, in Chicago featured a number of presentations relevant to bipolar illness. Highlights included the following:

### ECT Update

Dr. H. Sackeim of Columbia University reviewed the clinical efficacy and side effects of electroconvulsive therapy (ECT), presenting convincing data that low-dose, right unilateral (one-sided) ECT was ineffective in two different studies of major depression (i.e., 23% improvement or 17% improvement, respectively). However, high-dose right unilateral ECT was as effective as bilateral (two-sided) ECT, and bilateral ECT clearly produced more lasting amnesia and memory defects (Sackeim et al., 2000; *Arch Gen Psychiatry* 57: 425–434). In addition, he presented new data on ultra-brief pulse right unilateral ECT in major depression (0.3 msec pulse width vs. 1.5 msec), resulting in less cognitive defect and faster patient re-orientation after ECT (McCall et al., 2000; *Arch Gen Psychiatry* 57: 438–444).

- Thus, if right unilateral ECT is considered (which it should be, to minimize the cognitive deficits associated with ECT), high intensity ECT is recommended. Sackeim et al. found that "...the likelihood of both antidepressant response and cognitive deficits increased as stimulus dose increased relative to initial seizure threshold, up through 8 to 12 times the threshold."

Using brain imaging, Dr. Sackeim found that even at high intensity stimulation, right unilateral ECT's effects were located largely on the right side of the brain. This finding is likely to account for the lack of severe adverse effects on learning and memory with right unilateral ECT, which most prominently involve the left hemisphere.

Decreased blood flow or metabolism in the frontal lobe and increased slow waves on the electroencephalogram (EEG) are both correlated with the degree of clinical response to ECT. Patients who had substantial decrements in these indices of prefrontal activity tended to respond well to ECT, whereas those without these changes were generally nonresponsive.

Dr. Sackeim and colleagues have designed an ultra-powerful magnetic stimulator of the brain for eliciting a motor seizure (with more precision than ECT, because of the use of magnetic, rather than electric, seizure induction). The first patient successfully treated with magnetic stimulation therapy (MST) was rapidly oriented after the procedure and spoke to the investigators with a smile. Whether better control over the parameters of the seizure process with MST vs. ECT will provide a better therapeutic index remains to be determined.

- MST uses a specially designed magnetic stimulator and generally produces opposite effects of conventional repeated transcranial magnetic stimulation (rTMS) of the brain. During conventional rTMS only low stimulation intensities are given, sufficient to activate the motor cortex, produce minor muscle twitches, and have direct effects on other areas of brain, in each instance without the induction of a seizure.

### Neuropathological Findings

Dr. G. Rajkowska of the University of Mississippi presented findings from the brains of 10 bipolar patients examined at autopsy compared with 11 nonpsychiatric control subjects. Dr. Rajkowska found a decreased density of layer 3 in the dorsolateral prefrontal cortex (Brodmann's area nine), comprised of a decrease in the numbers of pyramidal cells but not other neuronal ele-

ments, a decrease in glial cell density, and an increase in glial size. In two of her separate autopsy studies of patients with schizophrenia (Selemon et al., 1995, *Arch Gen Psychiatry* 52: 805–818; Rajkowska et al., 1998, *Arch Gen Psychiatry* 55: 215–224), there were increases in neuronal density and non-significant increases in glial density in these areas, in contrast to the significant decrements in these brain areas in bipolar patients. Her findings in bipolar illness were similar to those in another study of patients who died with unipolar illness (Rajkowska et al., 1999; *Biol Psychiatry* 45: 1085–1098) and suggest some selective neuropathological changes in the affective disorders compared with schizophrenia on these measures of neuropathology.

Dr. R. Deicken of the University of California at San Francisco reported on measurements of *N*-acetylaspartate (NAA), a marker of neuronal/axonal integrity, in the dorsolateral prefrontal cortex of 11 medicated euthymic bipolar I patients compared with 11 control subjects. Using magnetic resonance spectroscopy (MRS), he found that bipolar patients showed: 1) decreased dorsolateral prefrontal cortex NAA bilaterally; 2) decreased prefrontal white matter NAA bilaterally; and 3) increased thalamic NAA bilaterally.

- These data thus supplement a growing amount of structural imaging data suggesting alterations in size or chemistry of the prefrontal cortex, amygdala, and hippocampus in bipolar patients compared with controls.

### rTMS Update

Dr. L. Grunhaus of Sheba Medical Center, Israel, presented data on 40 patients randomized to ECT versus 41 patients

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## Meeting Highlights: Biological Psychiatry (Continued from page 3)

randomized to repeated transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex at 10 Hz and 90% of motor threshold for 80 seconds/day for up to 20 days. Dr. Grunhaus found that rTMS and ECT were generally equally effective in patients with nondelusional major depression (19 of 26 [75%] responded to ECT, 16 of 28 [57%] responded to rTMS), but ECT was highly superior in those with delusional depression (i.e., nine of 14 [64%] responded to ECT, three of 13 [23%] responded to rTMS). Twelve of the patients who received ECT were complete responders, and 16 were partial responders; with rTMS, 11 were full responders and 11 were partial responders.

- These positive data of Grunhaus appear similar to those of Janicak et al. (2000) and in contrast to the reports of many other groups who used rTMS for patients with refractory depression. In these instances, the effects of active compared with sham stimulation are often statistically significant, but the magnitude of effect does not generally appear to be clinically robust.

Dr. A. Speer of the National Institute of Mental Health (NIMH) presented data on normal volunteers given different intensities (80, 90, 100, 110, or 120% of motor threshold) of rTMS at 1 Hz while they were in the positron emission tomography (PET) scanner. Different pathways were activated with stimulation over the motor cortex (M1) versus the prefrontal cortex; these data will help establish what areas and intensities may be more effective for approaching different neuropsychiatric illnesses. In particular, the higher intensities appeared to have a much wider distribution of neuroactivation measured on the PET scan, suggesting, potentially, the greater clinical utility of the higher intensities in some syndromes.

- These data are interesting in relation to the study of the effects of rTMS at 100%

of motor threshold over ten days in 10 depressed patients (Speer et al., 2000; *Biol Psychiatry*, in press). In this instance, 1 Hz rTMS was found to decrease activity in frontal cortex and left amygdala, whereas 20 Hz stimulation was found to more widely increase brain activity in the frontal cortex, thalamus, striatum, and cerebellum bilaterally as well as unilaterally in the left amygdala, providing the first evidence that the pulse frequency of rTMS may exert different effects on brain activity. These effects lasted for three days following the last rTMS stimulation, suggesting that some of these neural adaptations may be relatively long-lasting.

Dr. R. Hoffman from Yale University presented data on the effects of rTMS on auditory hallucinations in patients with schizophrenia. In one study, Dr. Hoffman and colleagues stimulated twelve schizophrenic patients with medication-resistant auditory hallucinations with 1 Hz rTMS at 80% motor threshold or sham for 4–16 minutes over 4 days in a double-blind, crossover design. Eight of 12 individuals with active stimulation showed significant improvement in auditory hallucinations compared with sham stimulation. However, in a second study using 90% of motor threshold and a different type of magnetic stimulator, a total of 132 minutes of rTMS over this area of brain (compared with 40 minutes of such stimulation in the first study) was associated with nonsignificant degrees of clinical improvement. This result was nonsignificant partially because some of the sham patients reported lasting improvement in their auditory hallucinations and whereas the patients who had intermittent hallucinations showed rather dramatic effects of active stimulation, those with constant hallucinations showed little change.

- Thus, the ultimate utility of rTMS for suppressing auditory hallucinations in schizophrenia remains to be further explored and better defined. Although

five of the six improved patients in the second study had sustained remissions following active rTMS, several of the patients who improved with sham stimulation also had sustained periods of improvement, indicating the importance of placebo controls in determining the actual therapeutic benefit related to the specific procedures involved rather than to the overall context of the experimental situation.

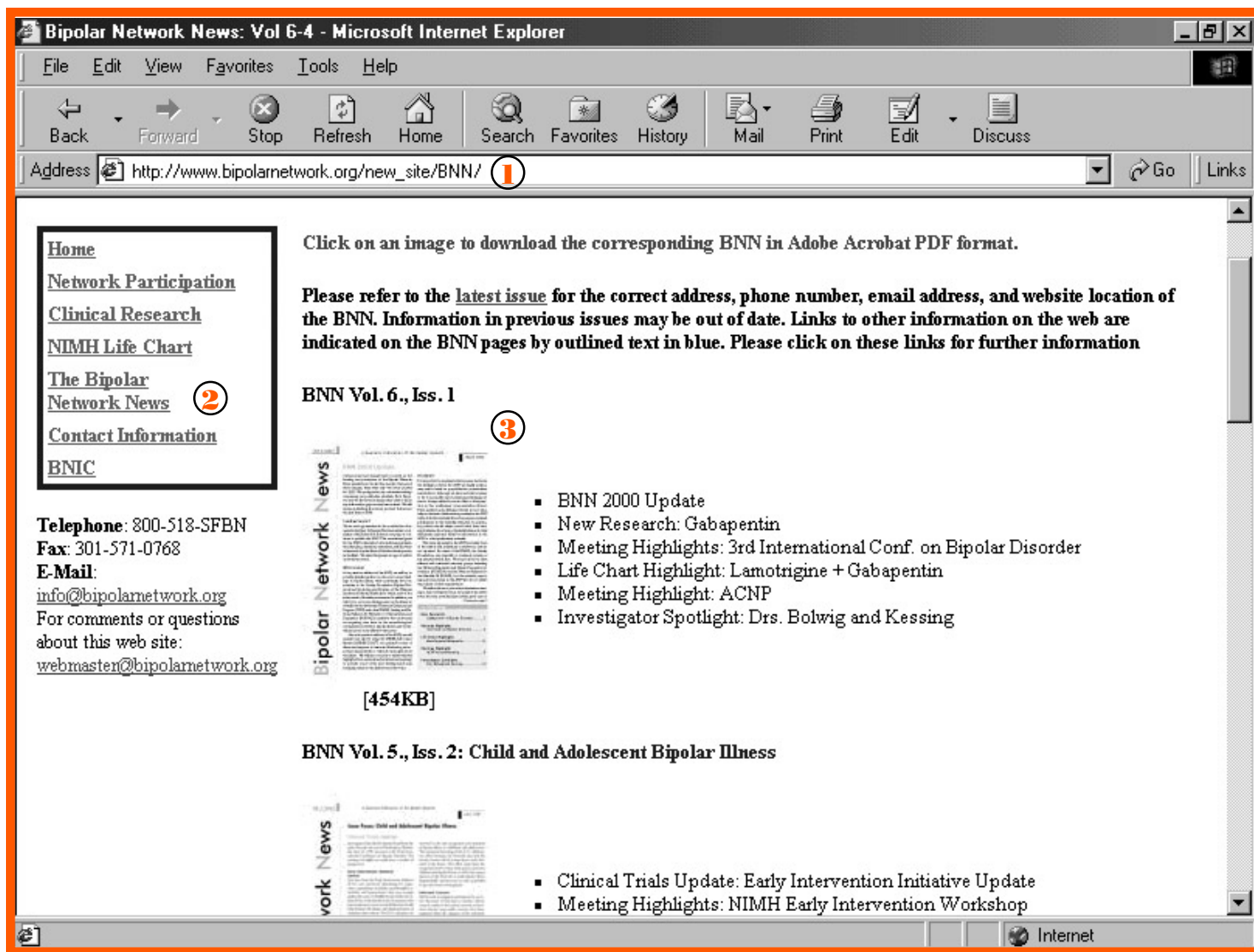
### The Vagus Nerve

Dr. P. Faris, Dr. B. Hartman, and Dr. E. Eckert, from the University of Minnesota, presented evidence that the vagus nerve (from the stomach to the brainstem) is hyperactive in bulimia, and inhibiting the vagus nerve with ondansetron (Zofran®) is highly effective in decreasing binge eating behavior. They presented data from a 4-week, double-blind clinical trial indicating the highly significant efficacy of ondansetron (24 mg/day, given in six 4mg doses) compared with placebo in 26 patients with severe bulimia nervosa (Faris et al., 2000; *The Lancet* 355: 792–797). There was a decrease in the number of binges, the urge to binge, the amount of food in the binge, and the feeling of bloating, and an increase in the normal number of meals. These patients also had a significant decrease in their Beck Depression Inventory scores on ondansetron. In animal studies, data were presented that the vagus nerve is important for learning and memory, and an optimal amount of vagus nerve stimulation after short-term learning has occurred is important for its long-term coding into memory.

- These observations are consistent with the preliminary efficacy of ondansetron and vagus nerve stimulation studies in humans. As reviewed in the last *BNN*, vagus nerve stimulation may be an effective treatment approach for patients with refractory depression, although controlled studies remain to be completed (Rush et al., 2000; *Biol Psychiatry* 47: 276–286).

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# New BNN Web Page!!



The *BNN* webpage was recently updated and revised for easier use. Every issue of the *BNN* is now available at [www.bipolarnetwork.org](http://www.bipolarnetwork.org) (1) Just click on the section “The Bipolar Network News” (2) on the left hand side of the page, and then click on the image of the issue (3) you want to view. Past issues of the *BNN* are now in Adobe Acrobat Reader format, a program that comes with most Internet browsers.\* Some *BNN* readers have called asking for specific back issues, and the new web site should be the fastest way to get specific issues of interest. As noted on the web page, links to other information (such as journal article abstracts) are indicated by text outlined in blue; click on these links for more information. If you have any problems with or suggestions for the *BNN* page, please contact us at [webmaster.bipolarnetwork.org](mailto:webmaster.bipolarnetwork.org).

\*If you need the Adobe program to view the issue you select, go to <http://www.adobe.com/products/acrobat/readstep.html> and follow the instructions for downloading.

## Life Chart Highlight

### Remission in a patient with bipolar illness and post-traumatic stress disorder (PTSD)

Bipolar illness is often associated with a variety of other comorbid conditions. Forty percent of bipolar patients in the Stanley Foundation Bipolar Network have experienced an anxiety disorder, and 40% have also suffered from an associated substance abuse disorder (either alcohol or other substances of abuse). In this life chart highlight, we discuss the pharmacotherapy of a patient with bipolar disorder who also suffered from many PTSD symptoms. Because of these two conditions, the patient had been almost completely incapacitated for several years and had not responded to a variety of conventional pharmacotherapies. As illustrated, the patient experienced a full remission on the combination of lamotrigine (Lamictal®), gabapentin (Neurontin®), and carbamazepine (Tegretol®).

#### Retrospective

The patient's retrospective life chart history (Figure 1) is striking for the occurrence of a series of horrific stressors, including a history of early physical and sexual abuse, many other psychological and physical assaults in her youth and adulthood, and an adult episode of sexual assault. In addition to her mania and depression, the patient had many PTSD symptoms, including an almost life-long sleep disturbance with insomnia, nightmares, and frequent awakenings; evidence of hyperstartle; spontaneous flashbacks; and a considerable degree of withdrawal and numbing. These symptoms are typical of the PTSD diagnosis, along with evidence of initial single or multiple severe stressors. The patient had previously inadequate response to a variety of mood stabilizers and antidepressants for both her bipolar and PTSD symptoms (Figure 1).

#### NIMH Treatment

As illustrated in Figure 2, this extreme incapacitation continued to be observed at the National Institute of Mental Health (NIMH) (1998–1999); she was often unable to leave her bed or room, overwhelmed by extreme anxiety, flashbacks, and associated depressive symptoms. She volunteered to participate in a clinical trial of repeated transcranial magnetic stimulation (rTMS) of the brain for her PTSD. This trial involved 1 month of randomly-assigned treatment with either sham or 1 Hz (active) rTMS over the right prefrontal cortex, with a frequency of one stimulation/second for 20 minutes/day and a crossover to the other treatment.

Disappointingly, the patient failed to improve to any substantial degree in either phase of the rTMS trial, and was offered the opportunity to participate in a double-blind, randomized controlled trial of lamotrigine, gabapentin, and placebo, with each phase lasting six weeks. Neither the staff nor the patient were aware as to which medication was used in any phase; only the pharmacist knew the code, in case there were problematic side effects and the blind needed to be broken for safety reasons.

In phase I, the patient showed very substantial improvement in her depression and PTSD symptoms, and this improvement continued to some extent in phase II (Figure 2). Her condition worsened convergent with a series of recurrent stressors. The patient had to return home for an important event in the family, and elected to continue on the blind drug phase II and enter phase III of the study upon her return. Phase III was associated with further return of her initial symptomatology, and therefore phase

III was terminated early. The patient then chose to be (blindly) reexposed to the agent associated with the greatest initial improvement, as observed in phase I.

The phase I agent was lamotrigine, the phase II agent was gabapentin, and the phase III agent was placebo (Figure 2). The patient's improvement on lamotrigine was not as complete as it was initially, so the phase II drug gabapentin (still on a blind basis) was added to lamotrigine. The patient continued to be moderately symptomatic, experiencing a recurrence of sleep disturbance, nightmares, flashbacks, and a generally heightened level of depression and anxiety.

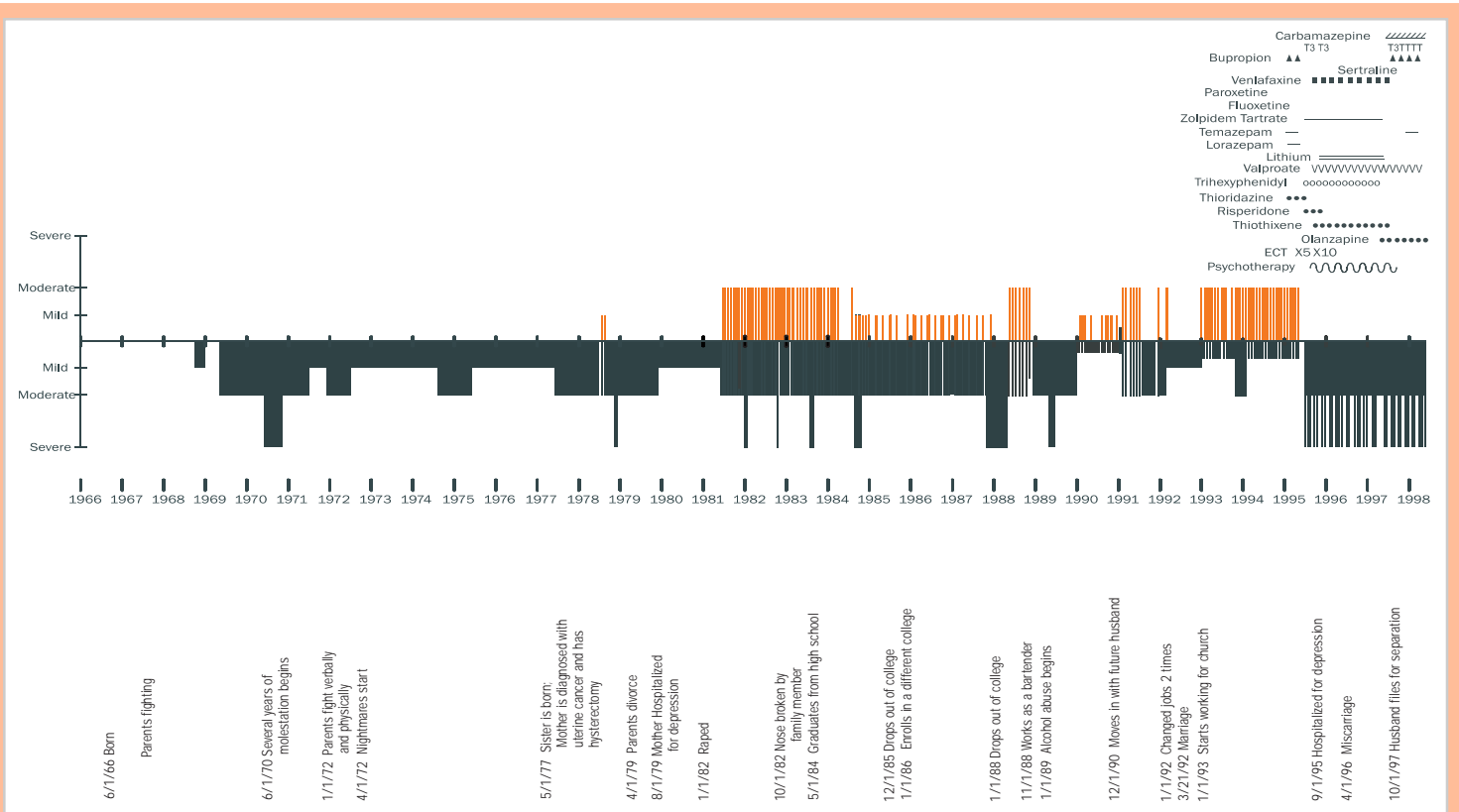
Carbamazepine was added to the two other anticonvulsant drugs, and remission was almost immediate, complete, and maintained for the rest of her inpatient hospital stay. The patient was able to experience positive affect, enjoy herself, and return to work for the first time in many years.

#### Therapeutic Lessons

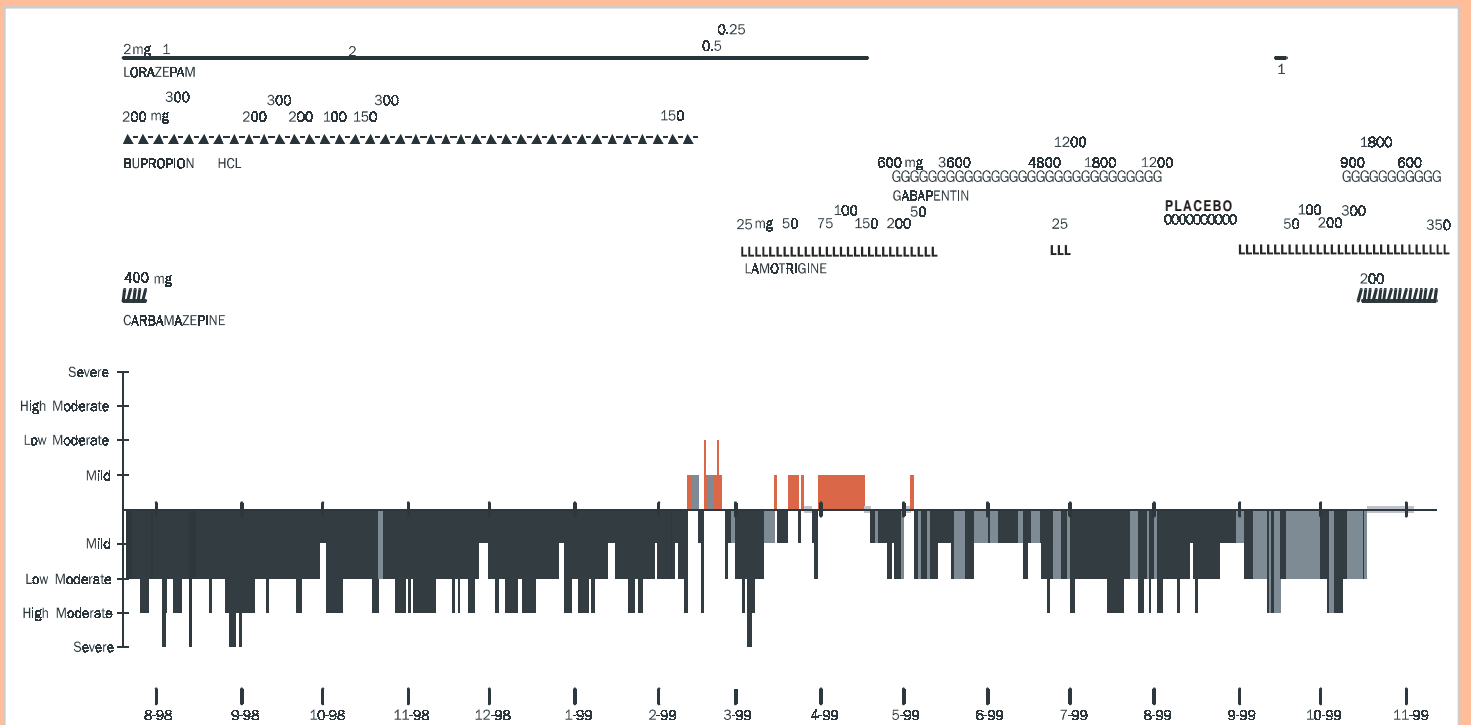
This life chart highlight illustrates a number of important principles in the treatment of bipolar illness and PTSD:

- Despite many unsuccessful clinical trials, new medications or combinations of drugs may still produce remarkable clinical improvement. Over the last 25 years, multiple medications have been increasingly used in order to achieve remission (Frye et al., 2000; *J Clin Psychiatry* 61:9–15); in this case, three different anticonvulsant drugs were used.
- Lamotrigine has emerged as a significant treatment option for patients

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**Figure 1:** Retrospective life chart showing a 28-year history of depression, ultra-rapid cycling, and PTSD.



**Figure 2:** Prospective life chart showing excellent antidepressant response to lamotrigine; remission achieved on lamotrigine and gabapentin combination therapy with the addition of carbamazepine. Note: Gray area is missing data.

## Life Chart Highlights

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whose illness has not responded to other treatments (Frye et al., 2000, *J Clin Psychopharmacol*, in press; Calabrese et al., 1999, *J Clin Psychiatry* 60: 79–88). However, lamotrigine must be used carefully and dosages increased very slowly, because rapid dose escalation appears to increase the risk of a very severe rash associated with exfoliative dermatitis (sloughing off of the skin), typically requiring emergency medical treatment and hospitalization (in approximately 1 in 300 adults and 1 in 100 children) (Guberman et al., 1999; *Epilepsia* 40: 985–991). Nonetheless, if one proceeds slowly, there is a reduced chance of developing a severe rash, and other side effects of the drug tend to be minimal, making it a generally well-tolerated and highly effective medication.

- A range of anticonvulsants may be effective in the treatment of PTSD. A preliminary report suggests that lamotrigine may be effective in PTSD (Hertzberg et al., 1999; *Biol Psychiatry* 45: 1226–1229), as it was in the patient illustrated (Fig. 2). Previous studies suggested that both carbamazepine and valproate (Depakote®) also helped some components of patients with PTSD symptoms, particularly insomnia, sleep disruption, and nightmares (Ford, 1996; *J Trauma Stress* 9: 857–863). The serotonin-selective antidepressant sertraline (Zoloft®) is the only agent currently approved for the treatment of PTSD; in this patient, a variety of serotonin-selective antidepressants had previously failed to produce any amelioration of her symptoms, however.

- Carefully charting a course of illness and response to treatment facilitates the optimal development of pharmacotherapeutic regimens which, in some cases, are complex. This patient was extremely diligent in charting her mood for both her bipolar illness and PTSD symptoms. Both types of forms

(retrospective and prospective) are available upon request. Life charting allows one to delineate subtle degrees of improvement or deterioration with the addition or subtraction of a different drug, and provides important clues to an overall assessment of the risk-to-benefit ratio of a given drug in the context of the entire treatment regimen.

- Gabapentin may play a role in some components of bipolar illness, despite several recent negative controlled studies, including our own at the NIMH (see *BNN* Vol. 6, Issue 1). Gabapentin has a quite benign side-effects profile even at high doses, and shows positive effects in anxiety disorders (particularly social phobia), pain syndromes, tremor, restless leg syndrome, obsessive-compulsive symptoms, Parkinson's disease, and alcohol withdrawal.

- Carbamazepine remains a drug with considerable utility in the treatment of bipolar disorder, even though it is often the third choice after lithium and valproate, largely because of the possibility of multiple drug interactions and the fear of exceedingly rare but serious hematological side effects.

- Even the most severe treatment-resistant mood disorder can sometimes be successfully treated; this patient heroically struggled with her traumatic abuse history and comorbid PTSD and bipolar illness to achieve remission. All patients may not achieve as dramatic a degree of a clinical response as this patient, but in our experience such a complete remission of symptoms can sometimes be achieved. The vast majority of patients with bipolar disorder, even with the additional burden of a comorbid condition such as PTSD, can have very substantial improvement in their illness, especially with careful mapping of its course and collaboration with one's treatment team. ■

## Meeting Highlights: Biological Psychiatry

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### Deep Brain Stimulation

Dr. R. Kumar, from the University of Colorado, presented data on deep brain stimulation (DBS). In DBS, a thin electrode is inserted directly into the brain; different currents are then applied at varying lengths until desired effects are achieved. Dr. Kumar used DBS in the frontal striatal loop of the brain in patients with Parkinson's disease. He noted that similar procedures in the dorsolateral, the lateral orbital, and the anterior cingulate loops may ultimately be used for patients with psychiatric illness as well. Both a direct and indirect pathway go from the striatum to the thalamus, and the indirect pathway goes through the subthalamic nucleus. When the subthalamic nucleus is stimulated in patients with Parkinson's disease, there is marked improvement in many symptoms, and subthalamic nucleus stimulation has become an important therapeutic tool in the treatment of drug-resistant Parkinson's disease. Two of the approximately 100 patients he studied had hypomanic symptoms, such as elevated mood, increased libido, and spontaneous and uncontrolled laughter. Laughter can be evoked not only by stimulation of the subthalamic nucleus, but also by stimulating the supplementary motor area, the anterior cingulate gyrus, and the basal temporal lobe. These data give insights into potential circuits relating to positive modulation of mood.

Conversely, Dr. Kumar noted the data of Bejjani et al. (1999; *N Engl J Med* 340: 1476–1480) wherein stimulation of the left substantia nigra, pars reticulata induced profound depression in a patient who became tearful 17 seconds after beginning the stimulation, and within four minutes was despairing, suicidal, and sobbing. One minute after discontinuing the stimulation, she was joking with investigators about the depth of her prior paroxysmal depression which she described as being "sucked into a black hole." Such depression induction

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## Meeting Highlights

Psychiatric Research Society  
Park City, Utah, February 9th–12th, 2000



The Psychiatric Research Society held its annual meeting from February 9<sup>th</sup>–12<sup>th</sup>, 2000, in Park City, Utah. Considerable data of interest to bipolar illness were reported.

### Lithium

A special symposium was held commemorating the 50<sup>th</sup> anniversary of the use of lithium. Dr. F. Goodwin of George Washington University began the symposium by noting the substantial database of double-blind studies using lithium; of 186 patients with bipolar illness randomized to lithium, 20% had episode recurrence, in contrast to 187 patients on placebo who had a 73% recurrence rate. Similarly, in unipolar depression, there was a 22% relapse rate for those on lithium compared with 65% on placebo. Dr. Goodwin noted the decreasing average age of onset of bipolar illness occurring roughly in parallel with the increasing use of cocaine and speculated about whether the two were related.

Dr. P. Grof of the University of Ottawa, Canada, reviewed the data from the study by Maj et al. (1998; *Am J Psychiatry* 155: 30–35), following 402 patients who had been on lithium for at least 5 years; of the 359 patients available for follow-up, only 68% were still on lithium, and of those 38% showed a complete response, 47% a partial response (i.e., at least one episode recurrence but 50% reduction in hospitalization), and 15% a poor response. Thirty-seven percent of patients discontinued their lithium because of lack of efficacy. Maj also found, as have other investigators, that patients with fewer prior episodes and hospitalizations before starting lithium prophylaxis were among the better responders.

- These latter data suggest the importance of starting treatment early and

maintaining it for prevention (pharmacoprophylaxis) to get the best lithium response.

Dr. L. Tondo of the University of Cagliari, Italy, discussed the antisuicide effects of using lithium, which in his studies resulted in an average seven-fold reduction in suicide during treatment compared with pretreatment. Moreover, in the first year following lithium discontinuation, the risk of suicide increased 20-fold, but by the second year was back to baseline. Rapid discontinuation of lithium was associated with both an increased risk of relapse into an affective episode and a suicide attempt, compared with a slow taper. In Dr. Tondo's private clinic, 65% of those patients who discontinued lithium did so because they felt well!

- The potentially catastrophic increased risk not only for episode recurrence but also for death by suicide following lithium discontinuation suggests that it may be important to continue lithium therapy even in instances where its effects on mood stabilization are not overwhelming, i.e., it may have significant antisuicide effects separate from its effects on mood disorder (Muller-Oerlinghausen et al., 1992; *J Affect Disord* 25: 261–269).

Dr. G. Moore of Wayne State University reported on data from his studies in collaboration with Dr. H. Manji. They found that lithium decreased brain choline levels in the frontal cortex after 3–5 days of treatment, and that this effect was larger in responders to lithium than nonresponders. Lithium was also found to increase the neuroprotective factor Bcl-2 in rat frontal cortex; Bcl-2 increases growth of central nervous system axons. Dr. Moore indicated

that even low lithium levels (0.3 mEq/L) increased Bcl-2 in the rat brain, suggesting the potential importance of this neurotropic factor in the normal range (0.5–1.2 mEq/L) of lithium clinical therapeutics. Moore et al. also found, using magnetic resonance spectroscopy (MRS), that lithium increased N-acetylaspartate (NAA) in all regions of brain. NAA is a marker of neuronal integrity.

- We have therefore arrived at the point where our pharmacotherapies not only have known effects on the biochemistry of the brain, but also on its substance and structure as they increase both neuroprotection and neurogenesis, providing another reason to remain on lithium. In addition to its proven efficacy in decreasing episode recurrence and lowering the risk of suicide, lithium may be not only neuroprotective, but also capable of engendering the birth of new nerve cells (neurogenesis).

Dr. Grof also reviewed data from his studies of a subgroup of patients who have long-term and complete remissions on lithium therapy. Dr. Grof found that the children of patients who respond well to lithium also have an excellent response to lithium compared with the children of lithium-nonresponders. Thus, lithium response appears to be consistent within families. In this subgroup of highly lithium-responsive patients, response also appeared to be associated with a specific M antigen, a normal MMPI profile, and weight gain (disappointingly). Response in this subgroup was not related to age, gender, or the number of previous episodes, in contrast to many other studies in nonselected patients

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in whom number of prior episodes conveys a negative prognostic impact for lithium response. Dr. Grof followed 164 patients with an average of 8.9 prior episodes for an average of 16 years on lithium monotherapy treatment. The children of these excellent lithium responders responded well if they had an *episodic* course, and 17 of 20 relatives also responded to lithium, even when their clinical course was not classically bipolar.

### Genetics

Given the homogeneity of this highly responsive patient population, Grof and colleagues examined 378 genetic markers and found a linkage between bipolar illness vulnerability and loci on chromosomes 15q14 and 7q11. They also replicated the finding of an allele on chromosome 5, which has been identified as the encoding phospholipase C gamma-1, the presence of which doubles the risk of inheriting bipolar illness. Phospholipase C is involved in phosphoinositol turnover, which some investigators believe is important to lithium's mechanism of action.

- These very exciting findings suggest the importance of studying homogeneous populations (in this case chosen for lithium responsiveness) in trying to discover linkages and vulnerability markers that might be involved in the pathophysiology of bipolar illness.

Dr. J. Rausch from the Medical College of Georgia reported that the affinity of the serotonin transporter and its different forms (polymorphisms) are associated with antidepressant response to the serotonin-active drug fluoxetine (Prozac®).

- These data provide a first glimpse into how the new genetics may help determine the most appropriate drugs for a given individual, long before the new genetics revolution is likely to provide the anticipated data about the pathophysiology of the illness itself.

Dr. Nurnberger from Indiana University reported that depression in conjunction with increased alcohol use appears to be passed down in families. Families of individuals with both depression and alcoholism show a 16% prevalence of such comorbidity in first degree relatives compared with 12% in relatives of individuals with alcoholism alone and 4% in relatives of control subjects. Dr. Nurnberger and colleagues found a gene locus on chromosome 1 that may predispose to alcoholism in some individuals and to depression in others.

Dr. Nurnberger also reported that, in males, bipolar I illness was associated with a 2.1 times increased risk of alcoholism, and bipolar II illness with a 1.9 times increased risk. Remarkably, in females, there was an 8-fold increased risk of alcoholism in those with bipolar I or II illness. Thus, even though there is a higher rate of alcoholism in males compared with females in the general population and in bipolar patients, females with bipolar illness are at an especially greater risk for development of such problems.

- A greater awareness of this association, and active therapeutic approaches for comorbid alcoholism in women with bipolar illness, are greatly needed. These could include direct queries about problems in this area and appropriate institution of preventive and, if needed, adjunctive therapeutic programs.

### Imaging

Dr. S. Taylor and Dr. I. Liberzon from the University of Michigan used positron emission tomography (PET) to study new opioid systems and the functional anatomy of emotions. They used a variety of provocative stimuli to evoke emotional responses in control subjects and demonstrated activation of limbic regions, particularly the amygdala and subthalamic areas. They also used a new opioid receptor ligand ([11C] carfentanil) as well as <sup>15</sup>O water to show that

the left amygdala and adjacent cortex were activated with exposure to pictures conveying negative affects.

- These data are highly convergent with the studies of Ketter et al. (1996; *Arch Gen Psychiatry* 53: 59–69) with procaine and George et al. (1998; *Behav Modif* 22: 192–204) with emotion induction, showing that the left amygdala increased activity with the induction of sadness and dysphoric or anxiety-provoking stimuli, whereas it decreased activity with the induction of happiness and procaine-related euphoria. In contrast, the right amygdala activated in proportion to any emotion regardless of its valence. NIMH patients with bipolar illness have been found to have increased activity (metabolism) in the right amygdala even at baseline.

### Antidepressants

Dr. F. Quitkin of Columbia University reviewed the validity of clinical trials of antidepressants, in light of the considerable negative press generated by some recent and widely published critics of antidepressant studies impugning the study designs, the adequacy of the double-blind, and other elements that led to a general questioning of their validity. Dr. Quitkin did a meta-analysis and examined the specific studies cited in these reports in a rigorous fashion. He found that: 1) the original sources failed to prove the assertion that standard antidepressants are no more effective than placebo; 2) contrary to what had been claimed, there was no evidence that active placebo offered an advantage over inactive placebo; 3) there was no substantial evidence to suggest that the raters' guesses about which subjects were on active treatment or placebo exceeded chance or that the raters in these studies were otherwise biased; and 4) standard, older antidepressants yielded a 65% response rate, the new antidepressants yielded a 66% response rate,

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and placebo had a 39% response rate, and thus there was no evidence, as claimed by critics, that standard antidepressants were no more effective than placebo in studies of the new antidepressants.

Dr. Quitkin suggested that some researchers have indicated that "allegiance effects" can complicate interpretation of psychotherapy trials. Although he acknowledged that the issue of bias and/or allegiance effects in both antidepressant and psychotherapy research is real and must be guarded against in clinical studies, he found that detailed examination of the literature did not yield the conclusive evidence that antidepressant trials were invalid as a few vocal critics had claimed.

Dr. P. McGrath, also from Columbia University, reported new data that fluoxetine and imipramine were both effective in the acute treatment of atypical depression in 154 subjects. Both medications were significantly better than placebo and did not differ from one another, although significantly more patients dropped out of treatment with side effects from imipramine than fluoxetine. He concluded that despite earlier data that serotonin-selective reuptake inhibitors (SSRIs) might be the treatment of choice, fluoxetine appeared to be no better than imipramine in atypical depression, although it was better tolerated.

### Early Onset Bipolar Illness

Dr. R. Post of the Biological Psychiatry Branch, NIMH, presented the data of Fergus et al. (2000) based on parental report of their children's behavior, indicating that there were four factors associated with early onset bipolar illness. Factor II, named "irritability and dyscontrol", included temper tantrums, poor frustration tolerance, impulsivity, increased aggression, decreased attention span, hyperactivity, and irritability. Factor II distinguished children with a later diagnosis of bipolar illness from the comparison groups (unipolar illness, attention deficit-hyperactivity disorder

### Research Update

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"The ethical criticism of placebo-controlled trials, however, has merit in drawing attention to the need for ethical scrutiny and justification of studies using this research design." (p. 714)

- **Franklin G. Miller**, NIH, Dept. of Clinical Bioethics: "Placebo-Controlled Trials in Psychiatric Research: An Ethical Perspective"

"...a variety of alternatives and modifications to the traditional randomized parallel group, placebo-controlled trial can be implemented that are better matched to the needs and illness characteristics of bipolar patients, balancing both ethical risks and scientific rigor. (p. 731)

"Individually designed off-on-off-on (B-A-B-A) clinical trials have underappreciated merit in ascertaining the initial potential efficacy of an agent, both with their ability to confirm individual responsivity early in a drug's evaluation...and sparing nonresponders from a mandated placebo period...that is, patients are blindly placed on an active compound (A) and if they do not respond, no further placebo phase (B) is required. If they do respond, however, a placebo phase may be utilized in order to ascertain whether the response was likely to be spontaneous (related to the course of illness) or drug A-related." (p. 729)

- **Robert M. Post, Kirk D. Denicoff, Gabriele S. Leverich**, Biological Psychiatry Branch, NIMH: "Special Issues in Trial Design and Use of Placebo in Bipolar Illness"

[ADHD], and other diagnoses) as well as controls (with no diagnosis) at the earliest age. By age three, five of these irritability and dyscontrol symptoms were 10% more prevalent in the bipolar group compared with the comparison groups. In contrast, factors relating to more classical components of bipolar illness, such as factor I (depression), factor III (mania), and factor IV (psychosis/suicidality), only began to discriminate the children with bipolar illness from the others by age eight for factors I and III, and by age 11 for factor IV. Of the seven symptoms in factor II, temper tantrums, hyperactivity, and poor frustration tolerance discriminated the bipolar children from the non-bipolar children the earliest (beginning at age 2), followed by impulsivity at age 3, irritability at age 8, decreased attention span at age 11, and increased aggression at age 14. See *BNN* Vol. 5, Iss. 2, 1999, for a more complete discussion of early childhood and adolescent bipolar illness, or the book *The Bipolar Child*, by Papolos and Papolos (2000; Broadway Books). ■

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has also been observed on occasion with left anterior thalamic stimulation, left amygdala stimulation, left orbit stimulation, as well as right parietal cortex stimulation.

Thus, whereas paroxysmal laughter associated with seizures (gelastic epilepsy) is generally related to a seizure focus on the right side of the brain, using DBS in patients with Parkinson's disease, depression appears more associated with left hemisphere seizure foci and direct stimulation of the left side of the brain. Dr. Kumar speculated on the eventual use of DBS for obsessive-compulsive disorder wherein a number of successes have been reported, and perhaps in Tourette's syndrome in which one case of bilateral thalamic stimulation was believed to be effective. ■

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## **Bipolar Network News**

NIMH

10 Center Drive

Bldg. 10, Room 3S239

Bethesda, Maryland 20892

[www.bipolarnetwork.org](http://www.bipolarnetwork.org)

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### **In This Issue:**

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Biological Psychiatry Annual Meeting

Bipolar Disorder and Comorbid PTSD

Psychiatric Research Society Meeting

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