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## Departments

### New Research

New developments in the magnetic stimulation of the brain offer new potential treatment options in the future, if substantiated in controlled clinical trials.

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### Meeting Notes

In part II of our coverage of the Fifth International Conference on Bipolar Disorder, we focus on presentations concerning pediatric bipolar disorder, neurobiology, and other topics.

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### Rapid Cycling

New data from the largest and most comprehensive study of rapid cycling versus non-rapid cycling bipolar patients reveals some surprising findings, some in contrast to previous research.

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## Meeting Highlights

American College of Neuropsychopharmacology (ACNP)  
42<sup>nd</sup> Annual Meeting, December 7–11, 2003

The 42<sup>nd</sup> annual meeting of the ACNP in December of 2003 featured a wide variety of interesting findings on bipolar disorder and related topics. These new data are summarized here. *Editorial comments are in italics.*

### Brain Imaging

The brain activation patterns of five children and adolescents (average age 12.7 years) diagnosed with bipolar disorder were studied before and after 12 weeks of divalproex (Depakote<sup>®</sup>) monotherapy by Dr. K. Chang (Stanford University) and colleagues using functional magnetic resonance imaging (fMRI). Each of the patients had a parent with bipolar I disorder. Decreases in brain activation were found while performing attention and affect-related tasks after 12 weeks of divalproex; the decreases were primarily seen in left prefrontal cortex, thalamus, striatum, and bilateral insula.

*These findings were consistent with earlier findings from these investigators of prefrontal, thalamic, striatal, and limbic overactivation in euthymic bipolar patients performing the same tasks, i.e., valproate may help normalize overactivated areas.*

Dr. M. DelBello (University of Cincinnati) and associates examined neurochemical effects and predictors of response to pharmacological treatments for adolescent bipolar disorder using magnetic resonance spectroscopy (MRS). In a study of 28 days of olanzapine (Zyprexa<sup>®</sup>) treatment in 20 manic adolescents hospitalized for the first time, MRS revealed that elevated baseline choline and gamma-aminobutyric

acid (GABA) in prefrontal gray and white matter, respectively, predicted remission with olanzapine (58% met remission criteria). Patients who remitted had a statistically significant increase in prefrontal gray matter N-acetylaspartate (NAA) compared with non-remitters. In a second study of lithium in 20 adolescents with bipolar depression, elevated baseline myo-inositol predicted treatment response.

Two different studies by Dr. J. Soares (University of Texas Health

New data on course of illness, response to treatment, predictors of response, childhood and adolescent bipolar illness, and neurobiology

Science Center, San Antonio) and colleagues found correlations between amygdala volumes and age in bipolar patients. The first study used MRI in adult unipolar (n=31) and bipolar patients (n=51), and healthy controls (n=71) to study the hippocampus and amygdala. They found that age was directly correlated with left amygdala gray matter volume in unipolar and bipolar patients. In the second study, Dr. Soares used MRI and MRS to study 16 bipolar adolescents and three healthy controls (ages 10–21). He did not find any significant differences in right or left hippocampus or right amygdala volumes compared with healthy controls, but did find a nonsignificant trend for smaller left amygdala volumes in bipolar patients. Dr. Soares saw a direct

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## Four Types of Magnetic Brain Stimulation Studies in Bipolar Illness

There has been renewed interest in the potential clinical utility of brain stimulation using exogenous electromagnetic fields from four different sources; these four sources (I-IV) are briefly summarized here.

### I. EP-MRSI

The most recent novel approach to brain stimulation treatment for patients with bipolar disorder was discovered by accident, by colleagues at McLean Hospital. First reported at the 2003 American



College of Neuropsychopharmacology (ACNP) meeting in December 2003, when these investigators were using echo-planar magnetic resonance spectroscopic imaging (EP-MRSI) during a study to determine how the brain chemistry of bipolar patients is different from people without the illness, several depressed patients with bipolar disorder emerged from the scanner happier than when they went in. Several patients were laughing when they came out. The researchers conducting the original study told Dr. B. Cohen, Chief Psychiatrist at the hospital, and told the director of the Brain Imaging Center at McLean Hospital, Dr. P. Renshaw, of their observations. Together with Dr. M. Rohan, an imaging specialist, they decided to conduct a study using active EP-MRSI versus sham EP-MRSI (non-active EP-MRSI).

In the study of Dr. Rohan et al. (*Am J Psychiatry* 2004; 161 [1]: 93–98), thirty patients with bipolar illness received active EP-MRSI; 10 patients with bipolar disorder

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## ACNP Meeting Highlights

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correlation between amygdala volumes and age in bipolar adolescents, and an inverse correlation in healthy controls. He suggested that pruning of the amygdala, which is seen in normal adolescence, may not be occurring properly in bipolar patients, which might explain the findings of an enlarged amygdala in adult bipolar patients.

Dr. S. Berretta (McLean Hospital, Belmont, Massachusetts) and colleagues investigated the volume, total numbers, and numerical densities of neurons in the amygdala of patients with schizophrenia (n=14) and bipolar disorder (n=8). They found highly significant decreases in volume and total neuronal numbers in the lateral nucleus of the patients with bipolar disorder, but no change in neuronal densities.

*These reduced numbers of neurons appear to coexist with glial deficits (Rajkowska et al., 2001; Biol Psychiatry 49 [9]: 741–752), suggesting fundamental structural alterations in bipolar illness of this key area involved in emotional modulation.*

### Course of Illness and Response to Treatment

The implications of discontinuing an antidepressant in long-term treatment of bipolar depression is being studied by the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Dr. N. Ghaemi (Cambridge Health Alliance, Massachusetts) reported an interim analysis from an open, randomized antidepressant discontinuation trial in bipolar depression, where half of the patients taking mood stabilizers plus an antidepressant discontinued the antidepressant. They found, in contrast to two studies by Altshuler and colleagues (Altshuler et al., 2001, *J Clin Psychiatry* 62 [8]: 612–616; Altshuler et al., 2003, *Am J Psychiatry* 160 [7]: 1252–1262), that antidepressant continuation in initial responders was not associated with better long-term outcome versus discontinuation.

However, it is possible that due to the small sample size at interim analysis, none of the differences were statistically significant.

*The optimal duration of continuing adjunctive antidepressants remains controversial. However, based on the data from Altshuler et al. noted above, if a patient is doing well for two months on an antidepressant, continuation of treatment should be considered.*

Dr. G. Sachs (Harvard Medical School) presented initial data on antidepressants from the STEP-BD program. He reported that in 1000 bipolar patients treated with antidepressants, 233 reported that they had switched moods on an antidepressant. If they switched on a serotonin selective re-uptake inhibitor (SSRI), they reported switching again on an SSRI (58.2%), on a tricyclic antidepressant (TCA; 38.2%), on bupropion (Wellbutrin®; 34.3%), on electroconvulsive therapy (ECT; 28.6%), and on venlafaxine (Effexor®; 26.6%).

*These data suggest that it is important to change the antidepressant if one switches into hypomania or mania on a given drug.*

Dr. Sachs examined nonrandomized data on those patients treated prospectively in the STEP-BD with and without antidepressants as adjuncts to mood stabilizers. The recovery rates in either instance were low (25–26%) and the switch rate on an antidepressant (18%) versus not on an antidepressant (11%) was not significantly different.

*These data are consistent with those in the former Stanley Foundation Bipolar Network (SFBN) that only about 15% of patients remit in a sustained fashion after the addition of an antidepressant to a mood stabilizer.*

Dr. Sachs also examined the bipolar treatment options of adding an antidepressant, adding lamotrigine (Lamictal®), adding both, or no additional medication, i.e., treatment with the mood stabilizer alone. This latter option (mood stabilizer alone) had the best outcome.

Recovery with an antidepressant ± the use of lamotrigine occurred only in 14.9% of the patients.

Dr. O. Vinar (Charles University, Prague) reported that out of 84 SSRI responders followed for 1–4.2 years, 23% had breakthrough depressive episodes despite ongoing medication; those patients where psychologically traumatic events clearly contributed to the origin of depression were at greater risk of having breakthrough episodes (56.2%) than those patients without these events (21.4%).

Antidepressant treatment can precipitate mania in vulnerable patients; Dr. A. Martin (Yale University) et al. conducted a retrospective pharmacoepidemiological study

*“... those [unipolar] patients where psychologically traumatic events clearly contributed to the origin of depression were at greater risk of having breakthrough episodes... than those patients without these events...”*

in 87,920 patients with mood and anxiety disorders (excluding patients with a bipolar disorder) to evaluate the risk of switching to mania according to antidepressant class and patient age. These investigators found that during an average follow-up of 41 weeks, the switch rate was three times higher in those exposed to antidepressants (7.7%) versus those not exposed (2.5%), and that the highest risk in patients not previously exposed to antidepressants was in prepubertal children in the 10–14 year range.

The prevalence of bipolar disorder and other comorbidities was studied by Dr. O. Elhaj (Case Western Reserve University, Cleveland) et al. After these researchers screened consenting inmates in a jail system, they found that 19 (44%) of 43 inmates met criteria for bipolar disorder, and of these 19, 90% had comorbid substance abuse (90% alcohol dependence, 47% cannabis, 26% cocaine, and 42% other) with 53% currently abusing more than one substance. Prevalence of anxiety disorders in the dual diagnosis

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## Bipolar Network News

**Editor-in-Chief:** Robert M. Post, MD **Associate Editor:** Gabriele S. Leverich, MSW **Managing Editor:** Chris S. Gavin

The BNN is published three times a year by investigators working with patients with bipolar disorder to better understand the long-term course and treatment of the illness. The newsletter is available free of charge to all who request it. 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.

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The opinions expressed in the BNN are solely those of the editors, and do not represent the views of the National Institute of Mental Health or any other scientific entity or foundation. For any comments or suggestions you may have, or to be placed on the mailing list, please contact us at: **BNN**, P. O. Box 7925, Charlottesville, VA 22906-7925; **Website:** [www.bipolarnews.org](http://www.bipolarnews.org); **E-Mail:** [info@bipolarnews.org](mailto:info@bipolarnews.org)

## Part II: Fifth International Conference on Bipolar Disorder June 12–14, 2003, Pittsburgh, PA

In part II of our coverage of the Fifth International Conference on Bipolar Disorder, we focus on presentations concerning pediatric bipolar disorder, neurobiology, and other topics. The previous issue of the *BNN* (Vol. 9, Issue 1) contains part I of our coverage of the meeting, reviewing data on treatments for, and course of, bipolar disorder. *Editorial comments are in italics.*

### Neurobiology

The effects of lithium treatment in the dorsolateral prefrontal cortex (DLPFC) area of the brain in 12 non-bipolar subjects were examined by Dr. P. Brambilla (IRCCS S. Giovanni di Dio, Brescia, Italy) et al. Using <sup>1</sup>H magnetic resonance spectroscopy (<sup>1</sup>H-MRS), these researchers found that after four weeks of treatment, lithium significantly increased right DLPFC glutamate levels, even in nonpsychiatric subjects.

*These data are consistent with previous studies of Dr. G. Moore and colleagues (Moore et al., 2000, Biol Psychiatry 48 [1]: 1–8; Moore et al., 2000, Lancet 356 [9237]: 1241–1242) showing that lithium increases N-acetylaspartate (NAA)—a marker of neuronal integrity—and the amount of gray matter, in the brains of bipolar patients, using MRS and magnetic resonance imaging (MRI), respectively.*

At the same meeting, Dr. P. Silverstone (University of Alberta, Canada) and colleagues presented data where they used <sup>1</sup>H-MRS and found that lithium, but not valproate (Depakote®), increased measures of NAA in the temporal lobes of euthymic patients with bipolar illness.

*The message from both of these presentations at the meeting is that*

*lithium may normalize some of the basic neurobiological deficits of bipolar illness.*

Dr. F. Cassidy (Duke University) et al. reported that treatment with valproic acid elevated levels of homocysteine and reduced folate levels in 28 bipolar patients; Dr. J. Levine (Ben Gurion University of the Negev, Beersheva, Israel) and associates reported at the meeting that 41 euthymic bipolar patients had elevated homocysteine levels as well.

*Elevated homocysteine is a high risk factor for Alzheimer's disease, cardiovascular insults, and increased mortality, and folic acid supplementation can reduce levels of homocysteine. The data from these two research groups suggest a strong case for the routine use of folic acid supplementation in all patients treated with valproic acid, and perhaps in most patients with bipolar illness. Folic acid, compared with placebo, has been shown to increase antidepressant efficacy (Coppen and Bailey 2000; J Affect Disord 60 [2]: 121–130) and lithium prophylaxis efficacy (Coppen et al., 1986; J Affect Disord 10 [1]: 9–13). Dr. A. Stoll of Massachusetts General Hospital recommends that women take 1 mg/day of folic acid and men 2 mg/day.*

Brain-derived neurotrophic factor (BDNF) gene polymorphism and prefrontal brain function was examined in 54 bipolar patients by Dr. J. Rybakowski (University of Medical Sciences, Poznan, Poland) and colleagues. They found that the patients with the Val66Met polymorphism, which is associated with dysfunctional BDNF secretion and long-term potentiation (LTP), was associated with a poor response on all domains of a cognitive

test of prefrontal function (the Wisconsin Card Sorting Test [WCST]).

*These data are consistent with performance deficits in normal volunteers and in schizophrenic patients (as reported by other researchers) in those with the ValMet form and begin to define this as a possible endophenotypic marker. Because many of the antidepressants increase BDNF, it will be of considerable interest to see whether those with the deficient BDNF function associated with the ValMet genotype benefit from antidepressant intervention either in terms of mood response or cognitive improvement.*

*“Seventy-four percent [of juveniles diagnosed with bipolar disorder] . . . evidenced psychopathology before the age of three, as revealed by prominent mood and sleep problems, hyperactivity, aggression, and anxiety”*

A number of studies have reported brain abnormalities in both gray and white matter structures in bipolar patients; investigators have also reported impaired performance on neuropsychological tests in bipolar patients. Dr. D. Schnur (Mount Sinai School of Medicine, New Jersey) examined the relationship between cortical gray and white matter volume and cognitive function in bipolar patients, and found that impairments in executive and memory function may be associated with bilateral reductions in posterior cingulate white matter, and that impaired memory performance also may be associated with reduced posterior cingulate gray matter volume bilaterally.

### Pediatric Bipolar Disorder

The phenomenology and course of pediatric bipolar disorder was



### Fifth International Conference on Bipolar Disorder

the subject of a retrospective study by Dr. G. Faedda (Lucio Bini Mood Disorder Center, New York) and colleagues. Of the 82 juveniles (average age 10.5 years ± 3.6 years) diagnosed with

bipolar disorder, 90% had a family history of mood or substance use disorder, but only 10% had previously been diagnosed with bipolar disorder. Seventy-four percent (74%) evidenced psychopathology before the age of three, as revealed by prominent mood and sleep problems, hyperactivity, aggression, and anxiety. Very frequent shifts of mood and behavior were highly typical, yet only 52% met Diagnostic and Statistical Manual (DSM) durational criteria for a given episode. At follow-up, seven features were reported in greater than 90% of the cases, including irritability, mood lability, sleep disturbance, anger, impulsivity, agitation, and aggression. Rapid cycling (four or more episodes/year) was found in 86% of the subjects and ultra-rapid cycling (four or more episodes/month) in 66%. Continued on Page 7

**High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure**

Kupka RW, Nolen WA, Post RM, McElroy SL, Altshuler LL, Denicoff KD, Frye MA, Keck PE Jr, Leverich GS, Rush AJ, Suppes T, Pollio C, Drexhage HA.



*Biol Psychiatry* 2002; 51 (4): 305–311

**Background:** We assessed the prevalence of thyroperoxidase antibodies (TPO-Abs) and thyroid failure in outpatients with bipolar disorder compared with two control groups.

**Methods:** The TPO-Abs of outpatients with DSM-IV bipolar disorder (n=226), a population control group (n=252), and psychiatric inpatients of any diagnosis (n=3190) were measured. Thyroid failure was defined as a raised thyroid stimulating hormone level, previously diagnosed hypothyroidism, or both. Subjects were compared with attention to age, gender, and exposure to lithium.

**Results:** The TPO-Abs were more prevalent in bipolar patients (28%) than population and psychiatric controls (3–18%). The presence of TPO-Abs in bipolar patients was associated with thyroid failure, but not with age, gender, mood state, rapid cycling, or lithium exposure. Thyroid failure was present in 17% of bipolar patients and more prevalent in women. It was associated with lithium exposure, especially in the presence of TPO-Abs, but not with current rapid cycling, although an association may have been masked by thyroid hormone replacement.

**Conclusions:** Thyroid autoimmunity was highly prevalent in this sample of outpatients with bipolar disorder and not associated with lithium treatment. These variables appear to be independent risk factors for the development of hypothyroidism, especially in women with bipolar disorder.

## Special Report

# Rapid Cycling vs. Non-Rapid Cycling Bipolar Disorder

Data from Dr. Ralph Kupka et al. (2003)

Dr. Ralph Kupka, M.D., Ph.D., recently completed a large volume of work concerning rapid cycling in bipolar disorder. Dr. Kupka recently received his Ph.D. degree from the University of Utrecht, The Netherlands; his doctoral dissertation was titled *Rapid Cycling: Discriminating Factors in Rapid and Non-Rapid Cycling Bipolar Disorder*. Much of the work from this dissertation has been published or is in press in the scientific literature. We highlight here a small number of the wealth of important key findings from this extraordinary work. Summaries of published papers that were part of Dr. Kupka's work for his dissertation are also summarized in the left and right margins.

## Analysis of Previous Rapid Cycling Studies

The term *rapid cycling* was first named in a study in 1974 by Dunner and Fieve (Dunner and Fieve 1974; *Arch Gen Psychiatry* 30 [2]: 229–233). These investigators arbitrarily defined rapid cycling as the occurrence of at least four distinct mood episodes within one year. This is the definition that is still used today in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition). Rapid cyclers have been reported in previous studies to be associated with poor response to lithium, female gender, bipolar II diagnosis, a longer duration of illness, a positive family history of mood disorders, the presence of clinical or subclinical hypothyroidism, and the use of antidepressants.

Dr. Kupka and colleagues performed a meta-analysis of all clinical studies published from 1974 to 2002 comparing subjects with rapid and non-rapid cycling bipolar disorder. Twenty studies, with a total of 3709 patients, were identified. In eight studies with 2054 bipolar patients, rapid cycling was present in 16.3%; these studies included patients who were consecutively admitted to an inpatient or outpatient facility, and did not select only rapid cycling patients before the study and did not match rapid cycling patients to non-rapid cycling control subjects. Rapid cycling was found to be slightly, but significantly, associated with female gender and bipolar II

subtype. Contrary to common opinion, lithium prophylaxis was found to be effective in rapid cycling patients, although to a lesser degree than in non-rapid cycling patients. The effect of hypothyroidism was significant in studies using current, but not lifetime, definitions of rapid cycling only, and was mostly related to lithium treatment, raising questions about the much-quoted relationship of hypothyroidism to rapid cycling (Kupka et al., 2003; *J Clin Psychiatry* 64 [12]: 1483–1494).

## Rapid versus Non-Rapid Cycling in 539 Outpatients with Bipolar Disorder

One key study that was part of Dr. Kupka's dissertation was based upon prospective daily ratings of 539 outpatients with bipolar illness for at least one year (419 bipolar I, 104 bipolar II, 16 bipolar not otherwise specified [NOS]). The study was conducted as part of the former Stanley Foundation Bipolar Network (SFBN), among research centers in the United States, The Netherlands, and Germany, from 1995–2002. In the SFBN, over 1100 patients with bipolar disorder were prospectively followed from a few months to seven years; the main instrument used to record the longitudinal course of the illness was the National Institute of Mental Health-Life Chart Method (NIMH-LCM™). Never before has such a large number of patients been rated prospectively in such detail. The work generated a number of striking findings. Of

those studied for a full year, there were 206 (38.2%) patients with confirmed rapid cycling by strict definition, versus 333 (61.8%) non-rapid cycling.

It had previously been assumed that rapid cycling (four or more episodes in a year) was an uncommon phenomenon, occurring in some 10–20% of patients as referred to in most textbooks and review chapters. In this highly-detailed study, 50.7% of the bipolar patients reported a *prior* history of rapid cycling, and 38% *continued to show* this pattern of illness recurrence over the course of the first study year, despite treatment with an average of four different classes of drugs. Rapid cycling patients showed a substantial increase in full-duration manic and hypomanic episodes, whereas the mean number of depressive episodes remained relatively stable as a function of cycle frequency. Likewise, the total time manic or hypomanic in the first prospective year increased with cycle frequency, whereas the total time depressed was on average constant regardless of number of episodes.

In a multivariate analysis, positive risk factors for rapid cycling in the prospective year were a bipolar I subtype, a lifetime history of rapid cycling, having ten or more prior episodes, having a lifetime history of drug abuse, and a history of physical and/or sexual abuse as a child. There were a number of pertinent negative findings that were

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# Rapid Cycling vs. Non-Rapid Cycling

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in contrast to those which are often associated with rapid cycling in the literature based on much smaller sample sizes. Kupka et al. did not find that female gender, bipolar II diagnosis, prior antidepressant exposure, hypothyroidism, age of onset, or duration of illness were independently related to continued rapid cycling in the prospective year.

There was a linear relationship between the number of episodes in the prospective year and the percentage of those with a lifetime history of dysphoric mania or hypomania. In those with zero prospective mood episodes per year there was a 25% incidence of dysphoric hypomania or mania in the past, gradually increasing up to 80% in those with eight or more prior episodes.

The 206 patients with rapid cycling compared with the 333 non-rapid cyclers had an earlier age of onset of illness (17.6 versus 23.1 years) and had a longer time from first symptoms to first treatment

lifetime anxiety disorder diagnoses (50.2% vs. 30.7%); a greater history of physical and/or sexual abuse as a child (40.1% vs. 24.1%); and a higher parental history of substance abuse (35.6% vs. 22.3%).

Dr. Kupka found that the traditional dichotomy of rapid and non-rapid cycling set at four episodes did not have an empirical basis in this study; in fact, he found a steady continuum of episode frequency with no clear point of demarcation between rapid and non-rapid cyclers. This finding implies that rapid cycling should not be regarded as a dichotomous subtype of bipolar disorder, but rather part of a continuum.

## Five-year Prospective Follow-up of Rapid and Non-Rapid Cyclers

The second part of Dr. Kupka's study of these 539 bipolar outpatients with or without rapid cycling was a 5-year prospective follow-up study to determine if the rapid cycling or non-rapid cycling

categories remained the same, or whether patients converted to the other category over time.

Patients were followed for one (n=539), two

(n=315), three (n=207), four (n=130), or five (n=84) years. After each year of completion, patients were re-categorized as rapid cycling, non-rapid cycling, or converters to the other category.

Kupka et al. found that many patients with initial rapid cycling converted to a non-rapid cycling course, whereas most patients with initial non-rapid cycling retained their stability in this category (i.e., they didn't convert to rapid cycling). Also, the majority of patients with initial rapid cycling who converted to non-rapid cycling retained this

non-rapid cycling over the course of follow-up, whereas most of the original non-rapid cyclers who at a later stage experienced four or more episodes per year eventually converted back to non-rapid cycling. The persistence of rapid cycling was associated with higher episode frequency, pole-switching pattern, and continuous cycling pattern in the initial year. No other variables distinguished between patients who initially were rapid cycling, and continued to be rapid cyclers, versus those patients who later converted to non-rapid cycling.

Overall, a greater percentage of patients entered a stable remission with outpatient treatment (i.e., had no further mood episodes) over time in the study, 13.7% in the first to 42.9% in the fifth year. The percentage of rapid cycling patients decreased from 38.2% initially to 20.2% at the end of five years. Of the patients with a rapid cycling pattern initially, 55% continued to show this pattern in the second prospective year, 49.4% in the third year, 45.3% in the fourth year, and 43.3% in the fifth year. Thus, about half the patients with an initial rapid cycling pattern were able to convert to a non-rapid cycling pattern with intensive treatment and follow-up. At the same time, there was stability of a non-rapid cycling pattern, with only 3.9–13.5% of patients initially presenting with non-rapid cycling converting to a rapid cycling pattern in any of the five years of prospective follow-up (see graph, p. 6). As may be expected, converters were typically those patients with episode frequencies close to the cut-off point of 4 episodes per year. Thus, persistence of a rapid cycling pattern is most likely in those patients with a very high (i.e., eight or more per year) initial episode frequency.

In addition, the degree of overall improvement, measured by the proportion of time ill, did not differ significantly in patients with a rapid cycling pattern and in those with a non-rapid cycling pattern in the first

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## High numbers of circulating activated T cells and raised levels of serum IL-2 receptor in bipolar disorder

Breunis MN, Kupka RW, Nolen WA, Suppes T, Denicoff KD, Leverich GS, Post RM, Drexhage HA



Biol Psychiatry 2003; 53 (2): 157–165

**Background:** Previously, we found an increased prevalence of thyroid autoantibodies in patients with bipolar disorder. In the present study, we investigated other signs of immune activation in bipolar patients, in particular an activation of the T cell system.

**Methods:** Fluorescence activated cell scanning (FACS) analysis was performed on lymphocytes of 64 outpatients with DSM-IV bipolar disorder using the T cell marker CD3 in combination with the activation markers MHC-class II, CD25, CD69 or CD71. In 34 patients, these assays were repeated after an interval of 2 years. In addition, T cell activation was determined by measuring serum soluble IL-2 receptor (sIL-2R) in 172 bipolar outpatients. Outcomes were compared with a healthy control group.

**Results:** Significantly higher numbers of circulating activated T cells and raised sIL-2R levels were found in euthymic, manic, and depressed bipolar patients when compared with healthy controls. In general, these abnormalities were stable over time. Manic patients showed significantly higher levels of sIL-2R in comparison with depressed patients.

**Conclusion:** The T cell system was found to be activated in both symptomatic and euthymic patients with bipolar disorder. The pathophysiological significance of these findings remains to be explored.

### Risk Factors for Prospective Rapid Cycling vs. Non-Rapid Cycling in Bipolar Patients over 1 Year

Positive Risk Factors:	Non-Risk Factors:
More than 10 Prior Episodes	Female Gender
Prior History of Rapid Cycling	Bipolar II Diagnosis
Lifetime History of Drug Abuse	Prior Antidepressant Exposure
Bipolar I Subtype	Hypothyroidism
History of Childhood Physical and/or Sexual Abuse	Age of Onset
	Duration of Illness

(11.2 years versus 6.8 years). Thus, both an earlier age of onset of illness and longer time to first treatment were associated with one measure of poor prospective outcome (i.e., rapid cycling) in the first year in this study despite a wide range of treatments. *These data strongly suggest the importance of earlier recognition, treatment, and prophylaxis of bipolar illness to prevent this indicator of a more difficult outcome.*

The rapid compared with non-rapid cyclers showed a statistically significantly greater percentage of

**Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies**

Kupka RW, Luckenbaugh DA, Post RM, Leverich GS, Nolen WA

**Background:** Rapid cycling, defined as 4 or more mood episodes per year, is a course specifier of bipolar disorder associated with relative treatment resistance. Several risk factors have been suggested to be associated with rapid cycling. The purpose of this meta-analysis was to compare clinical studies for the evidence of discriminating factors between rapid and non-rapid cycling.

**Data Sources and Selection:** We searched MEDLINE and reference lists of articles and book chapters and selected all of the clinical studies published from 1974 to 2002 comparing subjects with rapid and non-rapid cycling bipolar disorder. Prevalence rates and mean random effect sizes for 18 potential risk factors that were reported by at least 3 studies were calculated. In addition, we differentiated between current and lifetime diagnoses of rapid cycling.

**Data Synthesis:** Twenty studies were identified. Rapid cycling was present in 16.3% of 2054 bipolar patients in 8 studies that included patients who were consecutively admitted to an inpatient or outpatient facility, without a *a priori* selection of rapid cyclers and without matching the numbers of rapid cyclers to non-rapid cycling controls. Female gender and bipolar II subtype both had a small, but statistically significant, effect ( $p < .000$  for female gender,  $p < .001$  for bipolar II subtype). The further absence of recurrences with lithium prophylaxis was reported in 34% of rapid cyclers compared with 47% of non-rapid cyclers, a nearly



*J Clin Psychiatry* 2003; 64 (12): 1483-1494

significant difference, and a partial response was present in 59% and 65% of patients, respectively. The effect of hypothyroidism was significant ( $p < .01$ ) in studies using current, but not lifetime, definitions of rapid cycling. In 46% of cases, a rapid cycling course was preceded by treatment with antidepressants, but systematic data on their causal role are lacking.

**Conclusion:** Rapid cycling is slightly more prevalent in women and in patients with bipolar II subtype. In contrast to common opinion, lithium prophylaxis has at least partial efficacy in a considerable number of rapid cyclers, especially when antidepressants are avoided. Hypothyroidism may be associated with mood destabilization in vulnerable patients.

**Magnetic Brain Stimulation**

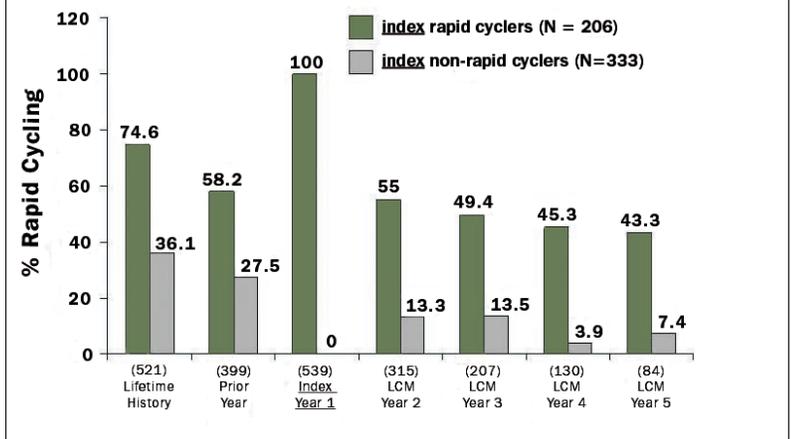
Continued from Page 1

received sham EP-MRSI; and 14 healthy subjects (without bipolar disorder) also received active EP-MRSI. The patients with bipolar disorder were either bipolar I or bipolar II, and between the ages of 18 and 65. None of the participants in the study were aware that the EP-MRSI evaluation was being investigated for mood effects, and they could not tell the difference between sham and active EP-MRSI. The active treatment consisted of four EP-MRSI sequences lasting a total of 20.5 minutes. Each sequence produced a series of 512 alternating pulses 0.256 msec long, repeated every 2 seconds for 4 minutes.

In 23 of the 30 patients with bipolar disorder, mild to marked mood improvement was seen, particularly in all 11 of the patients who were unmedicated at the time. Improvement in patients with sham EP-MRSI was seen in only three of 10 patients. Four of 14 control subjects without bipolar illness, who received active EP-MRSI, also felt better. The eventual clinical significance of this magnitude of improvement, and whether it can be converted into a time frame yielding lasting effects, remains to be ascertained.

Despite these ambiguities there is keen interest in this potential new technique because it uses ultra low-level magnetic fields (100 to 1,000 times weaker than repetitive transcranial magnetic stimulation [rTMS] fields). The electrical field (0.7 V/m) is some 500 times lower than that generated in

**Prevalence of Rapid Cycling by History and During 5-Year Follow-Up**  
(Kupka et al., 2003)



**Rapid Cycling vs. Non-Rapid Cycling**

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year. Thus, rapid cyclers are amenable to treatment, even if the residual symptoms are more prominent than in non-rapid cyclers. In conclusion, these results support the notion that rapid cycling should be conceptualized as a dimensional rather than a categorical course specifier for bipolar disorder.

**Postscript:** Dr. Kupka's thesis was sponsored by Dr. W. Nolen, Altrecht Institute for Mental Health Care, Utrecht, and the Department of Psychiatry, University Medical Center, Utrecht, The Netherlands,

and co-sponsored by Dr. R. Post, Biological Psychiatry Branch, NIMH, Bethesda, MD. Collaborators on this work included L. Altshuler, M. Frye, T. Suppes, P. Keck, S. McElroy, K. Denicoff, G. Leverich, J. Walden, and H. Grunze. The work of the thesis was supported by the Stanley Medical Research Institute, Bethesda, MD, and the Altrecht Institute for Mental Health Care, Utrecht, The Netherlands; all investigators associated with this research are appreciative and indebted for this generous support.

the rTMS paradigm (1-500V/m). The sequence utilized by Rohan and colleagues yielded a frequency stimulation of 1 kHz, or about 1000 times higher frequency than the 1-20 Hz that is typically generated with rTMS. Rohan and colleagues believe it is this ultra high frequency, and not the extremely low-level magnetic field (which is also unidirectional in character) that yields the acute therapeutic effects of the EP-MRSI sequence. Some neurons fire this fast (at 1k Hz) naturally, and it is thought these ultra high frequency, unidirectional, low-level magnetic fields might somehow re-train dysfunctional neural pathways to fire in a more organized fashion.

**II. rTMS**

In many previous issues of the *BNN*, we have reported on the use of rTMS of the brain whereby, using a figure-of-eight magnetic coil, one is able to induce relatively focal electrical discharges in the brain of the patient. For example, if the rTMS coil is placed over the motor cortex, it can discretely produce isolated hand (or even thumb) twitches, and more dorsally, leg and foot twitches. Most of the research with



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*These data add to a substantial consensus among many investigative groups, that a factor reflecting irritability, mood lability, anger, impulsiveness, and aggression often is the earliest prodrome (or manifestation) of bipolar illness (i.e., bipolar not otherwise specified), and these symptoms begin to differentiate bipolar from unipolar illness, attention-deficit hyperactivity disorder (ADHD), and normal controls at the earliest ages (3-6) (Fergus et al., 2003; J Affect Disord 77 [1]: 71-78). It is only after ages 7-9 that more classic manic and depressive symptom clusters begin to emerge in those eventually diagnosed with bipolar illness.*

Dr. R. Findling (Case Western Reserve University, Cleveland) et al. presented data from a randomized trial of divalproex sodium (Depakote®) vs. placebo in the treatment of youth at a genetically high-risk for developing bipolar disorder. Youths between 5-17 years old meeting DSM-IV criteria for bipolar not otherwise specified (NOS) or cyclothymia, who also had a parent with bipolar disorder, were randomized to placebo or divalproex treatment for up to five years. In the 53 youths randomized (average age 10.7 years) to divalproex and placebo, there were no differences in the time to discontinuation for a mood event or discontinuation for any reason (both groups did well).

Dr. K. Chang (Chang et al., 2003; J Clin Psychiatry 64 [8]: 936-942) saw a high percentage of responders in his study of offspring of parents with bipolar illness when treated with divalproex, but in the absence of placebo, it is not clear whether such an open study actually reflects drug efficacy.

Findling et al. also reported on a double-blind study of the combination of divalproex and lithium in 139 youths aged 5-17 years who met DSM-IV criteria for bipolar I or bipolar II. In this study, patients first received the combination for up to 20 weeks; if they met remission criteria for four consecutive weeks, they were then randomized to receive either lithium or divalproex monotherapy. After 8 weeks, a significant improvement in all outcome measures was found, and 43% of the patients met remission criteria and were randomized to monotherapy. The primary reason for failing to meet remission criteria on the combination was study non-adherence.

*This reasonable rate of response to combination treatment in these children differs from the data of Dr. J. Calabrese et al. (2003) wherein only 18% of the intent-to-treat group of adults with rapid cycling bipolar illness stabilized sufficiently on this combination. Taken together, these data suggest the possibility that adults may become more treatment-resistant, possibly as a function of experiencing increased number of episodes.*

*Consistent with this finding are the analyses from the lamotrigine (Lamictal®) vs. lithium vs. placebo 18-month prophylaxis study, where those patients with a greater number of prior treatments were less likely to respond, particularly with lithium; see BNN Vol. 9, Issue 1.*

Preliminary results from a randomized trial of an interpersonal/cognitive behavioral intervention for preventing bipolar disorder in depressed adolescents were reported by Dr. F. Kochman (EPSMAL, Lille, France) and colleagues. Thirty-six adolescents (aged 12-18 years) with major depressive disorder and at least one parent with a lifetime diagnosis of unipolar or bipolar disorder were randomized to 16 sessions of interpersonal/cognitive behavioral therapy or needs-based intervention. After 12 months, seven of the 18 adolescents in the needs-based intervention progressed to a hypomanic or manic episode, whereas only three in the interpersonal/cognitive behavioral therapy did so.

*Secondary prevention of the progression to bipolar illness in children and adolescents may be possible with the use of early psychotherapeutic interventions.*

Dr. D. Papolos (Juvenile Bipolar Research Foundation, Connecticut) et al. reported on a retrospective examination of antidepressant-induced adverse effects in 134 children and adolescents with bipolar disorder (2.4-18.8 years) exposed to at least one antidepressant trial. These investigators found that within the first four months of antidepressant treatment, 75.4% of those exposed experienced adverse effects including increased cycling within the day (79%), increased aggression (70.9%), and psychotic symptoms (23%). They added that aggression, violence, and suicidal ideation were not unusual sequelae of antidepressant exposure in these bipolar patients.

*These data mirror those of Biederman et al. (1999; J Child Adolesc Psychopharmacol 9 [4]: 247-256) and the views of most investigators in*

*the field, indicating that stimulants and antidepressants in the absence of mood stabilizers in patients presenting with juvenile onset bipolar disorder may not only be ineffective, but may also be associated with exacerbation of the illness.*



**Fifth  
International  
Conference on  
Bipolar Disorder**

A prospective comparison of risperidone (Risperdal®) vs. mood stabilizers in pediatric bipolar disorder was conducted by Dr. M. Pavuluri (University of Illinois at Chicago) and co-investigators. Eighty-seven outpatient children and adolescents (average age 12 years) with pediatric bipolar disorder were treated with a mood stabilizer, risperidone monotherapy, or combination treatment for six months. Improvement on all subscales of the rating instrument used was strong and significant regardless of medication group. Risperidone monotherapy was associated with a more rapid improvement on an overall improvement scale, whereas combination therapy resulted in more rapid improvement in symptoms of depression, psychosis, and sleep disturbance.

Dr. M. DelBello (University of Cincinnati) et al. conducted a study investigating the use of divalproex for the treatment of aggression associated with adolescent mania. Previous studies have shown that divalproex is effective in reducing aggression associated with adult mania. Fifteen adolescents (aged 12-18 years) who were hospitalized for a manic or mixed episode were treated with divalproex (average serum level = 104 mg/dL) for six weeks; Dr. DelBello found that divalproex significantly reduced aggression and irritability in this population.

A magnetic resonance imaging (MRI) study of thalamus volumes in adolescent bipolar patients (n=16) and healthy controls (n=21) by Dr. E. Monkul (Dokuz Eylül University School of Medicine, Izmir, Turkey) and colleagues found no significant differences between the two groups (no abnormalities in thalamic size). Dr. M. Sanches (Federal University of Sao Paulo, Brazil) and other investigators from this same group also found no significant differences in the volume of the subgenual prefrontal cortex in these same adolescent bipolar patients and controls (in contrast to reductions seen in bipolar adults).

## Four Types of Magnetic Brain Stimulation

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rTMS in bipolar illness and depression has used stimulation over the left prefrontal cortex, an area of the brain often underactive in depression based on functional brain imaging studies.

A number of controlled rTMS studies (using frequencies of stimulation from 1 Hz to 20 Hz) continue to yield positive results compared with sham control procedures (Schlaepfer et al., 2003; *Neuropsychopharmacol* 28 [2]: 201–205), but several negative studies have also been reported and this procedure is not yet clinically available. Dr. M. George and Dr. H. Sackeim and associates are conducting a large clinical trial which may yield sufficiently clear evidence to enable there to be an application to the Food and Drug Administration (FDA) for use of this procedure for general clinical treatment purposes.

Three studies have also compared intermediate (10 Hz, i.e. 10 stimulations/sec) or high (20 Hz) rTMS stimulation over the left dorsolateral prefrontal cortex using intensities of 90, 100, or 110% of motor threshold and found degrees of clinical efficacy approximately comparable to those of electroconvulsive therapy (ECT) (BNN Vol. 7, Issue 2). Should these observations be replicated in further studies, it would be clinically important, as rTMS would be substantially more convenient and less costly than ECT, without requiring anesthesia, the induction of a seizure, or the associated low incidence of retrograde memory loss.

### III. MST

Another new avenue of brain stimulation research is magnetic seizure therapy (MST),

developed by Dr. S. Lisanby, Dr. H. Sackeim and colleagues at Columbia University.

MST uses transcranial magnetic stimulation to generate a seizure like ECT treatment, but with much better control (than ECT) of the seizure parameters, because the magnetic pulse easily crosses the scalp and skull (in contrast to the high resistance generated with electrical stimulation).

Using this approach, Dr. Lisanby and colleagues have shown that the seizures induced by MST are clinically effective as an antidepressant and, at the same time, are less likely to cause neuropsychological impairment compared with ECT seizures (Kosel et al., 2003; *Neuropsychopharmacol* 28 [11]: 2045–2048). Although this may be a distinct advancement for the field, like ECT, MST is administered under general anesthesia in an operating setting, and thus carries much of the same inconvenience and expense associated with regular ECT.

### IV. LL-MF

In the study of EP-MRSI by Dr.

Rohan et al. (*see p. 1*), it is possible that it is the ultra low level magnetic fields (LL-MF) generated, and not their high frequency, that is related to the therapeutic benefit of EP-MRSI. We raise this alternative possible interpretation based on several types of indirect evidence.



Dr. M. McLean and Dr. R. Holcomb (Vanderbilt University) have used magnetic fields in this ultra low intensity range, but of a static variety, to generate anticonvulsant effects in animal models of seizures and pain, as well as clinically in patients with a variety of chronic pain syndromes. Dr. McLean initially used a specially configured magnetic disk



consisting of four powerful magnets arranged in an alternating pole configuration. This configuration generates a constant LL-MF, but one that has an inverted volcano-shaped field to it, and it is apparently this magnetic field gradient which is responsible for the therapeutic effects of MST. Other magnets not in this alternating pole configuration and not generating this type of differential field did not show efficacy. This magnet is effective in some seizure models on its own and markedly potentiates the anticonvulsant effects of phenytoin when doses of this drug are in themselves not effective (McLean et al., 2003; *Epilepsy Res* 55 [1–2]: 105–116).

McLean and associates have now gone on to use a constant LL-MF from a specially constructed electromagnet and found similar degrees of efficacy against seizures. Thus, while effects on mood have not been directly tested with this type of constant LL-MF, it is noteworthy that other anticonvulsant modalities such as valproate (Depakote®), carbamazepine (Tegretol®), and lamotrigine (Lamictal®) do exert positive therapeutic effects in patients with bipolar illness. It is possible that whatever is engendering the transcranial anticonvulsant effects of these LL-MFs could ultimately have implications for the treatment of other neuropsychiatric syndromes beyond those of the seizure disorders.

## Conclusions

A cautionary note is needed for readers of this article about the unproven nature of all of these approaches, as well as the unavailability at this time of any of these modalities for clinical therapeutics, except in specific FDA-approved studies and research protocols. It should also be emphasized that the type of magnets used by Dr. McLean and associates are very different from the ordinary configuration of magnets (usually less powerful as well) that are routinely available. Therefore, one should not assume that ordinary magnets would in any way have the same anticonvulsant or antipain effects as those using the alternating pattern developed by Dr. McLean and associates. Hopefully, further studies in all these areas will ultimately yield new therapeutic applications in the future.

### Further Reading on Magnetic Stimulation

#### Books:

*Transcranial Magnetic Stimulation in Neuropsychiatry* (2000). M.S. George, R.H. Belmaker (Eds.). Washington DC: American Psychiatric Press.

*Handbook of Transcranial Magnetic Stimulation* (2002). A. Pascual-Leone, E. Wasserman, N. Davey, J. Rothwell, B.K. Puri (Eds.). New York: Oxford University Press.

*Magnetotherapy: Potential Therapeutic Benefits and Adverse Effects* (2003). M.J. McLean, S. Engstrom, R.R. Holcomb (Eds.). New York: TFG Press.

## ACNP Meeting Highlights

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bipolar sample was 71%. The mean delay in receiving a diagnosis of bipolar disorder since onset of symptoms was 14 years in this prison population.

*The delay in receiving a diagnosis in this study disappointingly is not that different from the average 10-year lag from illness onset to treatment even in an academic outpatient bipolar network, such as the former SFBN. Better treatment and earlier intervention may help prevent the development of substance abuse comorbidities and other complications including hospitalization or incarceration.*

### New Treatment Data

Dr. M. Rohan (McLean Hospital) and colleagues reported positive effects of low-level magnetic field stimulation in bipolar patients, using an MRI scanner which produced low-level magnetic fields about 1/2000ths of the strength achieved with repetitive transcranial magnetic stimulation (rTMS). Twenty-three of 30 bipolar patients reported mood improvement compared with three of 10 subjects given a sham low-field magnetic stimulation (LFMS). The subgroup of medication-free bipolar patients responded best (11 of 11 subjects).

*For a more in-depth discussion of this exciting new finding and its implications for the field, see the article on page 1 of the BNN.*

A randomized study in the STEP-BD was stopped early because of the relatively low total response rates to either inositol (2.5–20 gms), lamotrigine (25–600 mg) or risperidone (Risperdal®; 0.5–6 mg) augmentation for refractory bipolar depression. Although this study did not have enough patients to reach statistical significance, the recovery rates on inositol (17.3%) and lamotrigine (24%) appeared superior to that of the addition of risperidone (5%).

*Two other studies have suggested near significant effects of inositol as well (Levine et al., 1995, Am J Psychiatry 152 [5]: 792–794; Chengappa et al., 2000, Bipolar Disord 2 [1]: 47–55).*

Dr. M. Tohen (Lilly Research Laboratories) and colleagues reported results from an 8-week, double-blind acute study of 833 patients with bipolar I depression, finding remission rates of 24.5% on placebo, 32.8% on olanzapine, and 48.8% on the combination of

olanzapine plus fluoxetine (Prozac®)(OFC). The switch rate (treatment-emergent mania) on each of these drugs ranged from 5–7%. Of the three hundred sixty-seven patients who completed the acute study, 192 patients in remission entered a 6-month open continuation phase, during which patients were treated with olanzapine 5–20 mg/day with the option of switching to OFC (6 and 25, 6 and 50, or 12 and 50 mg/day of olanzapine and fluoxetine, respectively) after one week if needed. In this 6-month open extension 62.5% were free of a depressive relapse and 94.3% were free of a manic relapse; the treatment-emergent mania rate was 6.3%.

*This study suggests better antimanic than antidepressant efficacy of olanzapine, even when used in combination with a serotonin-selective antidepressant. The acute phase of this study has now been published (Tohen et al. 2003; Arch Gen Psychiatry 60 [11]: 1079–1088). The olanzapine-fluoxetine combination has now been Food and Drug Administration-approved for the treatment of bipolar depression. The name of the new medication is Symbyax®. Whether Symbyax will prove more useful than individualizing patients to the best doses and options remains to be seen.*

An investigation of the drug memantine (Axura®) in patients with major depressive disorder was conducted by Dr. J. Ferguson (Pharmacology Research Institute, Salt Lake City) and associates. Memantine is a non-competitive, glutamate N-methyl-D-aspartate (NMDA) receptor antagonist that is typically used in the treatment of Alzheimer's disease and dementia. In this 12-week open evaluation in eight patients, memantine was effective in 62.5% of the patients in reducing depression, at a mean dose of 18.1 mg/day.

*These open study results deserve further exploration, but are consistent with a role for glutamate receptor involvement in depression since memantine is a glutamate NMDA-receptor antagonist. Previous studies have suggested better efficacy in Alzheimer's disease of the memantine-donepezil (Aricept®) combination than with either drug alone.*

Dr. P. Blier (University of Florida) and colleagues conducted a novel antidepressant study in which they hypothesized that initiating treatment with two antidepressants

(instead of one) for unipolar depression might improve the onset of action and/or the magnitude of response. In their double-blind study, mirtazapine (Remeron®; 30 mg at night) was combined with fluoxetine (20 mg/day), venlafaxine (75 mg/day titrated to 225 mg/day in two weeks), or bupropion (150 mg/day). Fluoxetine monotherapy was used as the control. After six weeks, patients who achieved remission on fluoxetine alone or fluoxetine + mirtazapine stayed on fluoxetine, whereas those patients taking bupropion + mirtazapine or venlafaxine + mirtazapine stayed on mirtazapine, with venlafaxine gradually discontinued over two weeks. In a preliminary analysis of the first 56 randomized patients, the combination treatments produced a significant improvement earlier (starting at day four), versus the fluoxetine alone group (starting at day 10). The venlafaxine + mirtazapine group showed the most robust efficacy versus the fluoxetine-only group. Forty-three patients then entered the 6-month continuation study

*"[in an uncontrolled study in unipolar illness] . . . memantine was effective in 62.5% of the patients in reducing depression, at a mean dose of 18.1 mg/day."*

(fluoxetine alone versus mirtazapine alone). Sixteen (37%) of these patients relapsed, 12 of them in the first month, i.e., remission was often not maintained if patients switched back to a single agent, suggesting the utility of continuing combination treatment in those who respond.

*These data support the view that what gets a patient well acutely may be the best strategy (in the absence of problematic side effects) for long-term prophylaxis, i.e., prevention of relapses.*

As noted in the last issue of the BNN (Vol. 9, Issue 1), the new anticonvulsant zonisamide (Zonegran®) has the potential to not only be an effective adjunctive mood stabilizer, particularly for mania or rapid cycling (McElroy et al., 2003, unpublished data), but also may possess the positive side effect of weight loss. Dr. T. Ketter (Stanford University) and co-investigators reported data from an open trial of adjunctive zonisamide for obesity in 11 medicated euthymic bipolar patients (on an average of 3.6 medications). Dr. Ketter found that weight decreased at a rate of 1.3 pounds/wk over an

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average of nine weeks, although five (45%) of the patients discontinued early due to adverse effects, mostly irritability or gastrointestinal problems. The final dose of zonisamide in this study was 418 mg/day.

*Lower doses of zonisamide may also be effective and cause fewer adverse side effects, as suggested from the study of McElroy et al.*

An 8-week study using lower doses (up to 300 mg) of zonisamide in bipolar patients with depression was conducted by Dr. A. Anand (Indiana University) et al. Twelve patients enrolled in the study, with eight patients completing eight weeks of treatment. Adjunctive zonisamide significantly decreased depression and severity of illness, but made no significant change in mania. There were no reports of significant weight loss. The major side effect reported was increased urinary frequency.

*The psychotropic profile of zonisamide in mania*

*“By day four of the study, in the 102 patients taking ziprasidone and lithium, rates of change in mania and related psychopathology were significantly greater than in those patients taking lithium and placebo . . . ziprasidone plus lithium may cause an earlier onset of clinical improvement than lithium alone”*

*and depression requires further studies, but it appears to be another good option (like topiramate [Topamax®]) for weight loss.*

Dr. R. Marcus (Bristol-Myers Squibb) presented results from a double-blind, placebo-controlled study on long-term use of the new atypical antipsychotic aripiprazole (Abilify®) in the maintenance treatment of bipolar disorder. One hundred sixty-one patients with bipolar I disorder who had experienced a manic episode and had been stabilized on aripiprazole for 6–18 weeks were randomized to double-blind maintenance treatment with either aripiprazole or placebo for 26 weeks. Time to relapse for bipolar disorder symptoms was significantly longer with aripiprazole, and total number of patient relapses (for mania, mixed, or depression symptoms) was significantly fewer in patients on aripiprazole. The only side effects that were more common (5–10%) with aripiprazole than with placebo were anxiety and nervousness.

*These data are of considerable importance given aripiprazole’s unique mechanism of antipsychotic and antimanic action as a partial agonist (rather than as an antagonist) at dopamine and serotonin type-1A receptors and its good tolerability profile.*

A study of rapid quetiapine (Seroquel®) administration in the treatment of acute mania was conducted by Dr. D. Fleck (University of Cincinnati) and associates. Although studies have suggested quetiapine is effective in treatment-resistant bipolar disorder, it is unclear whether doses of quetiapine can be quickly adjusted safely, which is often required in acute mania. Twenty patients hospitalized for a manic or mixed episode of bipolar I disorder with psychotic features were randomly assigned to receive either rapidly adjusted quetiapine (n=11) or divalproex (n=9), dosed with a loading strategy, for two weeks. The mean divalproex dose was 1500 mg, and quetiapine was increased from 150 mg on day one to >400 mg by day four. Both groups showed significant reduction in overall and manic

symptoms, however, significant decreases were seen in depressive symptoms only in the quetiapine group. Both treatments were well tolerated.

*These data of Dr. Fleck*

*support the findings of a study that will be presented at the American Psychiatric Association meeting in May, showing acute antidepressant efficacy of quetiapine monotherapy in acute bipolar depression. The study that will be presented shows rapid onset of improvement on quetiapine 300 mg/day or 600 mg/day versus placebo from week one on; improvement was seen in depression, anxiety, and sleep.*

The new atypical antipsychotic ziprasidone (Geodon®) was evaluated by Dr. L. Price (Brown University, Providence) and colleagues in a randomized, double-blind, placebo-controlled, 21-day trial in 205 patients with bipolar I disorder, most recent episode manic or mixed, who were already taking lithium. By day four of the study, in the 102 patients taking ziprasidone and lithium, rates of change in mania and related psychopathology were significantly greater than in those patients taking lithium and placebo. By day 14, rates of change were comparable between the two groups, with no statistically significant differences. The

ziprasidone and lithium combination was well tolerated (discontinuation because of adverse side effects was # 5% in both groups). The authors conclude that ziprasidone plus lithium may cause an earlier onset of clinical improvement than lithium alone.

A novel use of a combination of medication and psychotherapy was performed by Dr. B. Rothbaum (Emory University, Atlanta) et al. In 28 patients with a fear of heights (acrophobia), these investigators used behavioral exposure therapy along with two separate doses of d-cycloserine, a partial agonist at the NMDA glutamate receptor, and a putative cognitive enhancer. Three months following the two therapy sessions, those who received the d-cycloserine plus exposure therapy were the most significantly improved over those who received placebo.

*This study suggests that cognitive enhancers could accelerate the active learning process that extinction (or desensitization) with cognitive behavioral therapy requires. This approach could be groundbreaking for new combined approaches to cognitive behavioral psychotherapy.*

Dr. L. Arnold (University of Cincinnati) et al. reported that a double-blind, multicenter trial showed that the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine (Cymbalta®) was particularly effective in patients with fibromyalgia and with or without major depression, particularly in women.

*This study mirrors results with venlafaxine (Sayer et al., 2003; Ann Pharmacother 37 [11]: 1561–1565), strongly suggesting that SNRIs are better for chronic pain syndromes than SSRIs.*

### Predictors of Response

Dr. E. Vieta (Bipolar Disorders Program, IDIBAPS, Barcelona, Spain) et al. performed an analysis on the olanzapine versus OFC study (noted on p. 9) to identify clinical predictors of response. They found four variables that significantly predicted response to olanzapine monotherapy: non-Caucasian race, absence of rapid cycling, duration of current episode less than 60 days, and one or more previous episodes of mania in the past 12 months. For OFC, only one variable predicted response—onset of bipolar disorder before age 20.

In a re-analysis of a large double-blind, placebo-controlled trial of lithium versus divalproex versus placebo in bipolar I

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disorder (Bowden et al., 2000; *Arch Gen Psychiatry* 57 [5]: 481–489), Dr. C. Bowden (University of Texas Health Science Center, San Antonio) reported that patients with dysphoric mania appeared more sensitive to the side effects of maintenance treatment, particularly with lithium, and that those patients with acute euphoric mania appeared to be more responsive to the prophylactic antidepressant effects of divalproex compared with lithium or placebo.

The relationship between serum folate, vitamin B12, and homocysteine levels and time to onset of clinical response to fluoxetine in major depression was investigated by Dr. G. Papakostas (Massachusetts General Hospital) and associates. In 110 outpatients with major depressive disorder who had sustained acute response to fluoxetine, low serum folate levels were associated with delayed onset (average of 1.5 weeks) of antidepressant response in major depression.

*Folic acid lowers homocysteine levels, which is a risk factor for depression, cardiovascular disease, and neuropsychiatric illness. These data provide additional rationale for suggesting that women take 1 mg of folic acid per day and men 2 mg/day as a general dietary supplement (as recommended by Dr. A. Stoll) and to help better treat their depression (Coppin and Bailey, 2000; J Affect Disord 60 [2]: 121–130), and reduce the risks associated with elevated homocysteine levels. At this same meeting, Dr. R. Belmaker (Ben Gurion University, Beersheva, Israel) and colleagues reported data from a study showing that reducing homocysteine with folic acid (2 mg), pyridoxine (25 mg) and vitamin B12 (400 mg) was effective in improving chronic schizophrenic symptoms in those patients with baseline increases in homocysteine.*

### Childhood and Adolescent Bipolar Disorder

A double-blind, placebo-controlled study of up to 400 mg/day of topiramate monotherapy in children and adolescents with acute mania was conducted by Dr. M. DelBello (University of Cincinnati) and associates. The study was terminated early because of negative results of topiramate monotherapy in adult patients in four other studies in acute mania, but 56 patients (age range 6–17) were randomized into the study before termination. Mania rating scores were

significantly reduced in the topiramate group after 28 days of treatment, as were overall illness severity scores. Sixty-six percent (66%) of the patients in the topiramate group had attention-deficit hyperactivity disorder (ADHD) versus 52% of the placebo group; 72% of the topiramate group completed the study, versus 89% of the placebo group.

*Topiramate is ineffective in monotherapy of acute mania in adults, but questions of efficacy in childhood and adolescent mania remain.*

Dr. R. Perlis (Massachusetts General Hospital) and

associates reported on data from the first 1000 STEP-BD

patients, concerning early (between ages 13 and 18) and very early (before age 13) onset of

illness versus adult onset. They found that those patients with early and very early onset had a more adverse course of illness, with greater numbers of lifetime episodes (particularly depression), poorer functioning and quality of life, and a higher rate of suicide attempts.

*These data speak to the importance of early treatment, particularly in those with early onset bipolar illness, in an attempt to convert the illness to a more benign profile. In children at high risk by virtue of one or both parents with bipolar illness, one should be alert to early signs of illness, get proper evaluation accordingly, and treatment if indicated.*

A brief screening instrument for bipolar disorder in children and adolescents was developed and tested by Dr. E. Youngstrom (Case Western Reserve University, Cleveland) and colleagues, who tested a 10-item short form of the parent version of the General Behavior Inventory (PGBI) in parents of 512 youths (ages 5–17). The short form they developed showed good reliability (0.92), correlated 0.95 with the original scale, and showed significantly better discrimination of bipolar disorders than the full scale. The brief form also did well discriminating bipolar from unipolar disorder, and bipolar from ADHD cases. The best discriminating items on the PGBI concerned combinations of energy, irritability, and rapid changes in mood or energy; racing thoughts and difficulty falling asleep were the 9<sup>th</sup> and 10<sup>th</sup> best discriminating items, respectively, and grandiosity was not among the 10 most discriminating items.

### Neurobiology and Neuropsychology

Dr. S. Rapoport (National Institute on Aging, Bethesda) led a group study section suggesting that several mood stabilizing drugs effective in bipolar disorder downregulate brain phospholipase A2 (PLA2) and cyclooxygenase (COX)-2, enzymes that release arachidonic acid (AA) from brain phospholipids and convert AA to bioactive eicosanoids. These drugs also decrease AA turnover and its conversion to prostaglandin E2.

*"In 110 outpatients with major depressive disorder who had sustained acute response to fluoxetine, low serum folate levels were associated with delayed onset (average of 1.5 weeks) of antidepressant response in major depression. . ."*

*These mechanisms represent potentially new targets for therapeutics in bipolar illness.*

Although cognitive deficits have been found in patients with bipolar disorder in a number of studies, little research has been done on neuropsychological functioning in patients in the earliest phase of illness (first-episode patients). Dr. S. Gruber (McLean Hospital) and associates performed a variety of neuropsychological tests on 27 patients admitted to the hospital for their first episode of bipolar illness, and on 28 non-psychiatric patients. The first-episode bipolar patients performed significantly worse than control subjects on tests of psychomotor speed, executive function, and memory. The investigators suggested that their findings indicate that neuropsychological deficits are present early in the course of illness, even prior to the potential residual effects caused by repeated or prolonged affective episodes, and treatment with pharmacologic agents.

### Circulation Notice

For clarification, the *BNN* only published two issues from 2003 (Spring/Summer issue, and Fall/Winter issue). We have re-designed the newsletter with this issue to include more information in the same amount of space. There will be three issues published in 2004 as usual.

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