

Meeting Highlights

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

The remarkable number of interesting and informative research findings from the Fifth International Conference on Bipolar Disorder shows a renewed interest in bipolar research from pharmaceutical companies, national governments, and private foundations. So many excellent presentations were given that the *BNN* has divided this article into two parts; part I, covering data on treatments for, and course of, bipolar disorder will be presented in this issue. Data on neurobiology, pediatric bipolar disorder, and other topics will appear in the next issue of the *BNN*.

Mood Stabilizers

Dr. C. Baethge (Freie Universität Berlin, Germany) and colleagues assessed the efficacy of treatment with either **lithium or carbamazepine** (Tegretol®) in **long-term prophylaxis** of schizoaffective disorder. Both treatments were found to be effective after an average treatment duration of 6.8 years, reducing the number of days spent in the hospital from 71 (before maintenance therapy) to 11 days per year (during maintenance therapy).

The efficacy of an **extended-release formulation of carbamazepine** (Carbatrol®) in monotherapy treatment of 204 patients with manic or mixed episodes was studied by Dr. T. Ketter (Stanford University) and co-investigators. This study was a 3-week double-blind, placebo-controlled study, followed by a 6-month open extension phase. In the 47% of patients who completed the acute phase, the carbamazepine extended-release patients had significantly greater improvements in mania scores, and higher responder rates (41.5% vs. 22.4% with placebo). Acute improvements with the extended-release formulation were maintained during the 6-month open extension, and patients who were previously treated

with placebo showed significant improvements at the first visit (one month) when switched to carbamazepine extended-release.

The **extended-release formulation of valproic acid** (Depakote ER®) was assessed over one year in bipolar I or bipolar II patients by Dr. D. Marcotte (Fayetteville, North Carolina). Eleven bipolar I patients and eight bipolar II patients were converted from Depakote delayed release to the newer extended-release compound. Patients who were compliant with Depakote ER maintained a stable mania rating throughout the treatment. Those patients who discontinued their dosing demonstrated a significant increase in psychotic symptoms which was reversed with the re-institution of Depakote in two of the three patients.

Dr. I. Salloum (University of Pittsburgh School of Medicine) and colleagues investigated the combined use of the mood stabilizer **valproate and naltrexone** (Revia®), an opioid antagonist that blocks the reinforcing effects of alcohol, in patients with bipolar disorder and comorbid alcohol dependence and other substance use disorders. In the naltrexone plus valproate group (four patients), no one relapsed to alcohol use after eight

weeks, whereas three of the four patients in the valproate only group did relapse. The naltrexone plus valproate group also had better outcome on depression, mania, alcohol craving, sleep difficulties, functioning, and reported medication side effects.

- *Although the study size was small, it shows that naltrexone may be helpful in reducing alcohol intake in bipolar patients, much like topiramate (Topamax®) has been found to be effective in this comorbidity as well.*

Anticonvulsants

Two large placebo-controlled prophylaxis trials were recently completed comparing **lamotrigine** (Lamictal®), **lithium, or placebo** for 18 months in the prevention of manic and depressed episodes in 638 patients. These studies found that lithium was more effective than lamotrigine in preventing manic episodes, but lamotrigine was more effective in preventing depressive episodes. Several investigative groups examined different aspects of these two double-blind studies.

Dr. K. Davis (GlaxoSmithKline) and colleagues found that lamotrigine in these two studies **improved cognition** on two different self-report scales, and was significantly correlated with depression symptom severity, but not with manic symptoms. The **quality of life** was measured during these same two studies by Dr. S. Kennedy (University Health Network, Toronto) et al. Dr. Kennedy found that for all eight subscales (physical functioning, physical role, pain, general health, vitality, social functioning, emotion, and men-

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tal health) of a self-report scale of quality of life, statistical improvement was seen in both studies after lamotrigine treatment, with the exception of the subscale "vitality" in index mania.

Predictors of response in these two large controlled trials were examined by Dr. T. Ketter (Stanford University) and co-investigators. Overall, fewer than three depressive episodes in three years, later onset of illness, shorter time to stabilization on lamotrigine monotherapy, and lack of previous psychiatric hospitalization were predictive of treatment response. Predictors of response by treatment were a late onset of illness (age > 20 years; lithium) and fewer than three depressive episodes in three years (lamotrigine). **Weight gain** in these two prophylactic trials was studied by Dr. G. Sachs (Harvard University) and colleagues; they found that after 52 weeks of treatment, mean change in body weight was significantly smaller in the lamotrigine treatment group than in the placebo or lithium groups.

And finally, Dr. M. Frye (UCLA) and colleagues found that in this lithium versus lamotrigine trial, the risk for intervention was generally highest for patients with **more previous depressive episodes** and lowest for patients with fewer previous depressive episodes.

Dr. C. Bowden (University of Texas Health Science Center) and colleagues presented data from a subset of the patients in another lamotrigine trial, on the combined use of **lamotrigine and valproate** in 200 patients with bipolar I disorder. The lamotrigine dose was cut in half, because co-administration with valproate can dangerously increase lamotrigine levels. The majority of patients on the combination received at least seven weeks of co-treatment. Two global rating scale scores of efficacy showed that the combination was effective in the majority of patients, and that there was no significant increase in the rash rate in those who received combina-

tion therapy (14%) versus those who received monotherapy (10%).

Data from eight different studies were presented examining the use of **oxcarbazepine** (Trileptal®) in bipolar disorder. Four of the studies were retrospective chart reviews of patients who used oxcarbazepine (463 patients) and four studies were open prospective studies of oxcarbazepine monotherapy or adjunctive therapy (88 patients). All of the studies found oxcarbazepine to be effective in at least 50% of the patients. The patients with bipolar disorder that were studied were bipolar I and bipolar II, and oxcarbazepine was used for depression, mania, hypomania, psychosis, and prophylaxis.

The classic anticonvulsant **phenytoin** was found to be effective in prophylaxis when used as an adjunctive treatment after six months in 20 refractory bipolar patients by Dr. J. Levine (Ben Gurion University, Israel) and colleagues.

Atypical Antipsychotics

There were several abstracts and presentations on the use of the new atypical antipsychotic drug **quetiapine** (Seroquel®). In two large studies conducted by researchers from the AstraZeneca pharmaceutical company, 604 patients with bipolar I mania completed 12-week, randomized, double-blind, placebo-controlled trials with quetiapine. Quetiapine monotherapy (up to 800 mg/day) showed a statistically significant improvement in mania score over placebo by day four of treatment. By the 84th day, scores for lithium and haloperidol (Haldol®), the comparison drugs in the two trials, were similar to quetiapine in all efficacy measures.

In two other AstraZeneca studies in over 500 bipolar patients, quetiapine adjunctive therapy for acute mania showed statistically significant improvement over placebo and mood stabilizer treatment at day 21 of the study.

Dr. S. Ghaemi (Harvard Medical School) et al. found that quetiapine treatment (mean dosage of 197 mg/day), with or without a mood stabilizer, was an effective treatment for bipolar I rapid cycling; however, 70.7% of the 41 patients in this open prospective follow-up study dropped out.

Researchers from the pharmaceutical company Bristol-Myers Squibb conducted several studies using the atypical antipsychotic **aripiprazole** (Abilify®) in patients with acute mania. One double-blind, placebo-controlled 3-week study found that the response rate for 15–30 mg/day of aripiprazole (40%) was significantly higher in 262 patients than for placebo (19%). Aripiprazole was well-tolerated in this study. Another 12-week, multicenter, double-blind study in 347 inpatients and outpatients with acute manic or mixed episodes treated with 15-30 mg of aripiprazole or 10-15 mg of haloperidol found that significantly more patients responded and remained on aripiprazole (50%) than on haloperidol (28%).

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■ Dr. F. Colom (Hospital Clinic Barcelona, Spain) and associates presented data from a subanalysis of a larger randomized single-blind trial, on the efficacy of **group psychoeducation** vs. non-structured intervention plus pharmacological treatment in the prophylaxis of recurrences in bipolar disorder. This subanalysis showed that patients in the psychoeducation group had higher mean **serum lithium levels** at six, 18, and 24 months, suggesting that group psychoeducation may enhance lithium level stability.

■ Dr. T. Bschor (University Hospital Dresden, Germany) found that the thyroid hormone combination of **levothyroxine (T₄) + triiodothyronine (T₃)** in 12 prophylaxis-refractory affective disorder patients did not result in better cognitive performance than high dose T₄ alone. With respect to psychiatric state, the patients in this study seemed to benefit more from high-dose T₄.

Bipolar Network News

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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*.

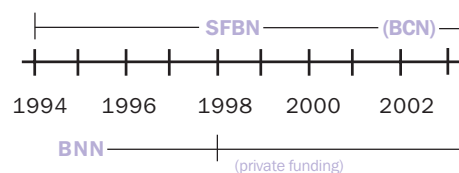
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Historical Perspective

The Stanley Foundation Bipolar Network (1994–2002)



The Stanley Foundation Bipolar Network (SFBN) underwent a number of revisions and transitions during its several years of existence. In this overview, we outline the events that led to the founding of the SFBN, some of its major research findings, the funding changes and termination of the Network, and its transformation to an investigator-initiated Bipolar Collaborative Network (BCN).*

Historical Background

In 1989 and 1994 the National Institute of Mental Health (NIMH) convened conferences on bipolar illness to explore and address the reasons for the marked underfunding of studies for therapeutic approaches to bipolar illness compared with other major psychiatric illnesses. These conferences identified many reasons for underfunding, including:

- (1) the misperception that lithium was a sufficient treatment for the majority of bipolar patients;
- (2) no consensus on accurate acute and longitudinal rating methodologies for bipolar illness (as there were for unipolar illness);
- (3) continuing strong controversy as to optimal clinical trial designs, especially given the difficulties in studying bipolar illness, including its vast heterogeneity of manic-depressive, mixed, and euthymic phases and cycle frequencies, and high incidence of medical and other psychiatric comorbidities;
- (4) a lack of pharmaceutical interest in bipolar illness compared with schizophrenia, anxiety, and depression;
- (5) the exclusion of bipolar depressed patients from most studies of antidepressants (for fear of switching patients into mania); and
- (6) the difficulties in acquiring large enough study populations

within single sites (Prien and Potter, 1990, *Psychopharmacol Bull* 26 [4]: 409–427; Prien and Rush, 1996, *Biol Psychiatry* 40 [3]: 215–220).

As many of these issues proved difficult to ameliorate, even during the five years between NIMH meetings, the Stanley Foundation Bipolar Network (SFBN) was founded to address many of these issues directly. From the generosity of Theodore and Vada Stanley of the Stanley Foundation, funds were initially provided and used for two purposes: (1) **drug study**, specifically nimodipine (Nimotop®); and (2) **rating and methods development**, specifically the Clinical Global Impressions scale as modified for use in Bipolar Illness (CGI-BP) and the National Institute of Mental Health Life Chart Method (NIMH-LCM™). The first patient was admitted in 1995.

Founding of the Network

Given the success of these initial endeavors¹⁻³, and the Stanley's hearing independently from Dr. R. Post and Dr. S. McElroy at a national meeting that a vast amount of treatment information could readily be acquired and used, they again decided to help expedite studies in the field. Further Stanley Foundation funds were made available to Dr. Post and colleagues for the formation of a collaborative network of clinical investigators who would focus on the longitudinal course of

bipolar illness, its response to treatment, and the development of new therapeutic approaches to the illness.

The SFBN began with five sites: the University of California at Los Angeles (UCLA) Ambulatory Clinical Research Center and VA Medical Center (Dr. L. Altshuler and Dr. M. Frye); the University of Texas-Southwestern Medical Center in Dallas, Texas (Dr. A.J. Rush and Dr. T. Suppes); the University of Cincinnati College of Medicine in Cincinnati, Ohio (Dr. P. Keck and Dr. S. McElroy); the Biological Psychiatry Branch of the NIMH in Bethesda, Maryland (Dr. K. Denicoff, Gabriele Leverich MSW, and Dr. R. Post); and the Altrecht Institute for Mental Health and the University Medical Center, Utrecht, The Netherlands (Dr. W. Nolen and Dr. R. Kupka). Dr. K. Kramlinger of the Mayo Clinic in Rochester, Minnesota, was also involved on a half-time basis.

In the initial formulation of the Network it was decided that it would have a **unique focus of longitudinal study**, that patients would *not* be excluded based on psychiatric comorbidities or rapid cycling presentations, and would *not* be discharged from the Network following completion of clinical trials. Instead, patients would be eligible for a sequence of clinical trials as necessary to maintain optimal responsivity and symptom remission. Consensus was reached on the use of a **core set of methodologies** including the NIMH-LCM for the daily prospective longitudinal assessment of patients, as supplemented by cross-sectional ratings using the Inventory of Depressive Symptomatology (IDS), the Young Mania Rating Scale (YMRS), and the CGI-BP.

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Further information on the NIMH-Life Chart Method that was developed by the SFBN is available on our website at: www.bipolarnews.org.

Complete instruction manuals and forms are available for downloading for patient, clinician, and parent life charting of bipolar disorder. Also see the special Life Charting issue of the *BNN* (Vol. 8, Issue 1) on our website.

*For corresponding bibliographic citations to references noted in this article, please see pages 10–11.

History of the SFBN

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To try and circumvent some of the controversies about clinical trial methodology, it was decided that studies would be run at **various levels of methodological control** from naturalistic open case series to randomized, double-blind, placebo-controlled studies, to use the most optimal strategy for investigating likely new treatment candidates on a preliminary basis and

stances identifying drugs with either problematic side effects or lack of apparent effectiveness, such as the gamma-aminobutyric acid (GABA) reuptake inhibitor **tiagabine** (Gabitril®)⁴. Promising antimanic effects of the atypical antipsychotic **olanzapine** (Zyprexa®) were identified by the Network⁵ a number of years prior to its FDA approval, and the potential antidepressant properties of the atypical antipsychotic **quetiapine** (Seroquel®) are now being further explored as well.⁶

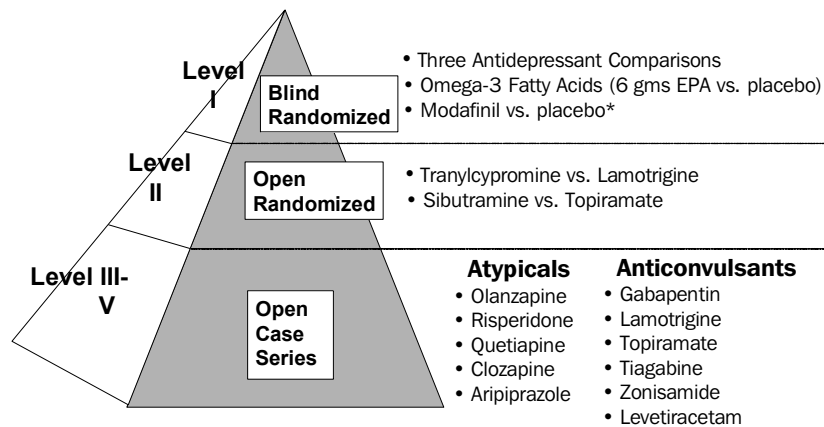


Figure 1: Clinical studies in the Stanley Foundation Bipolar Network at multiple levels of methodology and control

then bringing these patients into more formal clinical trials (Figure 1). As the SFBN became productive, additional sites were added in Europe (i.e., Dr. H. Grunze of the Psychiatrische Klinik der LMU in Munich, Germany, and Dr. J. Walden of the Zentrum für Innovative Therapie Bipolarer Störungen am Universitätsklinikum in Freiburg, Germany) to take advantage of the availability of some agents that were approved there prior to their Food and Drug Administration (FDA) approval in the United States, e.g., acamprosate (Campral®) for the treatment of alcohol abuse and suppression of associated alcohol craving.

Brief Overview of SFBN Findings

The SFBN attempted to address some of the research shortfalls and positive recommendations made by the NIMH meetings on bipolar illness in 1989 and 1994. The **effectiveness of more than 20 drugs for bipolar illness** was studied, with promising results observed in many studies, and in several in-

Similarly, the promising antidepressant and mood stabilizing effects of the anticonvulsant **lamotrigine** (Lamictal®) were seen in the Network⁷ many years prior to the recent FDA approval of lamotrigine for the prevention of depressed, manic, and mixed episodes in

the long-term treatment of bipolar illness. The potential utility for weight loss of the anticonvulsant **topiramate** (Topamax®)⁸, **sibutramine** (Meridia®), and most recently, the anticonvulsant **zonisamide** (Zonegran®)⁹, have been identified as well as a variety of other important side effects of other compounds.

In addition, a variety of **clinical, demographic, and illness variables**¹⁰ have been identified that appear associated with a relatively less positive response to naturalistic treatment in the Network, and thus provide new areas for exploration of more optimal treatment interventions for those at highest risk for an adverse outcome. The **high incidence of comorbidities** including anxiety disorders,¹¹ substance abuse,¹² and problems with overweight¹³ have been described and published by the Network, as well as correlates of previously medically-severe **suicide attempts**,¹⁴ including a history of early childhood environ-

mental adversities¹⁵ and a variety of other illness and health care-related factors.

In 2002, after eight very productive research years, the enrollment of more than 1,000 patients, and over 50 publications, the Stanley Foundation terminated funds for the SFBN. These Stanley Foundation funds were applied to a grants program for a wide range of investigators, specifically for the development of new treatment agents only, to increase the speed of new drug development in bipolar illness and schizophrenia. The Stanley Foundation was re-named the Stanley Medical Research Institute (SMRI) in 2001.

Progress in bipolar illness research has also been made in other areas. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), led by Dr. G. Sachs and Dr. M. Thase, used many of the general strategies employed by the SFBN, including the recruitment of large numbers of patients who might then be able to participate in a range of naturalistic to randomized, controlled, clinical trials. In the last decade, there has been renewed interest of the pharmaceutical industry in assessing both anticonvulsants and atypical antipsychotics for their potential antimanic effects. Thus, many of the areas and problems of underfunded bipolar illness research identified over the past two decades have begun to be addressed. At the same time, there is increasing recognition of the ongoing shortfalls in clinical treatment research of bipolar illness, and in achieving and maintaining remission.

The Bipolar Collaborative Network (BCN)

Given the successful collaborative efforts of the former SFBN group of principal investigators (PIs), all of the PIs decided to continue to collaborate closely, particularly around the analysis and publication of the wealth of data already collected and new findings preliminarily observed.

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History of the SFBN

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Analysis has just been completed of the largest randomized, placebo-controlled, double-blind study of **omega-3 fatty acids** in bipolar illness. More than 120 patients were randomized to 6 grams of the eicosapentaenoic acid (EPA) form versus placebo for four months, with the patient option for an open extension of treatment with EPA for a subsequent eight months. Disappointingly, an initial analysis of the data reveals a lack of overall benefit of active EPA compared with placebo for the treatment of either acute depression or cycling courses of illness. However, a sub-analysis suggests that younger patients with cycling presentations may respond better than older subjects to the active compound. Dr. Keck has submitted this manuscript for publication.

Dr. McElroy is preparing to submit the findings from the study on **zonisamide** as highlighted in this issue (see p. 6). Sixty-three patients were assessed during open adjunctive treatment with zonisamide; 80% showed a rapid antimanic response, and 30% showed a delayed onset response in depression. Weight loss was observed with zonisamide in parallel with that previously observed with topiramate and sibutramine. Dr. McElroy is also currently preparing to submit the results of the randomized open comparison of **topiramate** and **sibutramine** for publication.

Dr. Post is finishing a manuscript on the investigation of the new anticonvulsant **levetiracetam** (Keppra®). As reviewed in previous issues of the *BNN*, preliminary open assessments of this drug's effectiveness as an adjunctive agent were not as promising as that seen with zonisamide, and the potential for this anticonvulsant drug in the treatment of bipolar illness appears ambiguous at this time, perhaps deserving further preliminary investigation prior to more controlled studies.

Dr. Suppes and Dr. Grunze will be assessing the long-term effectiveness of **quetiapine** and **risperidone** (Risperdal®), respectively; Dr. Nolen is preparing the results of a randomized comparison of **lamotrigine** and **monoamine oxidase inhibitors**; and Dr. Frye will be publishing data on a soon-to-be-completed **comparison of modafinil (Provigil®) to placebo** for patients with residual bipolar depression and fatigue. Modafinil is the first nonpsychomotor stimulant medication that has been approved for the treatment of narcolepsy and previous small case reports suggested its potential utility in unipolar depression.

Dr. Post is also finishing the analysis of the large **double-blind, randomized comparison** of three different antidepressants (**bupropion, sertraline, and venlafaxine**) in the adjunctive treatment of bipolar depression. Results of this clinical trial have been published in terms of overall treatment response and switch rate,^{16,17} and assessment of the efficacy and side effects of the individual drugs is just beginning now that the blind has been broken.

The Bipolar Network News

Funding Sources:

The *Bipolar Network News (BNN)* newsletter, begun in 1995, was initially funded by the Stanley Foundation as an ongoing source of information about available clinical trials and novel results in the field. In 1998, the Stanley Foundation decided to place all funds in the service of new treatment development, and financial support for the *BNN* was terminated. The *BNN* has continued to publish with outside funds provided by *unrestricted grants* from pharmaceutical companies, including donations from Ciba-Geigy/Novartis, Janssen Pharmaceutica, and in 2003, Abbott Pharmaceuticals.

Disclaimer:

We wish to reemphasize that the viewpoints expressed in the newsletter are solely those of its editors and do not represent those of the SMRI, NIMH,

or any other funding agency. Given the highly preliminary nature of many of the communications included here, such as comments on unpublished work and abstracts in scientific meetings, the editors cannot be responsible for errors in fact or emphasis that are likely to occur despite the considerable care to avoid such errors.

Therefore, all of the information provided in the *BNN* should be considered in the context of its highly preliminary format, and all decisions about patient care should be carefully reviewed with the appropriate treating physician who will ultimately make the most informed treatment decisions based on more formal published evidence in the literature, FDA recommendations, and their own clinical experience. The *BNN* is designed to rapidly deliver highly preliminary observations, data, and opinions to trigger further study and dialogue among patients, physicians, and other family members. It is not meant to be an authoritative source upon which treatment recommendations for individual patients can or should be based.

Mission:

We will attempt to continue to identify both areas of progress and problems in the subsequent issues of the *BNN* and hope that this source of updated information from scientific meetings, the literature, and new findings from the BCN provides valuable assistance to a wide range of patients with bipolar illness, their family members, and clinicians and physicians involved in the treatment of this recurrent affective disorder.

The *BNN* has a hard copy circulation of about 10,000, and is available online at www.bipolarnews.org, and we welcome comments, insights, and novel observations about treatment of the illness from our readers. ■

For corresponding bibliographic citations to the references noted in this article, please see the bibliography on pages 10–11 of this issue.

For a complete list of publications by the Stanley Foundation Bipolar Network, please visit our website at: www.bipolarnews.org.

Life Chart Highlight

Possible useful effects of zonisamide in bipolar illness

Background

Zonisamide (Zonegran[®]) is a recently approved drug for the treatment of refractory seizure disorders when used adjunctively with other medications. Many other anticonvulsants appear to have useful antimanic effects (such as valproate, carbamazepine [Tegretol[®]], and oxcarbazepine [Trileptal[®]] or prominent antidepressant effects (such as lamotrigine [Lamictal[®]]); therefore it was important to study the possible psychotropic effects of this new anticonvulsant. In addition to this general rationale, data from preclinical studies shows that zonisamide increases the turnover of serotonin and dopamine in low doses and inhibits them at higher doses, further suggesting a mechanistic basis for antidepressant and antimanic effects beyond its anticonvulsant effects (which are thought to be related to the blockade of sodium channels and the inhibition of glutamate release).

In Japan, zonisamide has been commercially available since 1989. In 1994, Dr. S. Kanba et al. (1994; *Prog Neuropsychopharmacol Biol Psychiatry* 18 [4]: 707–715) reported the first open study of adjunctive zonisamide in 15 patients with bipolar mania, six with schizoaffective manic state, and three with schizophrenic excitement. In Dr. Kanba's study, 33% of the bipolar manic patients showed remarkable global improvement with the addition of zonisamide, and 80% of the bipolar group had more than moderate global improvement. No serious adverse reactions were found and no patients required zonisamide withdrawal.

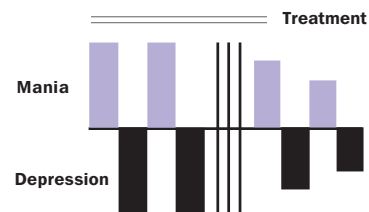
Zonisamide in Bipolar Patients

In a study led by Dr. S. McElroy of the former Stanley Foundation Bipolar Network (now the Bipolar Collabora-

tive Network), 63 patients were administered zonisamide in an open (non-randomized) fashion after they had been resistant to other treatment agents. One patient from this study, whose life chart is illustrated on page 7, was an ultra-rapid cyler (four or more episodes per month) despite treatment with the antipsychotics quetiapine (Seroquel[®]) and risperidone (Risperdal[®]), the anticonvulsants topiramate (Topamax[®]) and valproate (Depakote[®]), and the thyroid hormone levothyroxine (T₄, or Synthroid[®]). Following discontinuation of the monoamine oxidase inhibitor tranylcypromine (Parnate[®]), mood cycling continued; zonisamide was then added to the therapeutic regimen. With this zonisamide addition, there was an apparent decrease in the frequency and severity of hypomanic breakthrough episodes and a slight improvement in the average severity of depression from high moderate to low moderate.

This apparent moderate response to zonisamide can not be unequivocally attributed to zonisamide, because some of the observed decrease in cycle frequency may have been associated with the prior discontinuation of tranylcypromine. However, experience in other patients is more suggestive of positive effects of zonisamide.

Eighty percent (80%) of the patients treated for acute mania or cycling components of mania in the study by Dr. McElroy et al. showed clinical improvement (i.e., 50% or greater decreases in their Young Mania Rating Scale scores), usually within the first week of treatment. Zonisamide may have some antidepressant effects, because approximately 30% of these treatment-refractory patients showed 50% or greater improvement in their Inventory of Depressive Symp-



tomatology scores or Clinical Global Impression scale depression scores, with improvement usually beginning after the fourth week of treatment. Sleep improved in the majority of patients without undue increases in daytime sedation.

Moreover, patients on zonisamide experienced a small weight loss, averaging about one-third of a pound a week, in parallel with the rate previously observed on topiramate. Like topiramate, zonisamide is a carbonic anhydrase inhibitor and as such is associated with an approximately 1% incidence of kidney stones (renal calculi). However, this side effect was not observed in any of the first 63 patients studied by Dr. McElroy et al., and one or two glasses of water with each meal may be a useful preventive measure.

Because zonisamide has a long half-life of about 63 hours, the entire dose can be given at night, with the added benefit of nighttime sedation for those with insomnia, but without undue daytime impairment. Although the zonisamide dose for the patient in the life chart on p. 7 was titrated up to 400 mg/day, the average dose used in this study was about 250 mg/day.

Side Effects

In the medical literature, zonisamide has been associated with rare allergic reactions and occasional serious rashes. Minor decreases in hematological (blood) and renal (kidney) indices have been almost uniformly inconsequential. Zonisamide is associated with a decrease in sweating (hypohydrosis) and patients taking zonisamide should be warned about maintaining good hydration if they are planning to do extreme exercise for a considerable period of time. Several clinical case reports suggest that

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A number of studies looked at the effectiveness of **olanzapine** (Zyprexa®) and **risperidone** (Risperdal®) in bipolar patients. Olanzapine was found to be effective as an adjunctive therapy to lithium or valproate in two different studies: in 85 patients with dysphoric mania in one study (olanzapine dosage 5–20 mg/day), and in 36 patients with rapid cycling in another study (mean dosage 13.3 mg/day). Risperidone was found to be effective as an augmentation treatment in patients with acute mania and rapid cycling, and as monotherapy in mania. Several studies (conducted by Janssen Pharmaceutica) reported that risperidone was as effective as olanzapine, but less expensive.

Other Treatments

Dr. E. Evins (Massachusetts General Hospital) and associates conducted a 6-week, double-blind, placebo-controlled study of **inositol augmentation** to lithium or valproate treatment in 16 patients with bipolar depression. Thirty-three percent of the patients taking inositol (mean dosage 13.87 g/day) met response criteria

(\$50% reduction in depression rating scale score), versus 0% taking placebo.

• *Although not statistically significant, these data in bipolar depression mirror those of another positive study done by Chengappa et al. (2000; Bipolar Disord 2 [1]: 47–55) with inositol in bipolar depression. These two positive studies leave open the option of inositol augmentation for bipolar depression, just as it has been reported to be effective in unipolar depression, anxiety disorders, and obsessive-compulsive disorders by other investigative groups.*

A number of posters and presentations addressed **non-pharmacological treatment** for bipolar disorder. Dr. J. Scott (Institute of Psychiatry, London) noted that since 1999, nearly 20 randomized controlled trials of adjunctive psychological therapies have been published, are in press, or are being conducted around the world.

Dr. A. Zaretsky (University of Toronto, Canada) and colleagues compared adjunctive **cognitive behavioral therapy** (CBT) to psychoeducation in 87 patients with bipolar I or bipolar II in remission from mania and depression. All pa-

tients received seven weekly sessions of individual psychoeducation, and patients randomized to CBT received 13 additional weekly sessions of individual CBT. Only 3.2% of patients who received CBT had poor outcomes versus 30.8% of patients who received psychoeducation alone.

Dr. R. D'Souza (Monash University, Melbourne, Australia) conducted an open randomized control study using a **spiritually augmented cognitive behavior therapy** (SACBT) for demoralization and treatment adherence in patients with bipolar I depression. Thirty-four patients were randomized to receive either supportive case management or non-denominational SACBT by a trained clinician for 14 sessions over 10 weeks. These patients had rated spirituality as important in a spiritual needs questionnaire. There were greater improvements on the depression scale used in the SACBT group early, whereas at the tenth week the scores were less significantly different. There was also significantly better treatment adherence, and improved attitudes and beliefs to treatment, and

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Life Chart Highlight: Zonisamide

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this action of zonisamide may be useful in the treatment of excessive sweating in those in whom it has become problematic when taking serotonin-selective reuptake inhibitor (SSRI) antidepressants.

Conclusions

This preliminary open exploratory study of Dr. McElroy and associates was conducted to examine promising areas of potential efficacy which could then be later documented in more systematic controlled double-blind studies. The initial review of the data suggests possible robust antimanic effects, similar to those originally reported in the study by

Dr. Kanba et al. (1994) and in a case report by Dr. T. Berigan (2002; *Can J Psychiatry* 47 [9]: 887). Whether or not these effects or the more minor potential antidepressant effects of this drug will be revealed in more systematic studies remains to be confirmed in controlled clinical trials.

Experience in patients with seizure disorders, in this study, and in another by Dr. T. Ketter et al. (unpublished data) is that patients can experience a degree of weight loss parallel to that seen with topiramate. In contrast to topiramate, which has been associated with tolerability problems because of cognitive impairment in a small percentage of patients, zonisamide

appears well tolerated in this regard.

Thus, based on these initial uncontrolled observations, it is likely that zonisamide will emerge as a potential alternative agent for assisting in weight loss in those patients with problems with overweight and unstable bipolar illness, particularly if they are not able to tolerate the side effects of topiramate. With these initial areas of promise identified (mania and weight loss), further work is now indicated to better define and confirm the psychotropic profile of zonisamide and its potential utility for the treatment of different components of bipolar illness. ■

■ Dr. T. Berigan in 2002 published a case report on the use of **zonisamide** in bipolar disorder in a 51 year-old man with a 27-year history of bipolar disorder type I (*Can J Psychiatry* 47 [9]: 887). This patient had been non-responsive to a variety of mood stabilizers, anticonvulsants, antipsychotics, and antidepressants. When zonisamide was added to his mood stabilizer regimen at 100 mg/day, and then later increased to 300 mg/day, the patient's hypomanic symptoms disappeared.

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less rehospitalization in the SACBT group.

Course of Illness

Dr. A. Viguera (Harvard Medical School) sought to quantify recurrence risk and time to first recurrence in **pregnant women** with bipolar disorder who **discontinued versus continued** their mood stabilizers during pregnancy. In 50 pregnant women with bipolar disorder, the risk of recurrence during the first 40 weeks following discontinuation of a mood stabilizer was 80.6% (29/36) compared with only 28.6% (4/14) among women who continued on maintenance mood stabilization. Those women with the greater number of past episodes and who had other comorbid illnesses were the ones who were most likely to relapse. A faster rate of tapering off medications was not associated with an increased risk of relapse, as Dr. Viguera had previously observed for non-pregnant women who discontinued lithium.

- *These data continue to indicate the high risks of discontinuing effective pharmacoprophylaxis treatment, and given the adverse effects on child development of a mother with a depressed or manic episode, one should carefully consider the risks and benefits of discontinuing mood stabilizer treatment during pregnancy. Among other liabilities, new data indicate that children of depressed women gain weight more slowly than children of non-depressed women.*

The **protective effect of pregnancy** was studied in women with bipolar disorder by Dr. V. Sharma (Regional Mental Health Care London, Canada) et al. Compared to a 1-year baseline period, women with bipolar disorder had fewer relapses or recurrences during pregnancy and more relapses or recurrences during the immediate postpartum period.

Dr. E. Knoppert-van der Klein (Rijngeest Groep, The Netherlands)

and associates found that between 1994 and 2002, all 20 children whose **mothers were using lithium** during pregnancy in the city of Leiden, The Netherlands, were born without major problems; no congenital anomalies were observed.

After recruitment of 330 patients from 11 Veterans Administration medical centers (VAMC), Dr. G. Brown (Mountain Home VAMC, Johnson City, Tennessee) and colleagues found that military **veterans** with bipolar disorder who had a **history of early adversity** (physical or sexual abuse) were more likely to have a rapid cycling course and comorbid substance use and anxiety disorders. Physical abuse was associated with more depressive episodes, younger age of onset, and a mixed index episode; sexual abuse was associated with female gender, more suicide attempts, lower lithium levels at study entry, and poor cognitive performance on several standardized instruments.

- *These data are convergent with those of Leverich et al. (2002; Biol Psychiatry 51 [4]: 288–297) from the Stanley Foundation Bipolar Network and indicate that patients with a history of abuse need special and earlier attention to decrease their more aggressive course of bipolar illness in association with a positive history of these early adversities.*

Dr. A. Duffy (University of Ottawa, Canada) and associates presented data from a prospective study of the children of bipolar parents who were responsive or non-responsive to lithium treatment. **Children of parents who were lithium responders** had good premorbid functioning and classic mood presentations with an episodic course, whereas children of lithium-nonresponders had poor premorbid functioning and had mood disorders with a chronic course and associated comorbid conditions. Clinical course among mood-disordered offspring was predicted by the disease course of the parent.

- *These data mirror those of an earlier published study by this same investigative group (Passmore et al. 2003; Bipolar Disord 5 [2]: 110–114) indicating differential predictors of response to lithium versus lamotrigine. Lithium responders tended to have a positive family history of unipolar or bipolar illness with euphoric manias and an intermittent course of illness without comorbidities. In contrast, lamotrigine responders had a positive family and personal history of anxiety disorders, a more chronic continuous course, more rapid cycling, and other comorbidities. The relatives of lithium responders had significantly higher risk of bipolar disorder while relatives of lamotrigine responders had higher prevalence of schizoaffective disorder, major depression and panic attacks.*

The incidence rate of **manic switching during antidepressant use** was examined by Dr. S. Ghaemi (Harvard Medical School) and colleagues. Dr. Ghaemi found that in 155 trials (in 41 patients) of four classes of antidepressants (tricyclics, serotonin-selective re-uptake inhibitors, bupropion [Wellbutrin®], and other modern antidepressants) the manic switch rate was 18.7% and did not differ between the older and newer antidepressant drugs (in contrast to other meta-analyses). He also observed loss of antidepressant effect via a tolerance process in 26.5% of the trials, particularly prominent in fluoxetine (Prozac®) compared with the other antidepressants.

Dr. A. Schaffer (University of Toronto, Canada) et al. reported that **elderly bipolar patients** (≥ 66 years old) treated with an antidepressant had a decreased rate of hospitalizations for both depression and mania compared with elderly bipolar subjects not receiving an antidepressant.

A controlled study on the **outcome of antidepressant-induced mania** was

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■ In the week after the meeting in Pittsburgh, the Food and Drug Administration (FDA) approved **lamotrigine** for the prevention of an affective episode (manic, depressed, or mixed) in bipolar I illness. The 18-month study upon which this approval was based (see p. 1) indicated that lithium was more effective than lamotrigine in the prevention of manic episodes, but lamotrigine was more effective than lithium in the prevention of depressive episodes. Lamotrigine is the first drug FDA-approved for long-term maintenance treatment prior to its approval for an acute episode.

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*For corresponding citations to these references, please see pages 3–5

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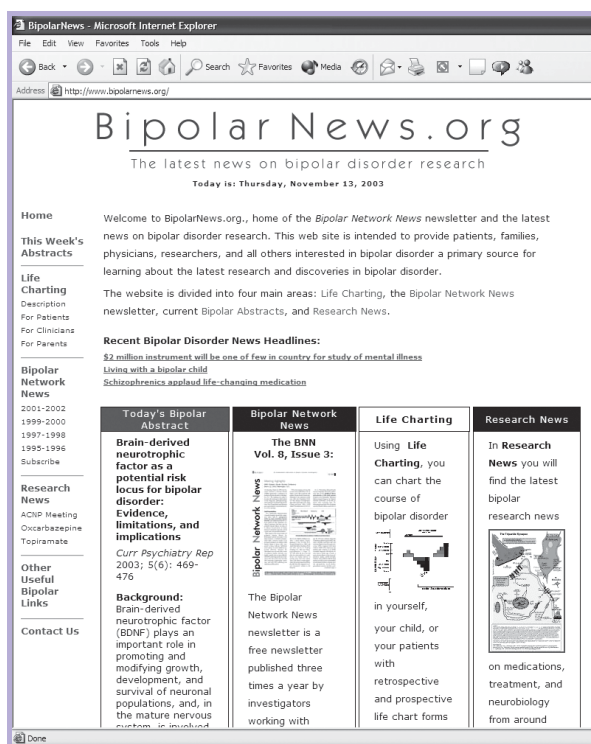
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conducted by Dr. R. Tamada (University of São Paulo Medical School, Brazil). The antidepressant-induced mania group, compared with the spontaneous mania group, had a significantly higher rate of depressive recurrences. Time to recurrence was significantly shorter in the antidepressant-induced mania group.

Two separate studies examined the **course of rapid cycling** disorder in large patient populations. Dr. R. Kupka (Altrecht Institute for Mental Health, Utrecht, The Netherlands) compared rapid (206) and non-rapid cyclers (333) in the Stanley Foundation Bipolar Network. Patients were outpatients with either bipolar I, bipolar II, or bipolar not otherwise specified (NOS), followed for one to six years with daily mood ratings. Rapid cyclers differed from non-rapid cyclers with respect to: earlier age of onset of depressive and (hypo)manic symptoms; longer duration of illness; more lifetime episodes; worse functioning in past year;

parental history of drug abuse; and lifetime histories of rapid cycling (including past year), dysphoric mania, exposure to antidepressants, drug abuse, anxiety disorders, and childhood physical or sexual abuse. All factors showed a gradual increase with the number of episodes per year, failing to indicate a non-linearity at four episodes per year. Therefore, this study did not support rapid cycling as a distinct subtype of bipolar disorder.

Dr. C. Schneck (University of Colorado Health Sciences Center) examined **rapid versus non-rapid cycling** in the first 500 bipolar I or bipolar II patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Rapid cycling occurred in 20% of the sample. Rapid cycling patients were more likely to be female, although the effect was significantly more pronounced in bipolar I patients than in bipolar II patients. Rapid cycling patients experienced a younger age of onset of illness, were

more often depressed at study entry, and had poorer global functioning in the year prior to study entry than non-rapid cycling patients. A lifetime history of psychosis did not distinguish between rapid and non-rapid cycling patients. ■

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